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Evaluation of Ph.D. thesis of mgr Vahagn Ivanyan, titled „Design and optimization of beam shaping assemblies for boron neutron capture therapy based on accelerators and DD/DT neutron generators".

Doctoral Thesis – scientific contents

The Doctoral Thesis consists of Introduction, five chapters, Appendix and Bibliography, 108 pages in total. The text of the thesis is written clearly, well-illustrated and thoroughly printed.

The main aim of the PhD thesis by Mr. V. Ivanyan is to contribute to the development of the design of Beam Shaping Assemblies (BSAs), highly important for the Boron Capture Neutron Therapy (BCNT) to be realized with application of C18/18 cyclotron, DD and DT neutron generators. This aim was realised through the simulation of several BSAs in order to make the best choice among materials and their configurations to meet the IAEA-TECDOC-1223 recommendations. This thesis includes a feasibility study for the development of BNCT based on the Armenian C18/18 cyclotron as well as DD and DT compact neutron generators with application of GEANT4 simulation package.

Detailed contents

In the Introduction mgr Vahagn Ivanyan begins from discovery of neutron, being "the particle basis" of the BCNT itself, lists and comments two main processes for the nuclear reaction $^{10}B(n,\alpha)$, which serve a fundamental nuclear physics issue for the BCNT. The presence of alpha-particle in the outgoing channel of this nuclear reaction makes it possible to use this ^{4}He nucleus with corresponding kinetic energy to pass the short path length within a cancer affected cell, killing a cancerous DNA and not affecting the healthy tissue of a live organism nearby. It was also noted that the BCNT as a method of cancer treatment is targeted against glioblastoma multiform of brain and neck. As any physics-based technique, the BCNT implementation requires application of corresponding neutron sources. Among them are listed nuclear reactors and accelerators of different types. Any of these neutron sources itself cannot be applied directly for the BCNT and therefore require the development of BSAs, necessary for the formation (thermalization, if necessary, and focusing) of neutron field, applicable for a medical treatment. The design of BSAs before manufacturing must be proven by corresponding simulations. Namely, the following was formulated as the main aim of this thesis: to design individual BSAs to be applicable for accelerator-based BCNT in the Armenian National Science Laboratory and for DD and DT neutron generators, as an alternative. Subsequently a brief description of all five chapters' content is provided. I would like to note that Fig. 1 presents results of total and neutron capture cross-section calculations have been done with less known JANIS code, but Talys, may be, and would be a better option for calculations (Fig.1). Then which of results are correct? Also, some experimental data could be shown to make sure calculations have been done correctly.

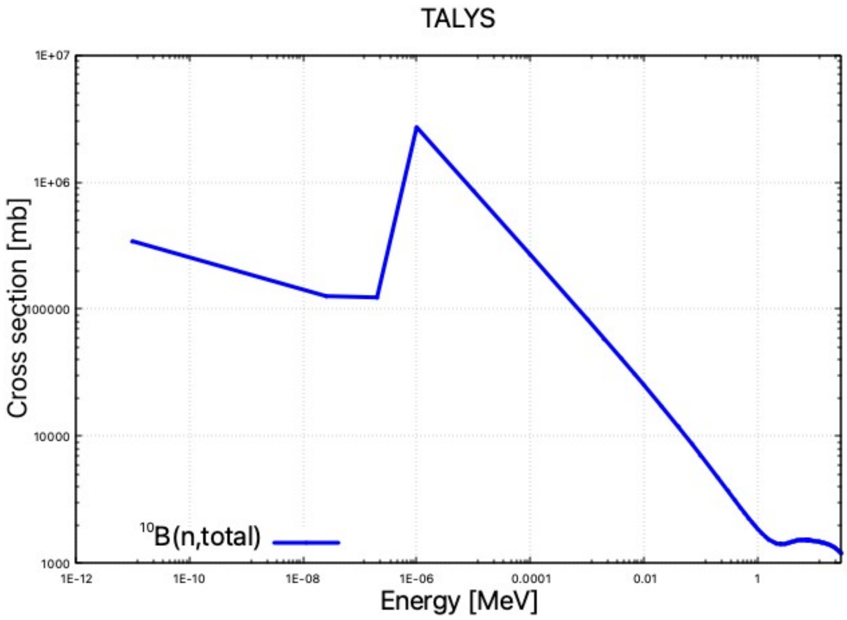

Fig.1

Chapter 1 is the review that discussed some of the neutron applications for non-military purposes. Thus, the basics of the BCNT are presented in details, followed by explanations of the IAEA recommendations for the implementation of this method of the therapy. Then several applications of neutrons in industry and for medical purposes are discussed, stressing the importance of the neutron usage in cancer treatment, in particularly the need for the development of the BNCT. Also, several neutron sources for the BCNT as well as the necessary equipment, which is already in use for BNCT worldwide, were presented. Also the accents were made on the BCNT details, in particularly, with respect to the importance of BSAs development to meet the necessary requirements to conduct the BCNT according to the IAEA recommendations. On page 20 of this chapter a repetition has been observed: it was presented both (n_{th},α) channels on ^{10}B (the same as in Introduction, page 7). Also on page 23 the half-live of ^{241}Am is given as 458 years, which is incorrect. The precise value is 432.6 years.

Chapter 2 details the most valuable applied achievements dealing with BSAs design of research groups in Greece, RF, Finland, Japan and Iran for cases of accelerated-based neutron sources, DD and DT generators from the point of view of the IAEA recommendations. Some features of their designs are presented and discussed. Comparing to some conclusions from Chapter 1 it was noted that for the BCNT implementation the accelerated based facilities for tumor treatment are much more preferable than the nuclear reactor based BCNT therapy. Also, it was stressed that some countries from the above-mentioned are already well-known with clinical or experimental achievements in the development of BNCT. Sources of neutrons and corresponding matching BSAs are discussed as well. Two last subchapters of this Chapter 2 present the algorithm for estimation of an absorbed dose for the BCNT therapy and the commonly accepted Snyder's head phantom model for brain tumor localization.

Chapters 3 and 4 are presenting the materials and methods as well as showing the major results obtained by the author. Chapter 3, being rather informatively weak, first discusses the Monte Carlos codes in general and GEANT 4 simulation package in detail. Then the Author provides justification for selection of neutron source configuration based on the $^{9}Be(p,Xn)$ nuclear reactions and states about the greatest neutron yield for 2.5 mm thickness Be foil. Also DD and DT nuclear reactions based compact neutron generators as BCNT neutron sources are briefly overviewed from the practical point of view but were not modelled.

Chapter 4 is dedicated to designing the so-called "optimal" BSAs for the BCNT. After MC simulations the GEANT4 study resulted in the selection of a BNCT applicable BSA model, including several moderator parts of nat-Mo, 45 cm thick nat-Fe, and 45 cm paraffin boric acid. The tube shape moderator was covered in MCNP model with 20 cm thick nat-Pb as a reflector. The epithermal neutron flux density is found to be about 10^8 n/ ($cm^2 \cdot s$) after such BSA. A higher neutron flux was obtained based on the multiplication property of the thick natural molybdenum placed as first layer for the moderation. At the same time, used/designed BSA was confined only to the thermalization of neutrons using moderately successful combinations and thickness of bismuth, iron or some other materials. The BNCT based on DD compact neutron generator was next for which GEANT4 simulations were performed to investigate its usability as a neutron source for the medical applications. The research and development study resulted in the design of 23 different BSAs with various parameters, taking into account the recommendations of the IAEA. An additional BSA, not intended for use in the clinical investigations a with 2.5 cm radius of the outlet and moderator of 8 cm thick ^{186}W, 45 cm thick mixture of nat-Fe (5%) AlF_3 (95%) and 1.25 cm thick nat-Cd with lead reflector surrounding the moderator, was designed. As a result, the ratio of the achieved epithermal neutron flux over thermal and fast neutrons were about 174 and 24, correspondingly.

The next part of the thesis in this Chapter 4 dealt with the design of the BSA for DT generator. The requirements of the IAEA were taken into account to design 27 BSAs for the DT based BNCT. The recommended more than 20 ratio for epithermal over thermal neutrons was possible to achieve in most of cases, especially with the usage of thick multipliers, such as natBi, nat-W, nat-U and nat-Mo installed separately as a first part of the moderation system. In addition, various simulations were performed with different combinations of more than 10 materials namely Al, Fe, Co, Cd, AlF_3, LiF, MoF, MoF_6,TiF_3,TiF_4 paraffin boric acid as well as $FeAlF_3$ with 5%/95% mixture of iron and AlF_3 (Section 4.3). It is worth noting that the need for the specific 10 keV neutron peak for the deep-seated tumors would be an important step toward the development of a progressive treatment based on BNCT. In Section 4.4, results were discussed based on the simulation of neutrons in wide energy range of neutron interactions with soft tissue, while the edge of the epithermal neutron energy range 10 keV gives the lowest number of gamma production in the soft tissue, as can be seen from the simulations provided. I would like to note, that the Author has chosen a neutron source as a point isotropic one. It is actually not a fully corrected approach when a CNG is considered. The problem is that neutrons, generated from DD and DT reactions have well-understood angle dependence. Then a corresponding simulation must include a neutron source with certain neutron field based on angle distribution of escaping neutrons, and subsequently this extended in space neutron source must be input data for further simulation of neutron field in BSAs.

In conclusion, this feasibility study covers the development of BSAs for the C18/18 proton induced nuclear reactions on ^9Be with neutron escape, DD and DT based neutron sources. The various combinations of materials and geometries for moderators, reflectors and collimators were studied with application of GEANT4 simulation package. As DD and DT options were considered as alternatives, the most attention was dedicated to the latest versions for C18/18 based neutron source with BSA to obtain neutron flux in better agreement with IAEA recommendations for BNCT. The composition of materials includes 20 cm thick nat-Mo, 45 cm thick nat-Fe and 45 cm thick paraffin boric acid were designed as moderator. Very important point is that for the first time it was possible to achieve in total about 10^9 n/($s \cdot cm^2$) neutron flux density containing ~70 % epithermal neutrons and less than 14% percent thermal neutrons. Such configuration looks quite promising for future development of the BNCT projects on the base of C18/18 cyclotron followed by not much delayed in time non-clinical investigations.

As for the DD neutron source based BCNT, the best variant among of all investigated ones allows to select a BSA that includes a moderator, consisting of 8 cm thick ^{186}W, 45 cm thick mixture of 5% Fe and 95 % AlF3, 1.25 cm thick LiF, 0.5 mm Bi and 1 mm thick lead, and the 20 cm thick back and 15 cm thick side Pb reflectors with 15 cm thick lead collimator.

With regard to the DT neutron source based BCNT, a significantly better design of BSA includes 27 cm thick Bi, 53 cm thick $FeAlF_3$, 3 cm thick Al, and 1 cm thick LiF moderator with 25 cm thick back and side lead reflectors and 10 cm thick lead collimator. Finally, achieved epithermal over thermal neutron ratio was more than 100, what is about 5 times greater than a corresponding IAEA recommendation.

The references include about 100 sources, quite recent and well selected. No excessive self-citations occurred.

Formal lay-out

The layout of the thesis is good. In particular, it is logically structured, its content includes all major topics to be thoroughly discussed first, then a clear link was established to go for a deep understanding of what is necessary to be done in order to make a step forward in the development of BSAs for specific neutron sources to meet the IAEA recommendations. The overall impression is good in perception of all the important information.

A minor note is that the English is somewhat difficult to read due to some too long sentences and some typos. However, the scientific contents is clearly understandable.

On several pages, the Author mentioned “optimal design” of BSAs; in particular, the title of section 4 includes the following statement: “Designing of the optimal BSA for BCNT”. The criteria for optimization were established as corresponding ratios of epithermal neutron flux density over thermal one and of epithermal neutron flux density over fast neutron flux density. I think such statements are not well justified. As majority of us were taught, the optimization task must be formulated in the form of the system of linear or differential equations along with the objective function, being, for example, a set of several terms to me maximized. Then, by solving such mathematical task, the optimal solution under the linear programming algorithm can be obtained. The procedure, taken by the Author, is rather a way to select to best of BSAs modeled for specific set of materials and their dimensions by means of the trial and error method. This does not mean the results obtained are wrong, but they may be falling short of being optimal in mathematical sense.

Another point is dealing with some specific issues in medical procedures. Thus, quality assurance in medical treatment is being accompanied with intensive quality assurance programs. For BCNT implementation it would be very important to perform on-line monitoring of the neutron flux. To do so it would be worthwhile to include into BSAs design a cavity with a neutron detector. This won’t cause significant neutron field distortion, but could serve as a very important element of quality assurance program while BCNT treatment.

Very important and clear are the graphical representations of main results, reviewed and obtained in this thesis.

Moreover, it is needed to stress that the data presented are the calculational results obtained with the participation of the Author, and thoroughly analyzed by him to make correct and justified conclusions.

Conclusions

The PhD Thesis by Mr. Vahagn Ivanyan is dedicated to solving a very important practical task dealing with the development of BSAs for three different sources of neutrons based on:

- C18/18 cyclotron with Be target and the (p,Xn) nuclear reactions on ^{9}Be;
- DD compact neutron generator;
- DT compact neutron generator.

For each of these neutron sources many materials and configurations were studied in detail with application of GEANT 4 simulation package. Such approach proves that the two fields – fundamental and applied science – are commonly interlaced to get new knowledge in order to solve a very important task of medical treatment of oncological patients.

The Author summarizes in Conclusion his most important achievement: “First time it was possible to achieve almost 10^9 n/(s·cm^2) flux containing ~70 % epithermal neutrons and less than 14% percent thermal neutrons.”

Some criticism in my review report exclusively serves the goal of further improving this well-executed work in order to enable further achievements in the future, targeted to improve the level of BCNT.

In conclusion, I state that the PhD Thesis and the overall scientific profile of Mr. Vahagn Ivanyan follow the criteria established by Polish “Ustawa o stopniach naukowych i tytule naukowym oraz o stopniach i tytule w zakresie sztuki” (Dz. U. z 2016 r., poz. 882) and the Author deserves to obtain a PhD Degree.

Kyiv, 16 May, 2022.

(Prof. Dr. Ihor Kadenko)