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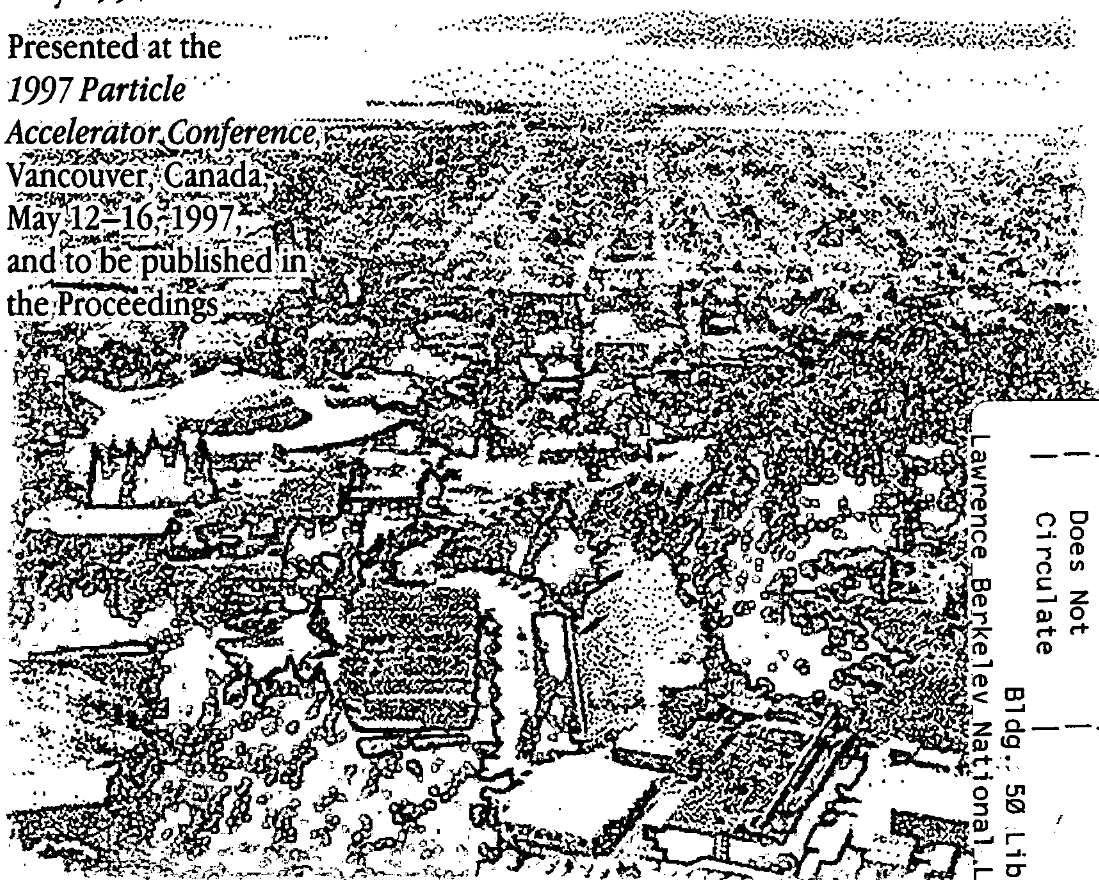

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CLINICAL REQUIREMENTS AND ACCELERATOR CONCEPTS FOR BNCT

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Abstract

Accelerator-based neutron sources are an attractive alternative to nuclear reactors for providing epithermal neutron beams for Boron Neutron Capture Therapy. Based on clinical requirements and neutronics modeling the use of proton and deuteron induced reactions in ^{7}Li and ^{9}Be targets has been compared. Excellent epithermal neutron beams can be produced via the ^{7}Li(p,n)^{7}Be reaction at proton energies of ~2.5 MeV. An electrostatic quadrupole accelerator and a lithium target, which can deliver and handle 2.5 MeV protons at beam currents up to 50 mA, are under development for an accelerator-based BNCT facility at the Lawrence Berkeley National Laboratory.

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1. Introduction

Neutron Capture Therapy (NCT) is a promising approach to cancer therapy for malignancies such as glioblastoma multiforme, a malignant brain tumor, where conventional radiation therapies fail. Boron Neutron Capture Therapy (BNCT) relies on a binary method for delivering a sufficient dose to the tumor cells. A pharmaceutical compound which carries ^{10}B and concentrates selectively in the tumor cells is administered to the patient. ^{10}B has a very large capture cross section (3830 barns) for thermal neutrons and decays into an alpha particle and a lithium nucleus, the combined ranges of which are ~10 μm, approximately one cell diameter. When a patient is irradiated with an epithermal neutron beam, the neutrons thermalized in the tissue may be captured by ^{10}B damaging the cells in which the capture took place. The success of this therapy depends on two factors, the selectivity of the ^{10}B carrying drug and the availability of a neutron beam with a suitable energy spectrum and sufficient intensity.

Epithermal neutron beams can be obtained at nuclear reactors. Clinical BNCT trials are ongoing at the Brookhaven Medical Research Reactor (BMRR) and at the research reactor at the Massachusetts Institute of Technology. However, because of the problems associated with reactor installations at hospitals, the development of accelerator-based neutron sources is pursued. In addition, such neutron sources can provide clinical advantages as discussed in section 3.2. Accelerator-based neutron sources consist of an accelerator, a neutron production target and a moderator and filter assembly for shaping the epithermal neutron beam. There are a number of nuclear reactions which can be exploited. The $^{7}Li(p,n)^{7}Be$ reaction offers the highest neutron yield, but the low melting point of lithium (179°C) is disadvantageous. On the other hand, beryllium targets have excellent mechanical properties, but higher proton beam currents or energies are required to compensate for a lower neutron yield. The evaluation of a particular reaction for BNCT requires the modeling of the primary neutron source and of the neutron transport through the moderator and filter assembly. In addition, the clinical properties of an epithermal neutron beam must be assessed by simulating the radiation transport in a phantom. Such a study, described in sections 2 and 3, led to the approach chosen for an accelerator-based BNCT facility at the Lawrence Berkeley National Laboratory (LBNL). It will be based on an electrostatic quadrupole (ESQ) accelerator capable of delivering up to 50 mA of 2.5 MeV protons onto a ^{7}Li target.

2. Clinical Considerations

Radiotherapy aims at delivering a tumoricidal dose without exceeding the clinical dose limits for surrounding normal tissues and organs. In BNCT the tumor dose is boosted by a high ^{10}B concentration in the tumor cells. However, several background reactions contribute equally to the dose in normal tissue and tumor. Thermal neutrons produce the so-called nitrogen dose (D_N) through the $^{14}N(n,p)^{14}C$ neutron capture reaction and are the main contributor to the gamma dose (D_γ) via the $^{1}H(n,\gamma)^{2}H$ capture reaction. Neutrons with higher energies generate recoil protons and deposit the fast neutron dose (D_f). D_f is sensitive to the energy spectrum of the epithermal neutron beam.

2.1 Dose Computation

The evaluation of the clinical efficacy of epithermal neutron beams for BNCT requires the calculation of the dose distributions in tumor and normal tissues. This task is complicated by the fact that the different kinds of radiation contributing to the total dose are of different relative biological effectiveness (RBE). Furthermore, the biological effectiveness of the physical dose from the neutron capture by the ^{10}B nuclei depends on compound specific properties and a so called compound factor (CF) has been introduced. The use of CF and RBE makes it possible to add the different dose components and express the total photon equivalent dose (D_{tot}) in gray-equivalent (Gy-Eq) units:

$$D_{tot} = CF \cdot D_B + RBE_N \cdot D_N + RBE_f \cdot D_f + RBE_\gamma D_\gamma \qquad (1)$$

For this study the dose calculation protocol [1] developed for the BNCT clinical trial at BMRR was adopted. It established boron concentrations and compound factors for the boron compound boronphenylalanine (BPA). The values listed below were used for all dose calculations: normal tissue ^{10}B concentration: 13 ppm; normal tissue compound factor: 1.3; tumor ^{10}B concentration: 45.5 ppm; tumor compound factor: 3.8; fast neutron RBE (RBE_f): 3.2; nitrogen capture RBE (RBE_N): 3.2; and γ RBE (RBE_γ): 1.0. The special purpose BNCT Radiation Treatment Planning Environment (BNCT_RTPE) software system [2] developed at the Idaho National Engineering and Environmental Laboratory (INEEL) for use at the clinical trials at BMRR was employed to calculate in-phantom dose distributions.

2.2 Clinical Requirements

The discussion in this paper is based on single beam treatments of brain tumors although in practice two or more fields, e.g., parallel opposed ports, are often used. As the most important clinical requirement the dose to the normal brain must be kept within its tolerance in order to prevent radiation injuries. Following the BMRR protocol the maximum normal brain equivalent dose was set to 12.5 Gy-Eq. The maximum entrance surface dose was limited to 10 Gy-Eq in order to limit radiation injury to the scalp. Also, doses to other organs and the whole body must be considered in the actual treatment planning process since they may impose limitations and may require special beam collimation and patient shielding in particular BNCT treatments.

In treatments of glioblastoma multiforme one tries to maximize the tumor dose. Thus, the patient is irradiated until the normal tissue dose limit is reached. However, delivering a tumoricidal dose to the distal end of a deep seated tumor is, at present, not always possible. Treatment protocols specify a minimum tumor dose. For future accelerator-based BNCT facilities it is desirable to limit the treatment time to less than one hour for the following reasons: First, the boron delivery drug gets washed out of the tumor cells over time. For example, the concentration of BPA, the only drug currently approved for U.S. clinical trials, is greatly reduced after several hours. Second, patient comfort can be a limitation and, third, short treatment times are desirable at future hospital-based BNCT facilities for operational reasons.

3. Accelerator-Based Neutron Sources

A variety of accelerator-based neutron sources for BNCT have been proposed and investigated [3]. This paper is restricted to p and d induced reactions in Li and Be targets. Other interesting options such as neutron production near the threshold of the $^{7}Li(p,n)^{7}Be$ reaction [4] or photoneutron sources [5] are not included.

3.1 Neutron production

The reaction $^{7}Li(p,n)^{7}Be$ has a threshold of 1.881 MeV and displays a large resonance in the forward direction around 2.3 MeV which extends to about 2.5 MeV. Neutron double differential distributions were calculated as function of incident proton beam energy using normalized Legendre coefficients [6] for predicting the $^{7}Li(p,n)^{7}Be$ cross section [7].

Neutron yield distributions for proton and deuteron induced reactions in thick beryllium targets were taken from the literature. However, as described below, complete neutron energy and angular distributions at the energies of interest were not available and, consequently, some neutron yield distributions were extrapolated from the available data.

The angular and energy distributions of thick beryllium target neutron yields published by Brede et al. [8] for a proton energy (E_p) of 19.08 MeV were used as the neutron source description for an evaluation of this reaction for BNCT.

Thick target neutron yields for the $^{9}Be(p,n)$ reaction at lower proton energies were recently measured by Howard et al. [9]. The published neutron yield energy spectra for Ep = 4.0 MeV at three angles, 0° 40° and 80° were used. The energy distribution at backward angles was approximated as being identical to the 80° spectrum with an upper energy cutoff at 1 MeV. The resulting total neutron yield of $6.3\cdot10^{11}$ n/mC is about a factor of 2 lower than the total neutron yield given by Hawkesworth [10].

The $^{9}Be(d,n)$ reaction was included in this study since it offers higher neutron yields than the $^{7}Li(p,n)$ reaction at beam energies below 3 MeV. Only limited neutron yield data could be found in the literature. Meadows et al. [11] published thick beryllium target neutron spectra at 0° for incident deuteron energies between 2.6 and 7.0 MeV, and Smith et al. [12] published angular distributions for the $^{9}Be(d,n)^{10}B$ thick target reaction at E_d = 7 MeV. Neutron yield distributions were constructed based on the 0° spectrum at 2.6 MeV and the angular distributions measured at 7 MeV. A total neutron yield of $2.3 \cdot 10^{12}$ n/mC was found compared to a yield of $1.5 \cdot 10^{12}$ n/mC given by Hawkesworth [10].

The neutron yields of the reactions listed above vary by two orders of magnitude. The $^{9}Be(p,n)$ reaction at E_p = 19 MeV produces the highest total neutron yield of $6 \cdot 10^{13}$ n/mC (for neutrons energies E_n > 0.7 MeV) but the energy spectrum extends to E_n ~15 MeV necessitating a thick moderator. At E_p = 4 MeV the upper neutron energy limit is ~2 MeV and the neutron yield is much reduced. The neutron spectrum of the $^{9}Be(d,n)$ reaction at E_d= 2.6 MeV exhibits its highest yield at neutron energies below 2 MeV, but also features a high energy component up to about 6 MeV. The upper neutron energy for the $^{7}Li(p,n)^{7}Be$ reaction at E_p = 2.4 MeV is 700 keV and the total yield is $7.69 \cdot 10^{11}$ n/mC.

3.2 Moderator and Neutron Transport Modeling

Modeling of the neutron beams from the production target, through a filter assembly, and into a phantom is necessary for evaluating different neutron sources for BNCT. This has been carried out in two stages. The first stage simulates the neutron beam from the production source through the moderator and filter assembly using the Monte Carlo program MCNP [13]. The same moderator and filter assembly has been used for all analyzed neutron sources. Only the moderator thickness has been varied to optimize the performance.

A cross section through the three dimensional geometry specified for MCNP is shown in Figure 1. This geometry includes a 5 cm radius flat circular neutron source, which is followed by a cylindrical moderator of variable thickness and material. Surrounding the entire moderator and production target is an Al_2O_3 reflector. In all simulations a mixture of 60% Al and 40% Al/AlF_3 has been used as the moderator material. This material has been shown to perform well at a fission reactor [14] and for the $^{7}Li(p,n)^{7}Be$ reaction [15].

Analyzing the transport of neutrons and photons through a head phantom is necessary to determine the clinical properties of a beam. This has been done in the second modeling stage using the Monte Carlo–based BNCT treatment planning code BNCT_RTPE [2]. The geometry and setup is depicted in figure 1. It includes a lithiated polyethylene beam delimiter and a head phantom. "Tally Surface" indicates the epithermal neutron source used as input to BNCT_RTPE

Figure 2 shows the total thermal neutron fluence for a treatment, which is roughly proportional to the equivalent tumor dose, as a function of depth for the accelerator beams and, for comparison, the BMRR beam.

The $^7Li(p,n)$ source produces the highest thermal neutron fluences. Significantly lower thermal fluences, particularly at more than 3 cm depth, were found for the sources for which the primary neutron energy spectrum extends to higher energies, $^9Be(p,n)$ at 19 MeV, $^9Be(d,n)$, and the fission reactor. This is due to the increased moderator thickness needed for the suppression of the fast neutron dose. At a

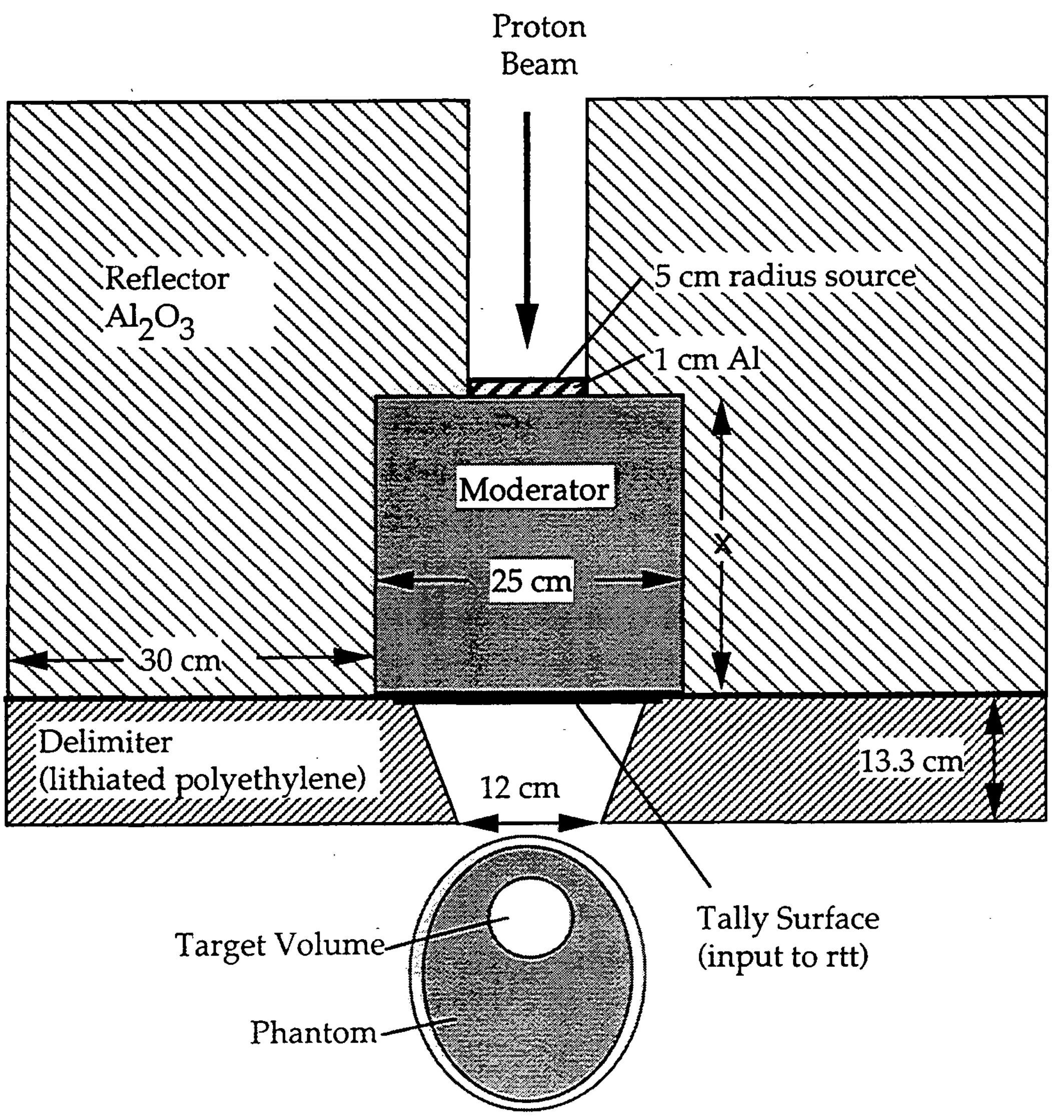

Figure 1: Moderator and filter assembly cross section with head phantom.

proton beam energies of 4 MeV the thermal fluence distribution of the $^9Be(p,n)$ source is closer to that of the $^7Li(p,n)$ source. Table 1 lists for each source the equivalent tumor doses at the point of maximum thermal fluence, at 5 cm depth, and at 8 cm depth. It also gives the beam currents required to match the BMRR treatment time of 40 min. The range given for the neutron sources using a beryllium target reflects the uncertainties in the neutron yield estimates.

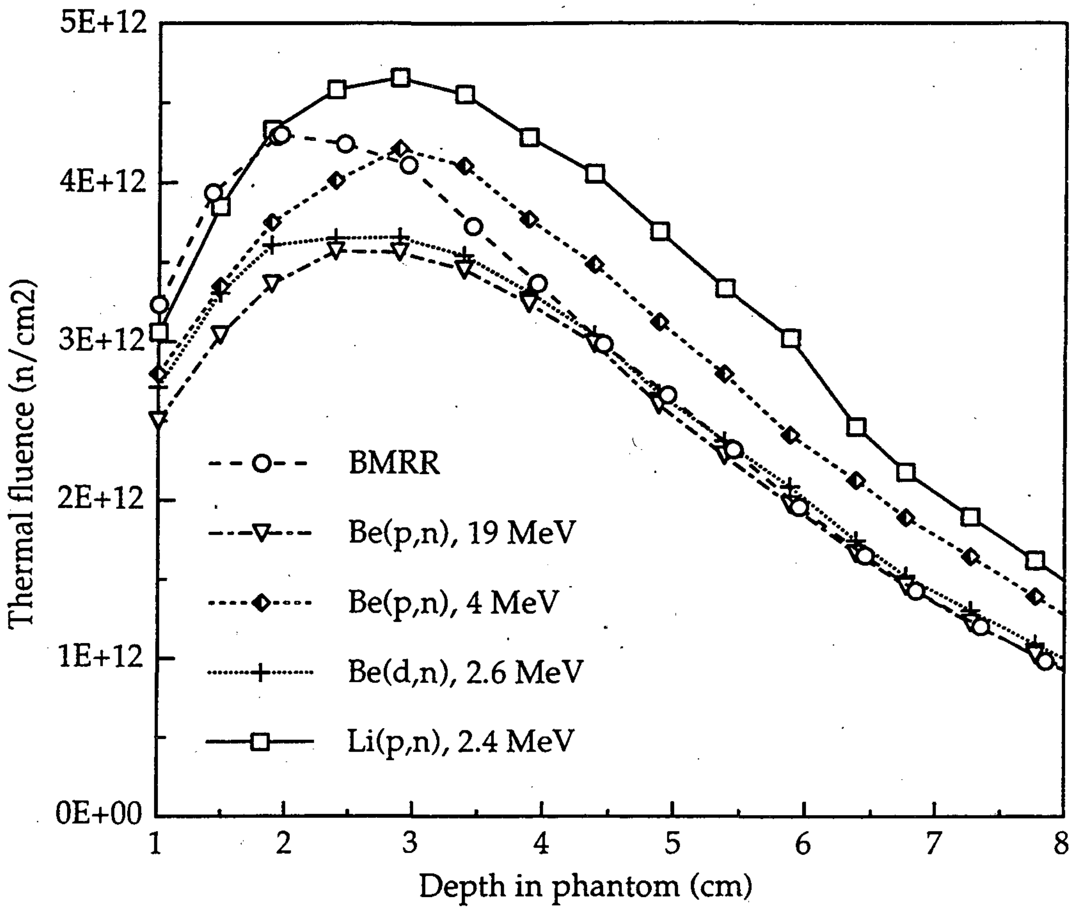

Figure 2: Thermal fluences as function of depth.

3.3 Accelerator options

As can be seen in Table 1 the beam current requirement is dramatically lowered when bombarding a Be-target with 19 MeV protons. Compact cyclotrons are an attractive option for providing beam currents of a few mA at energies between 10 and 20 MeV. Although such neutron sources may be suitable for BNCT, it may be difficult to match the quality of the epithermal neutron beams that can be produced at lower proton beam energies.

Neutron source		^{7}Li(p,n)	^{9}Be(p,n)	^{9}Be(p,n)	^{9}Be(d,n)	BMRR
Beam energy	(MeV)	2.4	4.0	19	2.6	3 MW
Beam current	(mA)	27	40–80	1.5 - 3	50 - 100	-
Moderator thickness	(cm)	34	42	70	70	-
Eq. tumor dose (max.)	(Gy–Eq)	66	61	53	54	62
Eq. tumor dose (5cm)	(Gy–Eq)	51	44	38	39	39
Eq. tumor dose (8cm)	(Gy–Eq)	22	20	16	16	15

Table 1: Comparison of epithermal neutron sources. The treatment time for all sources is 40 min.

The neutronics study points towards an accelerator neutron source utilizing a lithium target and a proton beam of about 2.4 MeV. A number of accelerator technologies have been proposed [3] including radiofrequency quadrupole (RFQ) and other linac structures. While some of these technologies still need significant research and development, others are quite mature. A prototype tandem accelerator [16] designed for a maximum energy of 4.1 MeV and currents up to 4 mA is operated at MIT and used for BNCT related research. At Birmingham, UK, it is planned to utilize a d.c. accelerator expected to deliver beam currents of 5 - 10 mA. However, the neutronic studies summarized in this paper indicate that higher proton beam currents are desirable for optimization of the epithermal neutron beam and increased flexibility in patient treatments. Accelerators with electrostatic quadrupole (ESQ) columns, which have been developed at LBNL for fusion applications [17], are capable of producing high current, megavolt beams and are therefore well suited for BNCT.

4. ESQ–Accelerator Based BNCT Facility

4.1 ESQ Accelerator

For applications that require high average beam currents or variable beam energy, d.c. electrostatic accelerators are most suitable. Accelerators using electrostatic quadrupole (ESQ) columns can be operated with high beam current and high reliability [18]. The electrostatic quadrupole lenses in the acceleration column provide a combination of converging and diverging lenses that produces a net focusing effect on the beam. This gives the key advantage of an ESQ accelerator that the transverse focusing can be very strong without incurring a longitudinal field exceeding the breakdown limit. In addition, the secondary electrons generated within the accelerator column are quickly removed by the strong transverse electric field instead of being allowed to multiply and then develop into a column arc–down.

At LBNL the supporting structure and high pressure vessel of a decommissioned injector are reused for the construction of an ESQ accelerator for a BNCT facility. A new ESQ accelerator column will be installed and the existing power supply (Dynamitron) replaced with an air-core multistage transformer-rectifier stack [19]. Figure 3 shows a schematic diagram. Located at the front end is a multiscup ion source that can deliver positive hydrogen ion beams with monatomic ion fraction higher than 90% [20]. Radio-frequency induction discharge is used to provide clean, reliable and long-life source operation. An extractable hydrogen ion current density of 100 mA/cm^2 has been achieved demonstrating that this ion source can meet the requirement for BNCT. Following the ion source is a 325 keV low energy beam transport section (LEBT) which consists of 6 electrodes. The main acceleration is done by 13 ESQ modules. The bore diameter is 6 cm. 70 alumina rings make up the 3.8 m long column. Cooling of the copper ESQ electrodes will keep the temperature rise below 100°C for a deposition of 100 W on each electrode. Computer simulation using the WARP-3D particle code showed that the column can accelerate a 125 mA beam. Further details can be found in Kwan et al. [21].

Modifications to the existing power supply for test measurements from capacitively coupled to inductively coupled have been completed. The primary to secondary coupling along the length of the acceleration column has been equalized to ±10% by adjusting the primary current density. It will ultimately be reduced to ±1% by adjusting the number of turns in the secondary coil. The low impedance of the inductively coupled system will allow operation at currents exceeding 50 mA.

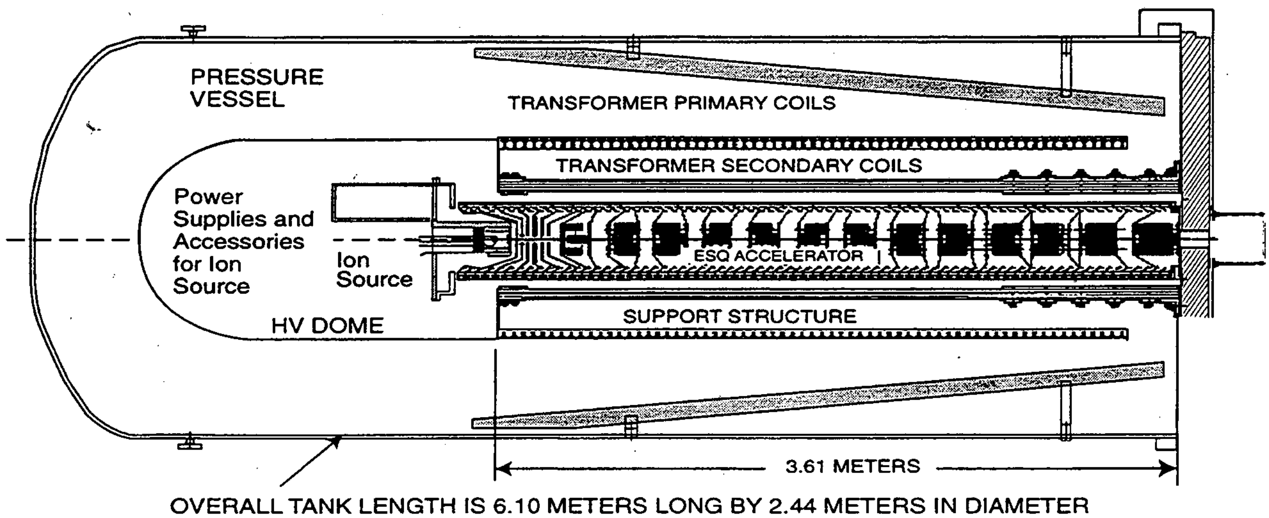

Figure 3: Schematic diagram of the 2.5 MeV ESQ accelerator

4.2. Neutron Production Target

The lithium neutron production target is a crucial component of the accelerator neutron source. Because metallic lithium has a low melting point of 179°C, very effective target cooling is mandatory. In our design a 50 μm thick Li layer is deposited on an aluminum backing. Applying the microchannel absorber concept, many channels are cut into the substrate for convective water cooling. The finite element code ANSI was employed to simulate the heat flow and perform a temperature and stress analysis. The results indicate that for a heat-load of ~600 W/cm^2 the surface temperature can be kept below 150°C. A recent heat-load test of a prototype aluminum panel, performed at the Plasma Materials Test Facility at Sandia National Laboratory, confirmed the simulations. The thermal fatigue reliability of the prototype was demonstrated by subjecting it to 50,000 heat cycles. A V-shaped target with the panels placed at a 30°angle in respect to the beam cuts the surface heat-load in half. Further analyses showed that by optimizing the beam profile and increasing the target area up to 15 cm x 15 cm beam currents of up to 50 mA can be handled.

5. Summary

ESQ accelerators capable of producing high d.c. current, megavolt beams are very well suited to exploit the $^7Li(p,n)^7Be$ reaction as a neutron source for BNCT. A d.c. ESQ accelerator is being designed for proton beams up to 2.5 MeV and beam currents exceeding 50 mA. The d.c. power to the ESQ electrodes is provided by an air-core transformer stack surrounding the accelerator column. A Li-target is being developed for proton beam currents up to 50 mA. The design of the moderator and filter assembly is driven by clinical requirements and geared towards high quality epithermal neutron beams while maintaining a short treatment time. Our work indicates that an accelerator-based neutron source for BNCT is practical and superior to reactor neutron sources.

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