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HADRON CANCER THERAPY: ROLE OF NUCLEAR REACTIONS

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Recently it has become feasible to calculate energy deposition and particle transport in the body by proton and neutron radiotherapy beams, using Monte Carlo transport methods. A number of advances have made this possible, including dramatic increases in computer speeds, a better understanding of the microscopic nuclear reaction cross sections, and the development of methods to model the characteristics of the radiation emerging from the accelerator treatment unit. This paper describes the nuclear reaction mechanisms involved, and how the cross sections have been evaluated from theory and experiment, for use in computer simulations of radiation therapy. The simulations will allow the dose delivered to a tumor to be optimized, whilst minimizing the dose given to nearby organs at risk.

1 Introduction

A number of research programs have been initiated whose aim is to accurately simulate the nuclear collisions and radiation transport involved in hadron therapy. The nucleon energy range below a few-hundred MeV is crucial for these studies. Proton therapy is typically performed with energies in the 60-250 MeV range, and fast neutron therapy utilizes energies up to about 70 MeV. The evaluation of proton and neutron interaction cross sections in this energy region requires particular care – the energies are too low for intranuclear cascade model assumptions to hold, and instead, nuclear reaction models that include more details of the nuclear structure properties should be applied. A further difficulty is the paucity of experimental data to test and validate the calculations. The present paper focuses on a description of models for direct, preequilibrium, and Hauser-Feshbach nuclear reaction mechanisms, and their use in producing cross section databases for radiation transport simulations.

The need for accurate nuclear reaction cross sections is greatest for fast neutron therapy. This is because neutrons interact with matter only through the nuclear force, and the energy deposition and transport depend sensitively on nuclear cross sections and emission spectra. Nuclear reactions are important to a lesser extent for protons as these also have electromagnetic interactions, and perhaps their greatest impact is due to neutron production processes which can influence absorbed dose distributions, and which need to

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be understood for shielding. To respond to these needs, a project to determine nuclear reaction cross sections up to 150 MeV for neutrons, and 250 MeV for protons, making use of advanced model calculations and measurements, has been underway at Los Alamos [1,2]. The cross sections are represented in the ENDF format in evaluated nuclear data files for H, Li, C, N, O, Al, Si, P, Ca, Cr, Fe, Ni, Cu, Nb, W, Hg, Pb, and Bi, the suite of evaluations being known as the "LA150 Library". This work has been documented in an International Commission on Radiation Units and Measurements (ICRU) report that has been recently issued [3].

Various laboratories have begun to develop radiation transport codes that can utilize accurate nuclear cross sections in evaluated data libraries that extend up to 150 – 250 MeV. At the Lawrence Livermore National Laboratory, the Peregrine code [4] is being developed specifically for cancer radiotherapy applications. Its main focus is on conventional photon therapy, but preliminary capabilities have also been developed for neutron and proton therapy. At the Los Alamos National Laboratory, the MCNPX transport code [5] can be used for a variety of transport applications.

2 Nuclear Model Calculations for Medical Applications

Nuclear reaction calculations have played an important role in determining reaction cross sections for hadron radiotherapy. A variety of codes, implementing different physics models, have been used in the past (*e.g.* intranuclear cascade calculations using Brenner and Prael's code [6], and the preequilibrium and Hauser-Feshbach calculations undertaken by the present author using the GNASH code [7]). Below, an overview of the different reaction mechanisms involved is given.

The total, elastic, total nonelastic, and inelastic scattering cross sections to low-lying nuclear states were determined through optical model analyses, which are also needed for generating transmission coefficients and wavefunctions in the equilibrium and preequilibrium calculations. Elastic scattering processes are important because elastic scattering frequently constitutes a significant fraction of the scattering, and the scattered particle's energy and angular distribution must be known to describe the transport through matter. In addition, the recoil energy of the target nucleus contributes to the kerma (and absorbed dose).

The Feshbach-Kerman-Koonin quantum mechanical theory [8], and the semiclassical exciton model, were the basis of calculations of preequilibrium nucleon emission in which the interaction of a projectile nucleon with a target nucleus is modeled as taking place through a number of stages of increasing

complexity [9]. Initially, the projectile interacts with a nucleon within the nucleus, exciting a particle-hole pair. The excited nucleons may then undergo further interactions until all the energy brought in by the projectile is shared amongst the target nucleons in an equilibrated state. Particles may also be emitted in the early stages of the reaction. These preequilibrium secondary particles typically have high energy and a forward-peaked angular distribution. After the preequilibrium phase of the reaction the residual nucleus, which is usually left in an excited state, decays by sequential equilibrium particle or gamma-ray emission, calculated with the Hauser-Feshbach theory.

2.1 Neutrons

In figure 1 (left) an illustrative example is provided, for the angle-integrated emission spectrum of protons following 60 MeV neutron bombardment on oxygen. The calculation, shown as a solid line, is compared with measurements by Subramanian *et al.* [10] and by Benck *et al.* [11]. The dashed line shows the intranuclear cascade results from Brenner and Prael [6]. The calculated solid line contains contributions from a number of different emission mechanisms: the increase at low emission energies is due to compound nucleus equilibrium decay processes; and the higher energy contribution to the spectrum, extending from about 10 MeV to 50 MeV, is due to preequilibrium reactions. The reader is referred to Refs. [1,3] for numerous additional comparisons.

Kerma, an acronym for "kinetic energy released in matter", is an important concept in neutron dosimetry. Since the kerma coefficient can be calculated from the product of the charged-particle production cross sections and their average energies, it represents the interface between microscopic nuclear reaction cross sections, and macroscopic calculations of energy deposition. Recommended total kerma coefficients for various biologically-important elements, as well as elements present in accelerator collimeter structures, are compared against measurements extensively in Refs. [2,3], and the agreement was found to be good. Figure 1 (right) shows on a logarithmic scale the total kerma coefficient for ICRU-muscle up to 150 MeV, and contributions from individual elements comprising ICRU-muscle. The hydrogen kerma coefficient is seen to play a crucial role, with the contribution from oxygen becoming dominant at the highest energies.

2.2 Protons

In proton therapy, nuclear reactions result in protons being removed from the primary beam. Reaction products include secondary protons, neutrons, photons, and heavier recoils, some of which deposit energy outside the path

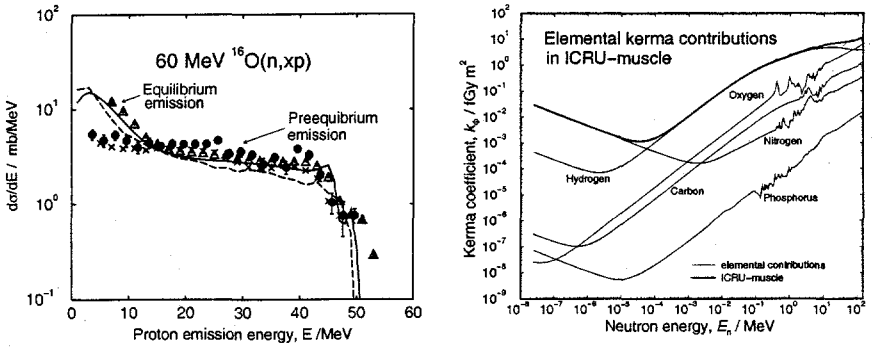

Figure 1. (a)*left:* The angle-integrated emission spectrum of protons from 60 MeV neutrons incident upon oxygen. The full circles indicate the data of Subramanian *et al.* [10], and the crosses indicate these same measured values but based upon a more accurate angle-integration procedure [12]. The triangles are the data of Benck *et al.* [11]. The solid curve represents GNASH calculations [3,12], and the dashed line shows calculations by Brenner and Prael [6];(b)*right:* The total kerma coefficient for ICRU-muscle up to 150 MeV, together with contributions from individual elements comprising ICRU-muscle [2,3].

of primary photons. Neutrons are particularly troublesome as they penetrate large distances and produce secondary heavy charged particles with enhanced biological effect, thereby complicating dosimetric and clinical results. Even more problematic are secondary neutrons generated by primary protons striking beam modification devices upstream of the patient. These neutrons pose a significant shielding problem and illuminate large portions of the patient outside the treatment volume.

One of the most important quantities is the proton total nonelastic cross section, since this governs the rate at which protons are removed from the primary therapy beam. Figure 2 (left) shows the evaluated proton nonelastic cross sections, based upon optical model calculations, for oxygen up to 300 MeV. This result is seen to be in good agreement with measured data. Figure 2 (right) shows an illustrative example of our calculated 200 MeV C(p, xp) proton emission spectra compared with measurements recently taken at the National Accelerator Center [13], for data at various angles. There is qualitative agreement between the measured preequilibrium data and the calculations, though significant quantitative discrepancies are evident, especially at the backward angles. This probably reflects the difficulties inherent in applying statistical preequilibrium and compound models for such light nuclei.

A particularly interesting application of nuclear reaction physics is the

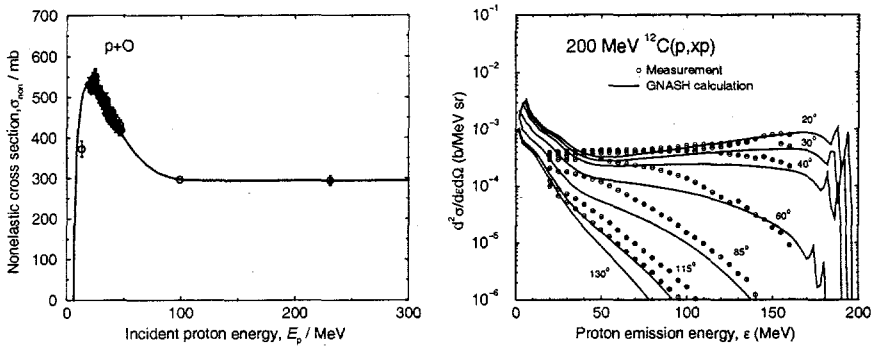

Figure 2. (a)*left:* Evaluated proton total non-elastic cross sections compared with data [14];(b)*right:* Calculated C(p,xp) emission spectra compared with NAC data [13]

proposed use of Positron-Electron Tomography (PET) to trace the location of the Bragg-peak in real time, to ensure that the proton therapy beam is depositing its maximum energy at the intended treatment volume [15,16]. Radionuclides that are beta-emitters (created in proton-nucleus collisions) produce positrons that quickly fall into an orbit with an electron, producing a positronium state that subsequently annihilates to produce two back-to-back gamma-rays. The detection of these gamma-rays in coincidence allows the location of the Bragg-peak to be inferred. This is because the excitation function for the production of β^+ emitters peaks at relatively low proton energies (*e.g.* the $^{16}O(p,\alpha)^{13}N$ cross section peaks in the 8–15 MeV region), near the range of the primary protons. Further details, and a comparison between the calculated and measured p+O excitation functions for the production of radionuclides, are given in the ICRU report [3].

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