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Epithermal neutron beams from the ^{7}Li(p,n) reaction near the threshold for neutron capture therapy

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Summary. — Two applications for neutron capture therapy of epithermal neutron beams calculated from the ^{7}Li(p,n) reaction are discussed. In particular, i) for a proton beam of 1920 keV of a 30 mA, a neutron beam of adequate features for BNCT is found at an angle of 80° from the forward direction; and ii) for a proton beam of 1910 keV, a neutron beam is obtained at the forward direction suitable for performing radiobiology experiments for the determination of the biological weighting factors of the fast dose component in neutron capture therapy.

1. – Description

Boron Neutron Capture Therapy (BNCT) [1] is an experimental form of radiotherapy based on the selective uptake of a boron compound by tumor cells and the subsequent irradiation of the tumor with a low energy neutron beam producing a thermal neutron field in the tumor. Thermal neutrons are captured by the boron atoms by means of a (n, α) reaction in which high-energy heavy charged particles are delivered locally to the tumor. These particles have a significantly higher linear energy transfer to the medium (tumor) than photons or electrons, and therefore are more biologically effective than conventional radiotherapy. Up to now, all clinical trials of BNCT have been performed from research reactor neutron sources. These neutron sources are scarce and are not practical for construction in hospitals. For this reason, accelerator-based neutron sources (ABNS) are in development in several countries, and in Kyoto (Japan), an ABNS is ready for medical applications [2]. The ABNS in Japan is based on collisions of 30 MeV protons

from a cyclotron with a Be target. Another option, which requires a lower energy proton beam, is based on the (p, n) reaction on ^{7}Li near the threshold. This produces a less energetic neutron beam thus requiring minor moderation for use in patient irradiation [3].

For BNCT, the spectrum of the neutron beam is critical. The neutrons should have enough energy to penetrate deeply in the body, but not so high as to produce a large background radiation dose, while also being able to thermalize within the body. These features require an initial epithermal spectrum for the neutrons, but the exact requirements should be determined with Monte Carlo simulations.

All the neutrons beams used in BNCT up to now have been obtained with some moderation from the source, in order to obtain a spectrum in which more than 90% of the neutrons are in the epithermal range. This is defined as the interval [0.5 eV, 10 keV]. However the upper bound is just a reference value and slightly greater energies can be also suitable for BNCT. For example, it has been shown by MC simulation how a monoenergetic beam of 13.5 keV can be very appropriate for BNCT [4].

The optimization of the neutron spectrum for BNCT is a question of compromise. Higher energies than 20 keV produce an undesirable maximum of the absorbed dose in the surface of the phantom (which raises steeply when increasing the neutron energy), and energies below 1 keV would reduce strongly the penetrability of the beam in order to reach deeper located tumors. The moderation of a neutron beam necessarily produce a strong broadening of the spectrum. Our aim in this work is trying to obtain a neutron spectrum as close as possible to epithermal energies around 10 keV. For this purpose we have analyzed the neutron spectrum obtained from the ^{7}Li(p, n) reaction near the neutron production threshold (between 1.88 MeV and 2 MeV) and at certain angles from the beam direction. Although the neutron yield reduces strongly when decreasing the proton energy from the 2.5 MeV resonance, and also at increasing angles from the forward direction, the possibility of not needing moderation could be enough for certain BNCT applications when a very high current accelerator (20–30 mA) as those recently available is used.

In this work we will perform calculations of an entire procedure for an accelerator-based BNCT application starting from the ^{7}Li(p, n) reaction. We will explore, for proton energies near the threshold and different exit angles, the possibility of obtaining an epithermal neutron spectrum which produces a depth-dose distribution in a body model appropriate for a BNCT treatment. A second problem would be obtaining a suitable beam for BNCT basic research (cell culture irradiation by epithermal neutrons), even with a low current accelerator. This is interesting for the experimental determination of the relative biological effectiveness (RBE) factors of epithermal neutrons.

2. – Methods

The form of the neutron spectrum as a function of the neutron energy and the exit angle, important ingredient in our simulations, is the thick target differential neutron yield that can be calculated as

$$\frac{\mathrm{d}^2 Y}{\mathrm{d}\Omega \mathrm{d}E_n}(\theta, E_n) = f_{^7Li} \frac{\frac{\mathrm{d}\sigma_{pn}}{\mathrm{d}\Omega'} \frac{\mathrm{d}\Omega'}{\mathrm{d}\Omega} \frac{\mathrm{d}E_p}{\mathrm{d}E_n}}{\frac{1}{n} \frac{\mathrm{d}E_p}{\mathrm{d}x}}, \tag{1a}$$

where $\Omega(\Omega')$ is the solid angle in the laboratory (center of mass) system of reference, $E_n(E_p)$ is the neutron (proton) energy in the laboratory system, $f_{^7Li} = 0.925$ is the fraction of ^{7}Li in natural lithium metal (target composition), $\frac{\mathrm{d}\sigma_{pn}}{\mathrm{d}\Omega'}$ is the differential

cross section of the reaction in the center-of-mass system, n is the density of atoms in the target and the whole denominator is the mass stopping power of protons in the medium.

In the same way as Lee and Zhou [5], we have adjusted a cubic spline to the experimental data of the differential cross section from Lisken and Paulsen [6] and we have used analytical expressions for the mass stopping power [7]. Further details can be consulted in [5].

2˙1. *A. Near threshold beam for BNCT.* – With the neutron spectra obtained from these calculations, we have performed MC simulations using the MCNPX code, version 2.5.0 [8]. For this application we have considered the geometry illustrated in fig. 1. The neutron field obtained from a proton beam of 1920 keV on a thick lithium target is transported in a cylindrical phantom of 8 cm radius, 10 cm height. The material in this cylinder is a representative soft tissue called 4-component soft tissue as defined by the International Commission on Radiation Units (ICRU) with the following mass composition: 10.12% H, 76.18% O, 11.10% C and 2.60% N. The axis of the cylinder is placed at an angle with respect to the proton beam direction of 80° and at a distance of 5 cm. This situation has been selected from different choices of angles because it has shown to be adequate for the depth-dose distribution inside the phantom.

2˙2. *B. Epithermal beam for in-vitro radiobiology experiments.* – The dose in a BNCT treatment is usually decomposed in different contributions: boron, thermal (mainly due to the protons emitted in the Nitrogen capture reaction), fast (mainly due to the recoiling protons from elastic collisions of the neutrons at epithermal energies) and photon dose. Our goal is designing a method to evaluate separately the RBE factors of the fast and thermal dose for the same type of cells. The RBE factors are defined as the ratio between the dose required for a photon irradiation and the actual field, producing both the same biological effect.

For obtaining these factors we can measure the biological effect after the irradiation with two different neutron beams, one producing much more thermal than fast dose and another just the opposite. The former case happens under thermal beams as those obtained from reactors after neutron moderation. In this work we will design an experimental condition producing much more epithermal dose than thermal, which would be the second case required.

The situation studied, representing the irradiation of adherent cells, is the following:

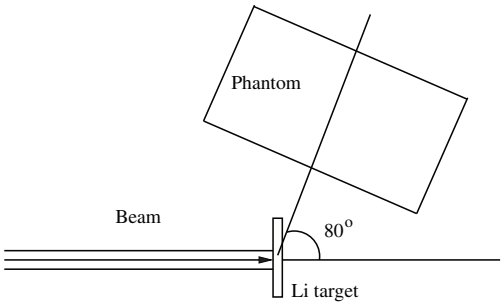

Fig. 1. – Schematics of the neutron irradiation of the cylindrical phantom of 8 cm radius, 10 cm height. The distance between the phantom and the center of the Li target is 5 cm.

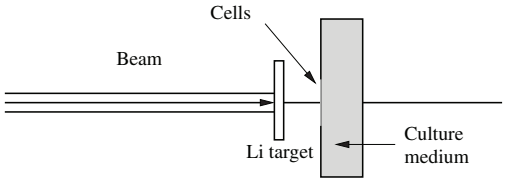

Fig. 2. – Schematics of the neutron irradiation of culture cells. The dimensions are as follows: beam diameter 6 mm, Li thick target of 2 cm diameter, distance target-cells 1 cm, diameter of culture 2 cm, 1 cm water beyond the cells.

the neutron field produced by a proton beam of 1910 keV (±1 keV) on a thick lithium target is directed to a very thin layer of cells (represented by the same 4-component ICRU tissue). This cells are in a box of basis 6 × 6 cm, and 2 cm height, filled by water (representing the culture medium). The situation is illustrated in fig. 2.

3. – Results

3˙1. *Application A.* – The absorbed dose depth profile at the phantom axis is illustrated in fig. 3. In both panels, the solid line corresponds to the tumor dose assuming a concentration of boron of 40 ppm, while the dotted line, representing the normal tissue dose, is found assuming a concentration of 10 ppm. In the left panel, it is noticed how the tumor absorbed dose is greater than the maximum of the normal tissue dose (horizontal dotted line) up to a depth of about 8 cm (advantage depth), and how in the range between 2 and 5 cm depth, the tumor dose exceeds twice the maximum normal tissue dose (horizontal solid line). In the right panel the biological dose is estimated using the weighting factors of use in BNCT: 3.2 for the fast and thermal doses, 1.0 for the gamma dose, and for the boron dose values of 3.8 (tumor) and 1.8 (normal tissue). We can see in the plot the important enhancement of the weighted dose delivered to the tumor compared to the normal tissue one.

The results are illustrated for a reference proton beam intensity of 1 mA. The low dose rates obtained for this intensity are expected because the low neutron yield near

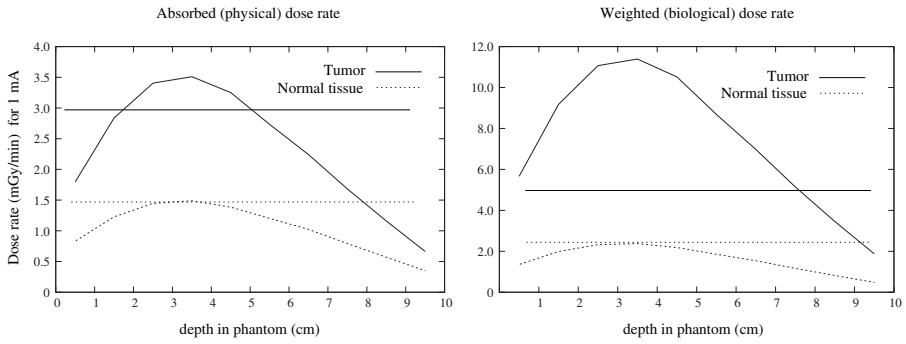

Fig. 3. – Absorbed (left) and weighted (right) dose rate depth profile in the phantom axis at tumor cells (solid curve) and normal cells (dotted curve). The horizontal lines represent the maximum value of the normal tissue dose rate (dotted) and twice this value (solid).

TABLE I. – *Dose rate components at the cell culture, for a proton beam of* 1910 keV *and a thick Li target for different beam currents.*

Component	Gy/min (1 mA)	Gy/h (10 μA)
D_f	1.370	0.822
D_t	8.34×10^{-4}	5.00×10^{-4}

the threshold and at this angle. However, with a high current accelerator (30 mA) the weighted dose rate at the tumor could reach values between 10 and 20 Gy/h (3.8 Gy/h maximum for normal tissue).

The reason of the high differences between the tumor and normal tissue dose can be addressed to the low values of the fast dose component, which is due to the low-energy spectrum of the neutrons. This is a difference with respect to previous calculations of the dose produced by this reaction in the forward direction, where a high peak at the surface of the phantom usually appears due to the higher energy delivered by the most energetic neutrons in their first elastic collision in the medium.

3˙2. *Application B.* – The results of the MC calculation of the absorbed dose rate produced at the cells represented by the disk of 2 cm in fig. 2 with the MCNPX code above mentioned are shown in table I. The fast dose component is much greater than the thermal one, which is the situation pursued. The values of the fast dose rate is high enough as to measure survival effects in cells (usually starting from 0.1 Gy) in a reasonable time, even if a low current accelerator (in the μA range) is available. This measurements then would complement those performed with a thermal beam in which the situation is the opposite (in terms of relative dose contributions).

4. – Conclusions

Epithermal neutron beams obtained from the ^{7}Li(p,n) reaction near the threshold can be useful for neutron capture therapy, both for basic research and for therapy. In the first case, with an energy of the proton beam of 1910 keV, the neutron beam at the forward direction is adequate for radiobiology experiments even if the accelerator has a low current. For the latter, in this work it has been analyzed a very simplistic case, but the results for a proton beam energy of 1920 keV and a phantom located at 80° are promising. Therefore it seems interesting to research further in this direction with more realistic calculations and experimentation.

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