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IMPROVED COMPUTATIONAL CHARACTERIZATION OF THE THERMAL NEUTRON SOURCE FOR NEUTRON CAPTURE THERAPY RESEARCH AT THE UNIVERSITY OF MISSOURI

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ABSTRACT

Parameter studies, design calculations and initial neutronic performance measurements have been completed for a new thermal neutron beamline to be used for neutron capture therapy cell and small-animal radiobiology studies at the University of Missouri Research Reactor. The beamline features the use of single-crystal silicon and bismuth sections for neutron filtering and for reduction of incident gamma radiation. The computational models used for the final beam design and performance evaluation are based on coupled discrete-ordinates and Monte Carlo techniques that permit detailed modeling of the neutron transmission properties of the filtering crystals with very few approximations. This is essential for detailed dosimetric studies required for the anticipated research program.

Key Words: BNCT, Cancer, Neutrons

1. INTRODUCTION

Neutron Capture Therapy (NCT) is an experimental binary cancer treatment modality that utilizes a neutron source coupled with a suitable nuclide to induce radiation damage in a tumor. In current practice the neutron capture nuclide is ^{10}B and therefore the therapy is referred to as BNCT. The ^{10}B is incorporated in a targeting agent molecular structure that provides in-vivo chemical stability and targets specific cell or tumor types. Following administration of the boron delivery agent and its subsequent uptake into the malignant tissue the treatment volume is exposed to a field of thermal neutrons. The neutrons interact with ^{10}B, producing an alpha particle and lithium ion. These highly-energetic (~2.35 MeV total energy) charged particles deposit their energy within a volume that is comparable to the size of the malignant cell, leading to a high probability of cell inactivation by direct DNA damage. In one sense, NCT can also be regarded as a high linear energy transfer (LET) targeted radionuclide therapy where the radionuclide can be switched on and off. BNCT treatment thus offers the possibility of highly selective destruction of malignant tissue while sparing healthy neighboring tissue.

Some limited initial human trials of BNCT treatment of brain tumors were conducted in the U.S. in the 1950s and early 1960s, and various investigations have continued in Japan since then. In September 1994 two sets of “Third Generation” human BNCT clinical trials for glioblastoma multiforme (a highly-malignant primary brain tumor) and for melanoma of the extremities were undertaken in the U.S. These Phase I studies were independently conducted at the Massachusetts Institute of Technology (MIT) and at Brookhaven National Laboratory (BNL) in New York. Results of the recent U.S. BNCT trials and similar trials currently ongoing at research centers in Europe, Japan, and Argentina show positive trends but much work remains. Observations based on the limited available data indicate that treatment efficacy for the tumors studied under the current protocols appears to be comparable to that of current standard treatments. In addition, key patient safety issues have been more effectively addressed in the modern protocols. As is often the case with new cancer therapies, the clinical results obtained so far with BNCT are thus not dramatic, but there is clearly significant promise to the concept.

The more recent (post-1994) BNCT trials differ from the earlier trials largely because of the availability of significantly improved research reactor based neutron sources and the implementation of much more accurate computational and experimental dosimetry, including the required analytical chemistry. In contrast, there have been essentially no improvements in the boron containing targeting agents approved for human applications in the last 30 years. The available approved BNCT compounds, while offering some attractive features, are still not optimal for the treatment of tumors of interest [1].

It has thus become apparent that the next quantum leap in clinical BNCT efficacy must come from improved alternatives to the current approved boron targeting agents. And it has also been demonstrated that improved BNCT agents are essential to take full advantage of recent improvements in neutron source technology [2]. Furthermore, it will be useful to study applications to a broader spectrum of tumor types, even with current agents [3,4]. Several highly-promising new boron agents that may offer improved biochemical properties *and* that are potentially capable of treating a wider variety of tumor types are in fact available [1], but for various reasons they have not been systematically evaluated in small- and large-animal models to a sufficient degree to permit human trials, and some have not been evaluated at all.

In this context, and under the leadership of the University of Missouri (MU) Institute for Nano and Molecular Medicine, the Idaho National Engineering Laboratory (INL), the Radiation Pathology Division of the National Atomic Energy Commission of Argentina (CNEA), and the University of Missouri Research Reactor (MURR) are collaborating in a new research initiative to further the development of improved BNCT agents and treatment protocols, with an emphasis on applicability to a broader array of tumor types. Key initial agents and delivery mechanisms to be investigated over the course of this multiyear planned effort include boron-containing unilamellar liposomes (ULL) delivering amphiphilic alkyl-substituted nidocarborane anion salt (MAC) as well as the sodium salt of a hydrophilic $[B_{20}H_{17}NH_3]^{3-}$ ion (TAC). The first step of this effort has involved the design and construction of new thermal neutron beam irradiation facilities for cell and small-animal radiobiological research at the CNEA RA3 facility in Buenos Aires [5] and at MURR. Some early results from the MURR thermal neutron beam design and performance characterization effort have been reported [6,7]. In this paper we present the results of detailed new performance calculations based on a much-improved computational model, and a comparison of these computational results with the earlier measurements of the beam spectrum.

2. FACILITY DESCRIPTION

The MURR reactor (Figure 1) features a compact light-water cooled and moderated fully-enriched annular core composed of eight plate-fuel elements with a maximum licensed power level of 10 MW. The outer radius of the core is approximately 14.9 cm, with an active height of 60.96 cm. The core is surrounded by a beryllium reflector, followed by a graphite reflector. Details of the new beamline design are shown in Figure 2. It is located in an existing 15.24 cm (6') diameter MURR beam tube, referred to as Beamline E, which extends from the outer surface of the beryllium reflector, through the graphite reflector, and out through the biological shield wall as shown in the figures. Key features of the new beamline include the use of a single-crystal silicon neutron filtering section followed by a single-crystal bismuth section in a manner similar to the HANARO facility design [8], but without cryogenic cooling of the crystals. The irradiation location is just downstream of the bismuth filter section, at a distance of approximately 3.95 meters from the central axis of the reactor. A shielding enclosure surrounds the exit port of the beamline as shown. A hydraulic lift inside this shield enclosure enables the remote placement of samples or animals being irradiated.

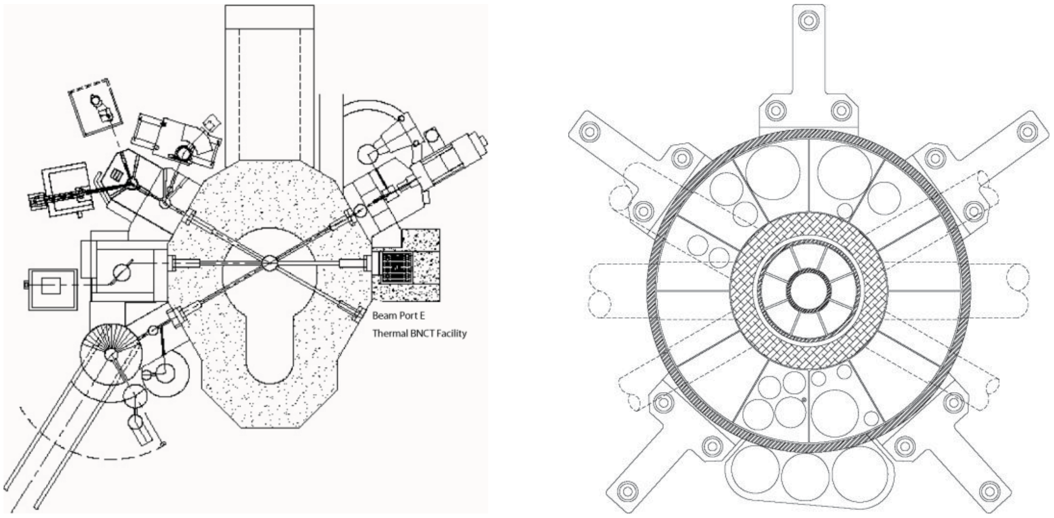

Figure 1. Top view of MURR reactor, shielding, and beamlines (L), and core detail (R) showing fuel annulus, beryllium reflector, and graphite reflector. Beamline E extends from the core horizontally to the right in this view.

The single-crystal silicon section in the beamline provides the bulk of the spectral filtering, while the bismuth section provides some final neutron filtering along with its key function of reducing the incident gamma component in the beam with minimal loss of thermal neutron flux. When the beam is not in use, the bismuth filter section rotates out of the beamline and is replaced by a Pb, steel, boral and polyethylene laminated shutter.

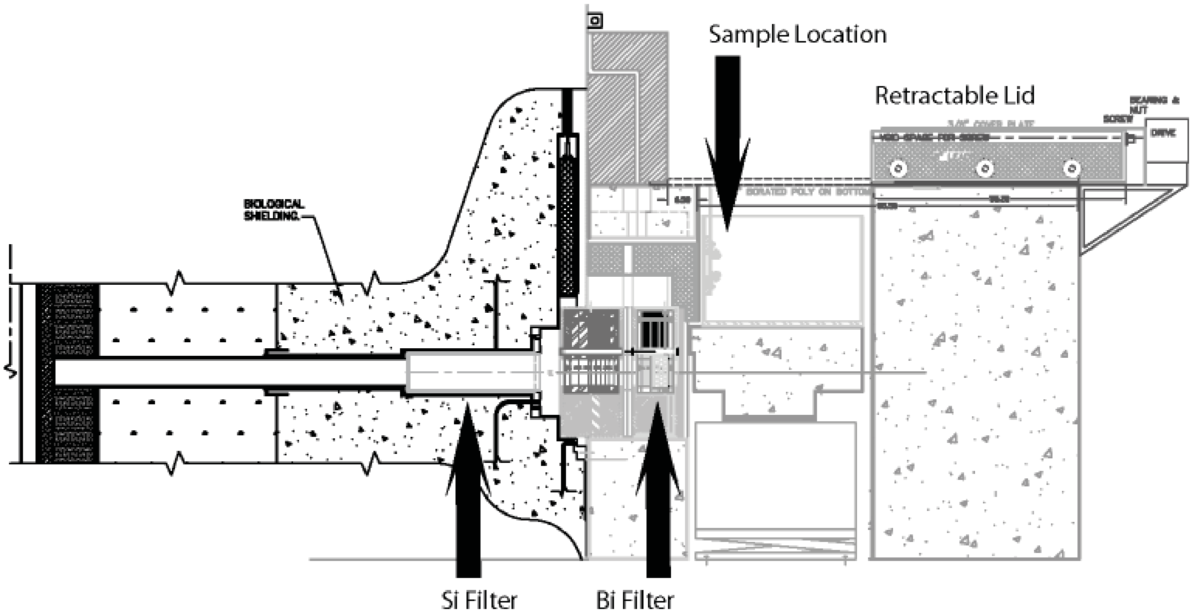

Figure 2. MURR thermal beamline design detail, shown in a closed configuration to allow access to samples.

3. COMPUTATIONAL METHODS AND MODELS

An initial scoping model of the coupled reactor core and beamline was developed using the DORT [9] two-dimensional radiation transport code, with a highly forward-biased angular quadrature set consisting of 315 angular directions. The BUGLE-80 47-neutron, 20-gamma group cross section library [10] was employed for the early DORT computations used for the beam design, in keeping with previous practice for analysis of a number of other NCT neutron facilities worldwide. Modeling of the MURR with the two-dimensional cylindrical geometry option in DORT required a vertically-oriented model for the core, coupled at the outer boundary of the bismuth reflector to a separate, horizontal, model for the beamline. In the case of the DORT model, the thermal (Groups 46 and 47) scattering cross sections for amorphous bismuth and silicon in the BUGLE-80 library were empirically adjusted [6] to approximately account for the single-crystal form of these materials.

A number of parameter studies were conducted with this early DORT model, varying the thicknesses of the silicon and bismuth filter sections to find an optimum that maximized the thermal neutron flux while maintaining the fast-neutron and gamma components of the beam within acceptable ranges. These computations led to the conclusion that the silicon filtering section should be approximately 50-55 cm in thickness along the beamline, while the bismuth section should be 8 cm in thickness.

Neutron spectra at the irradiation location, computed using the preliminary DORT/BUGLE discrete-ordinates model, are shown in Figure 3 for the unfiltered beamline, for the beamline with 50 cm of silicon only, and for the fully-filtered Si(50cm)/Bi(8cm) beamline. Modification of the spectrum to reduce the above-thermal component relative to the thermal component from one case to the next is apparent. The total calculated thermal neutron flux (0 – 0.414 eV) delivered to the irradiation location by the fully-filtered beam (Si/Bi) was approximately 9.6×10^8 neutrons/cm^2-s with an estimated uncertainty of approximately 10% based on previous experience at the INL with this type of computation for other BNCT neutron beams worldwide.

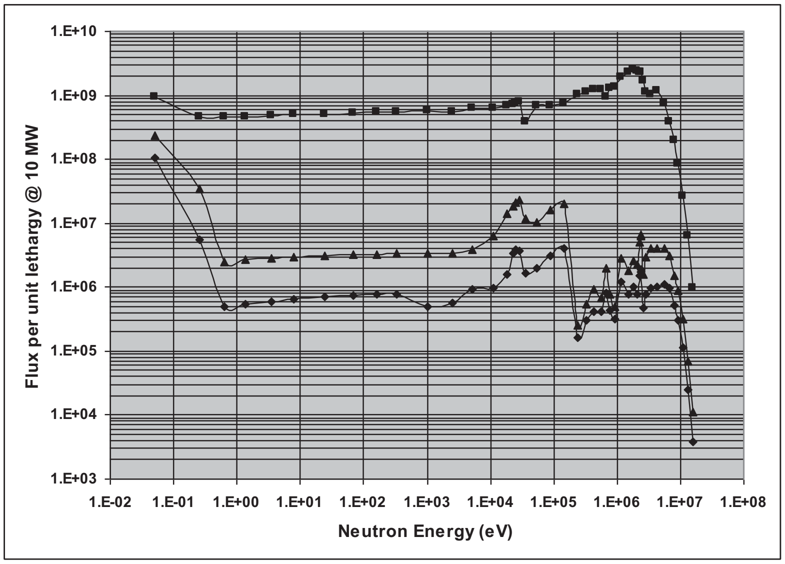

Figure 3. Computed unfiltered (■), silicon-filtered (▲), and Si+Bi filtered (♦) neutron spectra at the irradiation location for the baseline MURR thermal beamline design. Computations were performed with the DORT discrete-ordinates code with adjusted single-crystal silicon and bismuth cross sections.

The model described above proved sufficient for the initial beamline design and performance calculations, and the results were consistent with initial performance measurements [6,7]. However, it was clear that a significantly improved model would be needed for final performance computations and for detailed dosimetry support during the planned research program. In particular, a much higher energy resolution was required in the thermal energy range in order to permit an accurate a-priori calculation of thermal neutron transmission through the silicon and bismuth filters and to correctly define the neutron source term at the irradiation location. Some minor adjustment of the higher-energy group boundaries from the BUGLE structure was also done to obtain better fidelity in the resonance region for silicon.

Figures 4 and 5 illustrate the improved computational strategy, which is based on the use of coupled discrete-ordinates (DORT) and MCNP [11] Monte Carlo techniques. A 59-group neutron cross section library for all materials of interest in and around the beamline was generated using the COMBINE [12] neutron spectrum and cross section generation program, updated to process ENDF/B Version 7 basic data. The energy structure for this library included 17 thermal groups below 0.414 eV. The DORT calculations were run with this library assuming amorphous silicon and bismuth in the filtering regions.

The 59-group angular flux entering the upstream end of the silicon filter section was then used to construct a surface source for an MCNP calculation of the beamline starting from that source plane and continuing downstream to the irradiation point as shown in Figure 4. ENDF/B Version 6.8 cross section libraries were used with MCNP, except for two specialized cross section sets for the single-crystal bismuth and silicon filters in the MCNP calculations that were provided to MU and INL for this study by the Korean Atomic Energy Research Institute [13]. These cross section sets were prepared [8] according to models described by Freund [14]. A flow chart for the new computational process is shown in Figure 5.

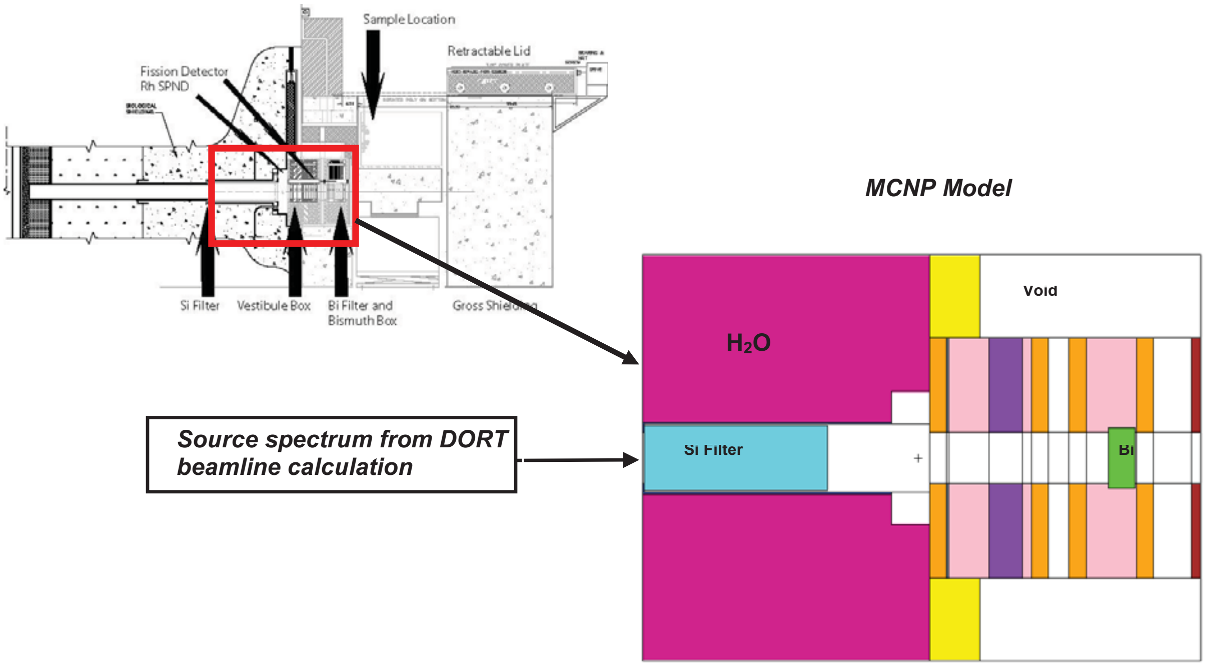

Figure 4. Coupled DORT/MCNP model of the MURR thermal-neutron beamline.

4. RESULTS

Basic beam neutronic performance measurements for an initial configuration of the beamline with 50 cm of single-crystal silicon and 8 cm of single-crystal bismuth were focused on quantifying the thermal neutron flux intensity and the approximate spectral quality of the resulting beam. The measurements were based on activation techniques using foils of various types. These included standard 12.7-mm (0.5”) diameter copper, manganese, tungsten, gold, and indium foils with cadmium covers to suppress the thermal-neutron response, as well as bare gold and manganese foils. Nominal thicknesses of these foils were in the range of 0.0254 mm (0.001”) to 0.127 mm (0.005”), depending on the material type.

A heavy (~4 g) indium foil, placed within a hollow sphere composed of ^{10}B was also used to provide additional spectral information in the neutron energy range above epithermal (> 10 keV). In addition to the prominent gamma lines from ^{116}In that result from neutron capture in ^{115}In there is also a relatively

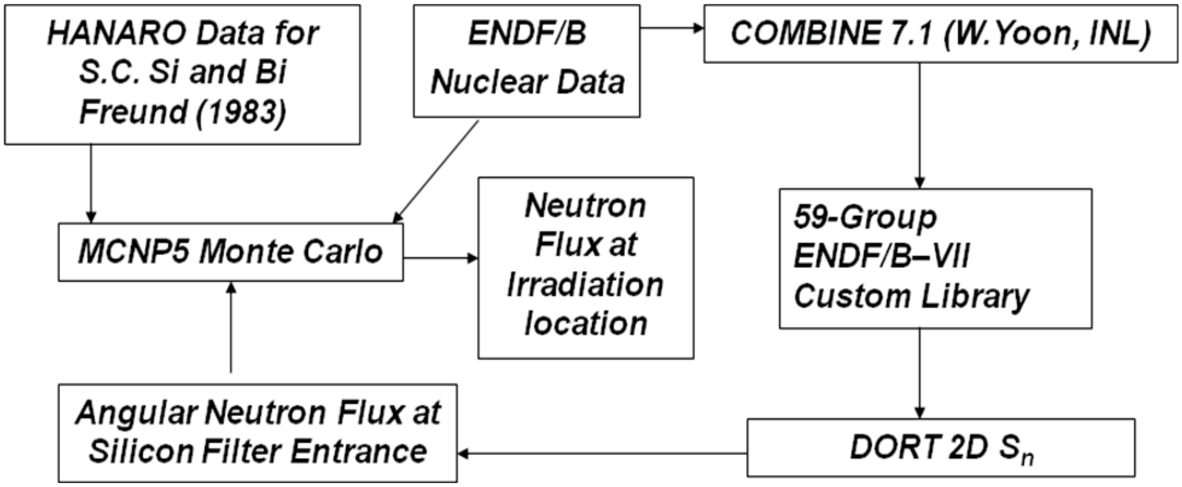

Figure 5. Data flow for the improved MURR neutron beamline computational modeling protocol.

weak 336 keV gamma line from an isomer of ^{115}In that is formed by inelastic scatter. This interaction can be used to gauge the neutron flux above its threshold (~400 keV). The ^{10}B cover (approximately 10 mm in thickness) suppresses essentially all resonance and thermal neutron capture interactions in the indium, making the desired 336 keV peak much more prominent in the gamma spectrum of the activated foil (and incidentally rendering the foil much easier to handle safely after activation).

Use of the foils as described provided 8 basic neutron response functions having a useful degree of linear independence. These response functions were: 1) resonance capture in the five cadmium covered foils with thermal neutron capture suppressed, 2) total neutron capture in the uncovered gold and manganese foils and, 3) inelastic scatter in the boron covered indium foil. The foils were placed at the irradiation location as shown in Figure 6, centered in a 127 mm diameter circular aperture cut into a plate composed of enriched lithium polyethylene that slides into position from above.

The measured saturation activities of the foils were used to estimate a 6-group neutron spectrum by way of a direct overdetermined least-squares unfolding procedure adapted by the INL for this type of application [15]. Effective self-shielded cross sections for the various foils were computed with MCNP for use in the unfolding calculations. The results are shown in Figure 7, along with the calculated neutron spectrum using the new model. The reduced χ^2 parameter for the direct fit is 0.3, indicating possible over-conservatism in the specification of the uncertainties in the measured foil saturation activities. As can be seen the new computational protocol produces more detail in the thermal energy range and somewhat different results in the silicon resolved resonance range compared to the bottom curve of Figure 3. The latter difference is largely attributable to the improved group structure and self-shielding treatment for silicon in the new cross section library generated by COMBINE.

The calculated thermal neutron flux (integrated below 0.414 eV) from the improved model was 9.20 x 10^8 n/cm^2-s, with an estimated uncertainty of about 4% based on the Monte Carlo statistics. As noted, the earlier calculations had given a somewhat higher value (9.62 x 10^8 n/cm^2-s). More importantly, the new model provides the required degree of spectral detail in the thermal range, as shown in Figure 7. The measured thermal (0.0 – 0.414 eV) flux from the direct least-squares fit was 8.8x10^8 n/cm^2-sec, with a

Figure 6. Placement of activation foils in the MURR thermal beamline aperture.

propagated uncertainty of approximately 6% (1σ). The measured cadmium ratio for the gold foils was 132. The corresponding measured fast-neutron dose rate in the beam (computed using the measured spectrum and KERMA factors from File 27 of the BUGLE-80 Library) is 1.37 cGy/min, compared to the calculated value of 0.7 cGy/min yielded by the early DORT/BUGLE model. This is still in an acceptable range, although we may elect to reduce this dose rate somewhat by adjustments to the silicon and/or the bismuth filter thickness. The measured boron dose rate attainable in this neutron spectrum is 0.43 cGy/min/ppm ^{10}B

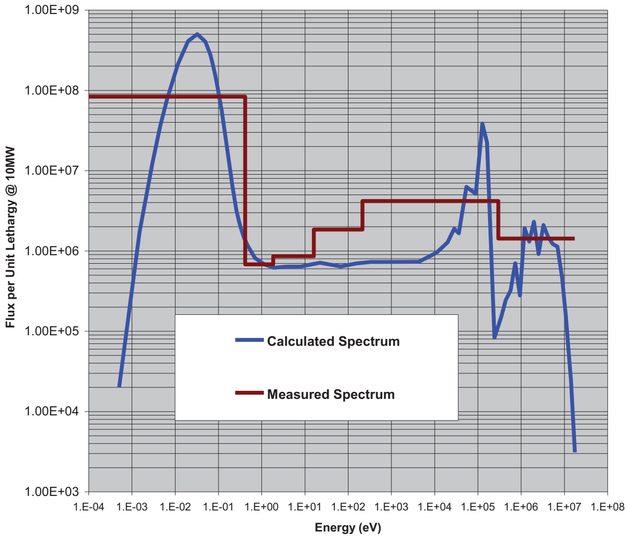

Figure 7. Calculated and measured neutron spectrum at the irradiation location of the MURR thermal neutron facility.

5. CONCLUSIONS AND FUTURE WORK

Parameter studies, design calculations and spectral performance measurements have been completed for a new thermal neutron beamline for neutron capture therapy cell and small-animal radiobiology studies at the University of Missouri Research Reactor. Results indicate that typical single-fraction irradiations to the required total accumulated dose for clinical relevance (6-10 Gy) can be conducted in an hour or less, depending on the tissue boron content, which is typically in the range of 20-100 parts per million by weight. A new high-fidelity computational model based on coupled discrete-ordinates and Monte Carlo techniques yields results that are highly consistent with the measurements, with excellent spectral detail in the thermal neutron energy range.

Additional measurements useful for estimating the spatial distribution of the thermal and above-thermal neutron flux at various locations in small-animal phantoms are currently underway. Finally, measurements of the incident gamma component of the MURR neutron source are also underway using a set of FarWest^{TM} paired ion chambers, in keeping with international recommendations [16]. Initiation of small-animal studies is anticipated in 2010.

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