Design and Performance Of A Thermal Neutron Beam for Boron Neutron Capture Therapy At The University Of Missouri Research Reactor

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ABSTRACT

The University of Missouri Research Reactor has designed and constructed a thermal neutron beam line for use in small animal boron neutron capture therapy (BNCT) experiments. Details of the facility have been previously reported by Brockman et al.[1] and Pozzi et al.[2]. The facility utilizes a 15.24 cm diameter beam tube that extends from the beryllium reflector to the biological shield, a distance of approximately 3.95 m. This design incorporates a neutron filter approach that is similar to that previously reported by Kim et al. but without cryogenic cooling [3]. The design combines single crystal silicon and single crystal bismuth at room temperature to remove fast neutrons and reactor gamma rays. The silicon crystal provides the bulk of the neutron spectral filtering while the bismuth crystal effectively reduces the reactor gamma ray component. A parameter study was undertaken to find the optimum combination of silicon and bismuth that maximizes thermal neutron flux while maintaining fast neutron and gamma ray components within an acceptable range. Both DORT and MCNP5 computations indicated that the optimal silicon filter is 50-55 cm in length and the optimal bismuth filter is 8 cm in length. The neutron spectrum of the facility has been experimentally characterized three times since 2009 using flux foils and an unfolding method developed by Idaho National Laboratory. The most recent measurements were made in 2012 and indicate that silicon and bismuth filter performance has not degraded. Before the beam enters the irradiation chamber it is collimated to 12.7 cm in diameter using enriched 6Li polyethylene. The thermal neutron flux profile of the beam varies by less than 10% over the active 12.7 cm diameter. A gantry system was built to allow simultaneous irradiation of 1-4 mice at a time. Each irradiation position incorporates a shield constructed of 6Li2CO3 that minimizes the neutron dose to healthy tissue.

1. Introduction

Boron Neutron Capture therapy is a binary cancer treatment that uses a neutron source and a tumor targeted drug that contains 10B. Following administration of the BNCT drug and its distribution to tumor cells the treatment is turned on by introducing thermal neutrons into the tumor volume inducing production of alpha and lithium ions with a total energy of 2.35 MeV. These charged particles deliver high LET radiation in the surrounding 5-9 µm. If one of the charged particles passes through a malignant cell nucleus there is a high probability of cell inactivation by direct DNA damage.

BNCT requires a drug that selectively delivers therapeutic levels of boron to a tumor cell. The drug should be non-toxic, persist in the tumor volume during BNCT therapy while clearing from healthy tissue, have a tumor to health tissue ratio of at least 3:1 and provide a minimum of 20
μg/g of boron in the tumor volume. A recent summary of the current status of BNCT published by Barth et al. reports that the only approved drugs for boron neutron capture therapy continue to be sodium mercaptoundecahydro-closo-dodecaborate (Na$_2$B$_{12}$H$_{11}$SH) also known as BSH and (L)-4-dihydroxy-borylphenylalanine also known as BPA[4]. While recent clinical studies using a combination of BPA and BSH in addition to traditional photon therapies show modest improvements in treatment of glioblastoma cancer patients it is clear that the next improvements in BNCT efficacy will come from development of new boron delivery agents for clinical use.

To facilitate new drug development the University of Missouri Research Reactor (MURR) has begun a collaboration with Idaho National Laboratory (INL) and the International Institute for Nano and Molecular Medicine (IINMM). This collaboration has resulted in a new thermal neutron source for small animal boron neutron capture therapy experiments. These experiments are critical for evaluating promising new BNCT drugs in animal models and ultimately providing data to justify human trials.

2. Facility

The MURR is a light water cooled and moderated reactor that operates at 10 MW. The MURR features a compact, annular core constructed of eight fully enriched fuel elements. The active height of the core is 60.96 cm and the outer radius of the core is 14.9 cm. The core is surrounded by a beryllium reflector and a graphite reflector with 6 radial beamports extending from the beryllium reflector and a thermal column.

The new thermal neutron beam line at MURR has been previously described [5]. The beam line is located in a 15.24 cm diameter beam tube that extends from the beryllium reflector to the biological shield, a distance of 3.95 m. Key features of the design include the use of 50 cm of single crystal silicon and 8 cm of single crystal bismuth and is similar to the BNCT facility at HANARO although without cryogenic cooling [3]. The silicon crystal provides the bulk of the spectral filtering while the bismuth also provides minor spectral filtering along with its primary function of reducing incident gamma radiation with minimal loss of thermal neutrons. The beam passes outside of the biological shield and threw a series of rotating shutters before entering the irradiation chamber. The shutters are used to turn the beam off during normal MURR operation at 10 MW. The bismuth crystal is rotated out of the beam during the off configuration to minimize production of $^{210}$Po. The 15.24 cm diameter beam enters the irradiation chamber and is collimated to 12.7 cm in diameter using a collimator constructed of polyethylene with enriched $^6$Li. The irradiation chamber volume is 2 m$^3$ and can be configured to treat small animals such as mice up to large dogs. When the beam is turned off a hydraulic lift table on the floor of the irradiation chamber lifts an additional concrete beam stop allows remote placement of samples, minimizing dose to researchers and animals. When the beam is turned on the hydraulic lift lowers the samples into a reproducible, indexed irradiation position and the shutters are opened. There are two fission chambers located near the shutters that provide real-time neutron flux measurements during sample irradiation.
Figure 1. Thermal neutron beam design located at MURR on beamport E. The closed configuration, with access to samples is illustrated.

3. Computational

An initial parameter study undertaken with MCNP5 and a DORT model were used to calculate the optimal length of the silicon crystal and bismuth crystal. The design goals were a thermal neutron flux near $1 \times 10^9$ n/cm$^2$/s, a Au-Cd ratio greater than 100, and a minimal gamma dose. The MCNP model used ENDF/B Version 6.8 cross section libraries with the exception of the single crystal silicon and single crystal bismuth. Cross sections for single crystal Si and Bi were provided by Lee and prepared by the Korean Atomic Energy Institute [6] according to methods described by Freund[7]. The DORT [8] model used the BUGLE-80 47 group neutron and 20 group gamma cross section libraries. Correction factors for the cross sections of amorphous Bi and Si in group 46 and 47 in the BUGLE-80 library were adjusted to approximately account for the single crystal form of Si and Bi. Details of the DORT model has been described previously [8]. The initial studies indicated that the optimal length of Si crystal was 50-55 cm and the optimal length of Bi crystal was 8 cm. An improved computational model was developed in 2009 with an updated 59 group cross section library for all materials to provide higher energy resolution in the thermal region. The upgraded model has been described by Slattery et al [9] and was necessary to improve animal dosimetry calculations. The DORT model with upgraded cross sections was used to produce a 59 group surface source card for MCNP calculations. The new source is located just upstream of the silicon crystal. The MCNP model with the Si and Bi crystal libraries from KAERI were used to calculate the neutron spectrum as the irradiation position. The model was used to create an MCNP surface source file inside the irradiation chamber, upstream of the foil irradiation position. This source file was used to calculate volume averaged cross sections for flux foils used to experimentally characterize the neutron spectrum.
Figure 2. MCNP model of beamport E with 59 group DORT providing the surface source

4. Experimental and Discussion

The neutron spectrum of the facility was measured in 2008, 2009 and 2012. The measurements were based on activation of cadmium covered copper, manganese, tungsten, gold and iridium foils (12.7 mm diameter) and bare gold and manganese foils. The thickness of the foils ranged from 0.0254 mm to 0.127 mm depending on the materials type. The fast flux was characterized using a 4 g indium foil irradiated inside a hollow sphere of $^{10}$B which allowed measurement of the $^{115}$In(n,n')$^{115m}$In inelastic reaction with a threshold of 336 keV. The neutron reactions are shown in Table 1.

Table 1. List of activation monitors used to characterize the neutron spectrum

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Response</th>
<th>$\gamma$ (keV)</th>
<th>Over determined group structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{197}$Au (n, $\gamma$) Bare Foil</td>
<td>Thermal</td>
<td>411</td>
<td>1</td>
</tr>
<tr>
<td>$^{55}$Mn (n, $\gamma$) Bare Foil</td>
<td>Thermal</td>
<td>847</td>
<td>1</td>
</tr>
<tr>
<td>$^{115}$In (n, $\gamma$) Cd Cover</td>
<td>1 eV Resonance</td>
<td>1293</td>
<td>2</td>
</tr>
<tr>
<td>$^{197}$Au (n, $\gamma$) Cd Cover</td>
<td>5 eV Resonance</td>
<td>411</td>
<td>3</td>
</tr>
<tr>
<td>$^{186}$W (n, $\gamma$) Cd Cover</td>
<td>18 eV Resonance</td>
<td>686</td>
<td>4</td>
</tr>
<tr>
<td>$^{55}$Mn (n, $\gamma$) Cd Cover</td>
<td>340 eV Resonance</td>
<td>847</td>
<td>5</td>
</tr>
<tr>
<td>$^{63}$Cu (n, $\gamma$) Cd Cover</td>
<td>1 keV Resonance</td>
<td>511 (Positron)</td>
<td>5</td>
</tr>
<tr>
<td>$^{115}$In (n,n') Boron Sphere</td>
<td>300 keV Threshold</td>
<td>336</td>
<td>6</td>
</tr>
</tbody>
</table>
In 2008 and 2009 the foils were irradiated in a Teflon holder provided by INL but without the animal gantry which was not in use until 2011. In 2012 the activation foil experiment was repeated with the animal gantry system installed to determine if the neutron spectrum had degraded since it was measured in 2008 and 2009. Figure 3 shows the placement of the Teflon holder that contains the activation foils. In this experiment we also included animal gantry. The gantry contains four mouse phantoms constructed of PMMA. The outer white tubes are packed with $^6\text{Li}_2\text{CO}_2$ and reduce the thermal neutron flux to healthy tissue during an animal irradiation.

![flux foils](image)

**Figure 3.** Experimental setup for the activation foil measurements in 2012. Shown on Left is the Teflon holder with four animal phantoms in the gantry. Shown on the right is the view into the irradiation chamber with the samples in the index position in the beam closed configuration (shown in Figure 1).

The measured saturated activities of the activation foils were used to estimate a 6-group spectrum using an a calculated neutron spectrum (a-priori) and an over determined, least squares unfolding method developed by INL [10]. The volume averaged cross sections of the foils was computed with MCNP for the unfolding calculations [9]. The six group flux spectrum measured in for 2012 in Figure 4 with the calculated (a-priori) spectrum along with the results measured in 2008 and 2009 which were re-computed with the new 59 group cross sections.
**Figure 4.** On the left is shown the unfolded 6 group spectrum measured in 2012. The blue trace is the a-priori neutron spectrum calculated with MCNP. On the Right is the 6-group spectrum measured in 2008, 2009 and 2012.

The results in 2012 compare well with the measurements taken in 2008 and 2009 and demonstrate that the neutron spectrum of the beam has not changed significantly since the beam was built in 2008. The thermal neutron flux measured in 2012 with the new 59 group energy structure was $7.65 \times 10^8$ n/cm²/s with a fractional standard deviation of 8.6%. This compares well with the 2008 measured thermal neutron flux of $8.18 \times 10^8$ n/cm²/s with fractional standard deviation of 6.0% and the 2009 measured thermal neutron flux of $8.85 \times 10^8$ n/cm²/s with fractional standard deviation of 8.3%. The measured results for all 6 adjusted energy groups are plotted in figure 4 and show that the neutron spectrum has not significantly changed since 2008.

The radial neutron flux distribution of the beam was measured using flux wires (1.55 wt% Au and 98.45 wt% Cu). The flux wires were distributed radially at 1.27 cm intervals as shown in Figure 5. The average saturation corrected gold specific activity was $9.73 \times 10^{-14}$ dps/n and the fractional standard deviation was 4.2% with no observable trends from top to bottom or left to right. This result demonstrates that the radial neutron flux is homogenous when it enters the irradiation chamber. The copper and gold flux wires also provide the opportunity to crudely monitor spectral hardening. The reaction $^{197}$Au(n,y)$^{198}$Au has a thermal and epithermal activation
component while the $^{63}\text{Cu}(n,\gamma)^{64}\text{Cu}$ reaction is dominated by thermal activation. In a purely thermal spectrum the theoretical ratio of the Au/Cu saturation corrected specific activity is 22. A ratio higher than 22 is an indicator that the neutron spectrum is hardening. The ratio of the Au/Cu ratio in this experiment was 22.1 with a relative standard deviation of 1.7%. These results show that the neutron spectrum is homogenous across the radial beam profile as it enters the irradiation chamber and that the entire 126.7 cm$^2$ area of the beam may be used for sample or animal irradiation.

A series of measurements were undertaken to determine the neutron flux distribution on poly methyl methacrylate mouse phantoms in the neutron beam. The experiment setup is shown in figure 6.

In this experiment the thermal neutron flux peaks in the center of the phantom approximately 1 cm from the edge of the phantom. The peak thermal neutron flux in this experiment, measured at the center of the phantom was approximately 50% larger than the neutron flux measured in the center of the beam. This effect is likely due to scatter of thermal neutrons by hydrogen in the mouse phantom back into the wire volume. The measured wire activity measured inside the $^6\text{Li}$ enriched lithium carbonate shielding (position -3.0 cm in Figure 6) is less than 20% of the center flux wire activity and indicates that the shielded healthy tissue is receiving a lower neutron dose.

5. Conclusions

A series of spectral measurements have been completed for the thermal neutron beam for small animal neutron capture therapy at the University of Missouri Research Reactor. The measurements demonstrate that the neutron spectrum has not changed significantly since 2008. The measurement of the radial flux profile indicates that the thermal neutron flux is homogenous over the entire 126.7 cm$^2$ surface area of the beam. A measurement of the neutron flux profile in a mouse phantom showed that the thermal neutron flux at the surface of the phantom is enhanced by up to 50%. The profile also showed that enriched $^6\text{Li}$ lithium carbonate shielding can
decrease the thermal neutron flux in healthy tissue by 80%. Future work includes developing animal dosimetry models for evaluating radiation dose from boron neutron capture therapy.

6. References


