The epithermal neutron beam for BNCT under construction at TAPIRO: Physics

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Abstract. A column to provide an epithermal neutron beam suitable for experimental and clinical BNCT is nearing completion at the TAPIRO reactor (ENEA Casaccia, Rome). TAPIRO is a compact, low power (5 kW), helium-cooled, fast reactor. It has a hard neutron spectrum relative even to other fast reactors. In this paper some of the basic physics aspects of designing an epithermal neutron beam are considered, with reference to the TAPIRO beam.

1. Introduction

1.1 Basics of BNCT
BNCT (Boron Neutron Capture Therapy) is an experimental radiation therapy based on the principle of the binary modality: the combination of two components that kept separate have relatively minor effects on cells but that when brought together result in cell destruction. These components are firstly the isotope $^{10}$B, administered in a boron compound prior to the irradiation and secondly irradiation with neutrons with an appropriate energy spectrum. The neutrons are captured by $^{10}$B (which has a high neutron absorption cross-section at thermal neutron energies – see figure 1) with reaction products that are heavy charged particles ($\alpha$ particle and $^7$Li nucleus). These charged particles have a high LET (Linear Energy Transfer) and an energy such that their range is similar to the size of a cell (of the order of a few microns). Therefore to kill the cell (for example to provoke a DNA break) the boron compound does not have to be situated within the cell nucleus but can be in the cytoplasm (as is the case with the boron compound BPA [p-(dihydroxyboryl)-phenylalanine]).

1.2 TAPIRO
TAPIRO is a compact fast reactor situated at ENEA, Casaccia (near Rome). It has a very small core (11 cm height, 12 cm diameter, 93.5\% enriched uranium), cooled by helium and with a copper
reflector. It has a relatively low power (5 kW or $4.3 \times 10^{14}$ neutrons/s) with a hard neutron spectrum relative even to other fast reactors.

1.3 Producing neutron beams for BNCT

Material structures attached to the main body of a reactor, called “columns”, are employed to modify the energy spectrum of the neutrons and reduce the gamma ray contamination. Their components called “spectrum shifters”, “filters” or “moderators” and “shields” play different roles. BNCT columns for epithermal beams can be divided into two general categories: those employing spectrum shifters and filters (involving packing long, relatively narrow, tubes) and those, as at TAPIRO, employing moderators (involving accessing a large solid angle relatively near the reactor core).

Current reactor-based neutron beams for BNCT employ thermal reactors [1]. Instead fast reactors may hold certain advantages for providing BNCT beams: the absence of a high thermal neutron flux in the core means that the capture gamma ray flux is far less intense. Therefore the gamma ray shield may be much thinner or may not even be required. Furthermore if an epithermal (in the BNCT context considered as between 0.4 eV and 10 keV) rather than a thermal neutron beam is desired, a thermal neutron shield may not be required in a fast reactor. In this case shielding the gamma rays produced in the thermal neutron shield will also not required. Both these favourable situations result at TAPIRO so that, as will be seen, thermal neutron and gamma shields are not used. As a consequence, notwithstanding the relatively low power, a sufficiently intense epithermal neutron beam with acceptably low fast neutron and gamma ray contamination can be produced.

1.4 Summary of paper

In the following we discuss firstly the necessary changes in the neutron energy spectrum from the fission source to an acceptable profile for therapeutic purposes. Then we look at the differences between dose profiles in human tissue from thermal and epithermal beams. Thirdly we consider the neutron cross-sections of various candidate materials and material mixtures for the column. Finally we present the results for the TAPIRO beam.

2. Required changes to the neutron energy spectrum

In figure 2 a diagram of TAPIRO’s core is shown with the copper reflector and the window in the direction of the therapy position. In figure 3 are illustrated four neutron spectra:
- as they are born (a fission spectrum);
- leaking from TAPIRO’s core (assuming no back reflection from the copper reflector);
- entering the window in the copper reflector (see figure 2);
- at the therapy position (a typical epithermal spectrum appropriate for BNCT).

We see that the source spectrum must be strongly modified to be suitable for therapy by increasing the epithermal component and reducing the fast component (> ~10 keV). The fast component must be reduced because recoil protons produced from the elastic scattering of fast neutrons in body tissue have a sufficient energy to cause cell damage. Figure 4 in which the epithermal spectrum of figure 3 is compared with the profile of the in-air neutron flux-to-dose in tissue response function (units: Sievert), clearly illustrates the complementary nature of the epithermal spectrum and the flux-to-dose profile.

3. Comparing dose profiles from thermal and epithermal incident spectra

In figure 1 we see that the target reaction is predominantly sensitive to thermal neutrons. In some cases (intra-operative (IO) BNCT [2], melanoma therapy [3], explant therapy [4]), thermal neutrons are employed (although it should be noted that mixed thermal-epithermal beams are also employed in melanoma therapy [5] and in IOBNCT [6]). Instead when a greater penetration is required, epithermal beams are used (brain tumours [7], possible in loco liver treatment [8]). The epithermal neutrons are moderated to thermal energies by the nuclei of the human tissue. The diffusion process during the moderation moves the thermal peak to a greater depth in the body.
To illustrate this, we see in figure 5 the dose profiles from a mono-directional thermal neutron spectrum on a phantom (a semi-infinite slab, 8 cm thick, composed of ICRU-46 brain tissue [9]). The incident neutron beam has no gamma impurity and impinges on one face over a cylindrical area of ~140 cm² with same intensity as that of the epithermal beam at the aperture of the TAPIRO column. The doses in the phantom were calculated around the source axis and employed generally accepted RBE and C/RBE factors when using BPA for brain glioma’s [10] and assumed a $^{10}\text{B}$ concentration in healthy tissue of 10 $\mu$g/g. In figure 5 there are three dose components: the neutron dose [recoil protons and protons from $^{14}\text{N}(n,p)$ – for an incident thermal spectrum the latter predominates], the photo-electric dose (mainly from gamma rays from neutron capture in hydrogen) and the $^{10}\text{B}$ dose.

Under exactly the same conditions with the same beam intensity but with an epithermal incident energy spectrum identical to that at TAPIRO, in figure 6 are shown the resulting dose profiles. We see that the maxima of the $^{10}\text{B}$ and the photo-electric dose profiles have been shifted to a greater depth in the tissue. [Note that the neutron dose which shows a maximum at around 1 cm depth, instead in more realistic situations (angular distribution of the beam, realistic phantom shape) is maximum at the surface.] The maximum of both the $^{10}\text{B}$ dose and the total dose is between 20 and 25 mm depth, typical values. At this depth, the total epithermal dose (figure 6) is around double that of the total thermal dose (figure 5). This ratio increases at greater depths. (In more realistic situations and with the skull modelled, this ratio may be higher.)

Note that the dose profiles in figures 5 and 6 are in healthy tissue. For tumour tissue (e.g. brain glioma) the $^{10}\text{B}$ dose increases by a factor of about 10 (due to the greater $^{10}\text{B}$ concentration and the higher C/RBE factor [10]) whilst the other two components remain the same. Also in the absence of $^{10}\text{B}$ the dose from an epithermal beam is actually higher than that from a thermal beam both at depth and at the surface, a result not widely appreciated. This should hold also in more realistic situations.

4. Considerations of the neutron cross-sections in the design of an epithermal column

We have already mentioned in §1.3 the two general categories of columns. TAPIRO in figure 7 corresponds to the “moderator” type in which all the components of the neutron transport - collisions, slowing down and diffusion – play a role. In this case the total neutron cross-section is not the only parameter that needs to be considered; the ratio of the inelastic to elastic cross-sections, the average logarithmic energy decrement for elastic scattering, etc. are also important. The other category (see for example [11]) requires similar considerations for the spectrum shifter, whilst instead, the filter requires consideration only of the total neutron (and gamma) cross-section (as it just removes particles from the beam). We shall limit the following discussion to the moderator type of column.

4.1 Comparing the fast to the epithermal total cross-section

Whilst not the only parameter of interest, the total cross-section is still important. We wish the total cross-section above ~ 10 keV (“fast” energies) to be as high as possible with respect to the total cross-section between 0.4 eV and 10 keV (epithermal energies).

In figure 8 we compare the total (microscopic) cross-section of aluminium with that of water from 1 eV to 10 MeV. Whilst aluminium looks helpful for our purposes, water is the opposite of what we desire, with a comparable cross-section to aluminium above ~ 500 keV and a cross-section that is an order of magnitude higher than aluminium at epithermal energies. As aluminium, with a mass number of 27, does not over-moderate in elastic scattering, it is considered as a standard as an epithermal moderator. In figure 9 the aluminium total cross-section is compared to that of titanium. Titanium has a wide resonance with maximum just below 20 keV. Although it removes neutrons in this energy range that contribute to the unwanted dose, it also removes neutrons that may be captured in $^{10}\text{B}$. Oxygen shows no advantages over aluminium and has a worrying window in the MeV region. Carbon is grossly similar to oxygen. Fluorine and magnesium are possible candidates although neither look as good as aluminium. However fluorine has other advantages as will be discussed. (The cross-sections of oxygen, fluorine and magnesium are shown in §4.3 when consideration is given to mixing
elements.) Sulphur, not presented here, has a favourable ratio of epithermal to fast total cross-sections compared with aluminium. It has however a deep window around 70 keV. In figure 10 aluminium is compared with copper. We see that copper does not have the same favourable feature as aluminium. Nickel, steel and lead are grossly similar to copper, with nickel having the greatest (i.e. least favourable) ratio between the epithermal and the fast cross-sections (see figure 11). However this makes nickel a good candidate as a reflector: a relatively thin (~ 75 mm) thickness acts as a discriminating filter between the fast and epithermal components, transmitting and therefore removing the former and reflecting the latter.

4.2 Considerations of the inelastic cross-section
Inelastic scattering is particularly effective in reducing in one collision the energy of neutrons from hundreds of keV and MeV to much lower energies: hundreds of eV to some keV. In figure 12 the inelastic scattering cross-section of fluorine to the 1st nuclear excitation level is compared to those of copper, steel and lead (materials regarded as good inelastic scatterers). We see that fluorine’s cross-section is notably higher.

4.3 Mixing materials to match resonances in the fast energy range
It is of interest to mix materials to attempt to superpose the resonances in the fast energy range so that windows in one material are filled by resonances from the other. In figure 13 are shown the total microscopic cross-sections in the range 1 keV – 10 MeV of aluminium and oxygen separately, together with alumina (Al₂O₃). In a similar fashion figure 14 shows aluminium and fluorine separately, together with aluminium fluoride (AlF₃). It is well-known that there is a favourable superposition of the aluminium and fluorine resonances, but in figure 14 this is not obviously apparent: there is some favourable superposition in the tens of keV range and at 300-400 keV but it is not as complete as one would wish. Figure 15 shows aluminium and magnesium separately, together with a 1-to-1 mixture of each element. Al and Mg may possibly superpose better than Al and F, but of course there is not the advantage of the fluorine inelastic effect. Finally in figure 16 is shown a comparison of AlF₃ and MgF₂. The latter has been proposed recently as a candidate moderator for compact columns [12] because of the high densities that can be achieved. The cross-section profile looks similar to that of AlF₃. These general considerations point to possibly a combination of MgF₂ (first) then Al but detailed calculations are required. It is anyway worth noting that all these materials have intermediate atomic masses, so that they moderate to an extent with elastic scattering, but do not over-moderate.

5. The epithermal column at TAPIRO
At TAPIRO, aluminium fluoride was the moderator of choice, packed into aluminium boxes to a density of 1.85 g cm⁻³. A typical thickness of the moderator (along the axis of the column – see figure 7) is 37 cm. A number of boxes of different thicknesses are available to allow some flexibility in the shape of the spectrum. A nickel reflector of thickness 75 mm is present and no thermal neutron absorber or gamma shield is employed. A relatively long collimator of lead is used. Lead has a very low neutron absorption cross-section, is a reasonable reflector and does not modify the energy spectrum much. The lead has a high purity to avoid possible neutron activation issues. The collimator has two angles – see figure 7. Such a design increases the neutron flux at the aperture [13]. It also allows to modify the size of the aperture without much change in the flux levels. Following the lead there is a 50 mm thickness of lithiated polyethylene neutron shield. Lithium is employed to absorb the neutrons as the capture gamma rays from ⁶Li are of a much lower energy than those from other neutron absorbers such as ¹⁰B.

5.1 Results
The calculated standard free beam parameters, which give the level of epithermal neutron flux, relative fast neutron and gamma impurities and directionality of the beam and allow a gross comparison with
the beams of other facilities are given in table 1. The current-to-flux ratio, $J_{\text{epth}} / \Phi_{\text{epth}}$, is a measure of the directionality of the beam. Its maximum value is 1 for a mono-directional beam.

Dose profiles in a realistic anthropomorphic phantom, ADAM [10], are given in figures 17 and 18 for a single beam lateral irradiation and twin parallel-opposed beams respectively. The RBE and C/RBE factors and $^{10}$B concentrations are those used in [10]. As well as the three dose components to healthy tissue already discussed in §3, also the $^{10}$B and total dose to tumour tissue are presented, again using the hypotheses detailed in [10]. To summarize the in-phantom results, with the constraint of a maximum 12.6 Gy Eq to healthy tissue, the treatment time for a single beam is 50 min and for two beams is 45 min per beam. The Peak Therapeutic Ratios [10] are 4.30 and 4.04 for one and two beams respectively both at a depth of 13 mm in the brain (27 mm in the cranium). In the case of two beams the therapeutic ratio never falls below 2.25. For a single beam the Advantage Depth and Therapeutic Depth [10] are 86 and 66 mm respectively (measured from the skin surface). Note all these results are for a conservative (i.e. low) hypothesis for the $^{10}$B concentration in healthy brain of 10 $\mu$g/g.

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Table 1. Calculated free beam parameters for the TAPIRO column

| Parameter                                                   | Value                        |
|-------------------------------------------------------------|------------------------------|
| $\Phi_n$ epith (0.4 eV – 10 keV)                           | $8.0 \times 10^8$ neutrons cm$^{-2}$ s$^{-1}$ |
| Neutron dose in water > 10 keV / $\Phi_n$ epith             | $3.4 \times 10^{-13}$ Gy cm$^2$ |
| $\gamma$ whole body dose / $\Phi_n$ epith                   | $4.1 \times 10^{-13}$ Gy cm$^2$ |
| $J_n$ epith / $\Phi_n$ epith                               | 0.73                         |
Figure 6. Dose profiles in phantom for incident epithermal spectrum (Gy Eq in 40 min irradiation)

Figure 7. The TAPIRO epithermal column

Figure 8. Al and H\textsubscript{2}O total neutron cross-sections between 1 eV and 10 MeV (barn)

Figure 9. Al and Ti total neutron cross-sections between 1 eV and 10 MeV (barn)

Figure 10. Al and Cu total neutron cross-sections between 1 eV and 10 MeV (barn)

Figure 11. Ni total neutron cross-section between 1 eV and 10 MeV (barn)

Figure 12. Inelastic scattering cross-sections to 1\textsuperscript{st} excited level: fluorine, copper, steel and lead
Figure 13. Al, O and Al₂O₃ total neutron cross-sections between 1 keV and 10 MeV (barn)

Figure 14. Al, F and AlF₃ total neutron cross-sections between 1 keV and 10 MeV (barn)

Figure 15. Al, Mg and Al-Mg (1-1) total neutron cross-sections between 1 keV and 10 MeV (barn)

Figure 16. AlF₃ and MgF₂ total neutron cross-sections between 1 keV and 10 MeV (barn)

Figure 17. Profiles of dose components in ADAM cranium (single beam) (Gy Eq min⁻¹)

Figure 18. Profiles of dose components in ADAM cranium (2 parallel-opposed beams) (Gy Eq min⁻¹)