

# Neutron Stimulated Emission Computed Tomography of Stable Isotopes

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## ABSTRACT

Here we report on the development of a new molecular imaging technique using inelastic scattering of fast neutrons. Earlier studies demonstrated a significant difference in trace element concentrations between benign and malignant tissue for several cancers including breast, lung, and colon. Unfortunately, the measurement techniques were not compatible with living organisms and this discovery did not translate into diagnostic techniques. Recently we have developed a tomographic approach to measuring the trace element concentrations using neutrons to stimulate characteristic gamma emission from atomic nuclei in the body. Spatial projections of the emitted energy spectra allow tomographic image reconstruction of the elemental concentrations. In preliminary experiments, spectra have been acquired using a 7.5MeV neutron beam incident on several multi-element phantoms. These experiments demonstrate our ability to determine the presence of Oxygen, Carbon, Copper, Iron, and Calcium. We describe the experimental technique and present acquired spectra.

## 1.INTRODUCTION

In this manuscript, we introduce a technique for in vivo spectrographic imaging of stable isotopes. We call the technique Neutron Stimulated Emission Computed Tomography (NSECT) and present the motivation, methods, and current state of results as a demonstration of feasibility. NSECT can be pictured as a modification of conventional emission computed tomography (ECT) where the gamma emissions are not from naturally radioactive isotopes (as is conventional), but instead are from stable isotopes that have been stimulated to emit characteristic gamma photons through inelastic scattering of an external neutron beam. These stable isotopes can be either a natural part of the body composition or could be introduced as a label that is tagged to a molecule of interest. The neutron beam can be scanned (or the gammas detected) with a geometry that generates tomographic projections. These projections can then be reconstructed into image voxels consisting of characteristic gamma energy spectra from which the elemental composition in the voxel can be determined. This reconstructed spatial distribution of the different elements that make up the body may provide insight into the molecular processes and may form the basis for new diagnostic techniques.

The underlying physical principals of NSECT are not new. Several similar techniques have been developed for a variety of purposes. Most of these techniques have been developed for remote detection of various substances of interest for the specific application. In the discussion section, examples will be presented along with a comparison of NSECT to previous work. It will be helpful to distinguish the physical principal of NSECT from Neutron Activation Analysis (NAA) also known as Instrumental Neutron Activation Analysis (INAA). The latter terms usually refer to the process of placing a sample of a material inside a nuclear reactor for several hours to several days time during which the nuclei in the material will capture thermal neutrons from the reactor flux and thus will be transmuted into neutron-rich isotopes. These isotopes are predominantly unstable and will decay. Some of the decays will be accompanied by gamma emission that is characteristic of the decaying isotope. After irradiation in the reactor, the sample is placed in a gamma spectrometer and the multiple decay processes will be monitored for up to a week to identify the elemental composition of the sample. This technique can be very accurate and can detect small quantities of some elements.

Previous research has demonstrated a statistically significant difference in the concentration of trace elements between benign and malignant tissue for several cancers including breast<sup>1-4</sup>, lung<sup>4</sup> and colon<sup>4</sup>. Unfortunately, the techniques employed in these studies were either destructive to the tissue or could not penetrate deep into the body and thus could not be translated into in vivo clinical diagnostic tools. We are developing NSECT as a technique that may be able to perform these measurements of the concentration of trace elements in vivo with little intervention and thus may eventually lead to a new molecular imaging technique for the diagnosis of several diseases including cancer, diseases of the liver involving iron overload such as hemochromatosis, or unusual levels of copper such as Wilson's disease. The research presented here will serve as an introduction to the NSECT technique and will describe some preliminary experiments performed to explore the potential of this technique for discriminating between different elements. The motivation for this work is to develop quantitative imaging tools to provide new diagnostic techniques, new methods for monitoring the progress of treatments, and new research tools to study molecular processes in living organisms including humans.

## 2.METHODS

A low-intensity beam of fast neutrons illuminates the region of interest in the body. The primary interaction of the incident neutrons with the nuclei of the body is through both elastic and inelastic scattering. When the scattering is inelastic, some of the neutron's energy is transferred to the nucleus thus exciting one of the quantized nuclear energy states. The excited nucleus promptly decays to a lower energy state by emitting a gamma photon whose energy is equal to the difference in energy of the states. The energy states of the known isotopes are unique and the energy of the emitted gamma photon is characteristic of the emitting isotope. The energy spectra of the emitted gamma photons are detected as tomographic projections. Reconstruction of these projection spectra provides a four dimensional image: three spatial and one energy dimension. The energy spectrum of each reconstructed voxel can to reveal the mixture of elemental concentrations by analyzing the intensity of the characteristic emissions from each element.

With NSECT, the spatial distribution of stable isotopes is then reconstructed by stimulating these isotopes to emit gamma photons that are characteristic of the emitting isotope. Exciting the atomic

nuclei in the body stimulates this emission. This excitation and the subsequent gamma emission will occur if the incident neutron energy is higher than the first quantum energy level in the nucleus from which the neutron scatters. All atomic nuclei have these energy levels with the exception of Hydrogen. With the exception of Hydrogen and Helium, a neutron beam with energy greater than 6.5 MeV will excite all atomic nuclei. The experiments described in this manuscript were conducted with neutron beam energy of 7.5 MeV.

One of the most straightforward ways to perform this imaging would be to uniformly illuminate the object to be imaged with neutrons and then collect the emitted gamma photons in a standard gamma camera. While in principle this would provide projections that could then be reconstructed into tomographic images, in practice the gamma photons emitted from stimulated stable nuclei have energies that are too high for a standard gamma camera. These energies range up to over 6 MeV for  $^{16}\text{O}$  and 4.5 MeV for  $^{12}\text{C}$ . Even at the lower energies that are characteristic of iron and copper (800keV to 2 MeV), practical collimators provide little spatial resolution and the typical crystals are too thin to provide either reasonable efficiency or sufficient energy resolution for this technique. For these reasons we have adopted a raster scanning approach to acquire the projection data. Here, we use a collimated neutron beam that can be scanned over the subject and acquire the emitted gamma photons in a detector that returns no spatial information. In this method, the path of the neutron beam through the subject defines the path and the detector integrates all photons emitted by nuclei along the path of the neutron beam.

To perform NSECT, three components are required: 1) a source of neutrons; 2) a spectroscopic gamma detector; 3) a geometric arrangement of either the neutron beam or the gamma detector to satisfy the requirements for tomographic imaging.

These experiments have been performed at the shielded neutron source of the Triangle Universities Nuclear Laboratory (TUNL) located a short walk from the medical center. The neutron beam is produced in a reaction, noted as  $^2\text{H}(d,n)^3\text{He}$ , by directing an accelerated and pulsed beam of deuterons onto a deuterium gas target located behind a meter-thick shielding wall composed of lead and paraffin that is loaded with boron and lithium. The neutron beam created by the reaction in the gas cell passes through the wall in a collimated channel. The collimator has inserts that can be exchanged to provide collimated beams of different dimensions from 1 mm square to 60 mm square. The neutron energy from this reaction is adjustable from 7.5MeV to 20MeV. Other reactions can provide lower energy neutron beams. The beam is pulsed to provide 1 nanosecond wide bunches at the target to allow measurement of neutron and gamma time of flight. A computer controlled sample holder allows remote horizontal, vertical and rotational positioning. This holder allows tomographic acquisition by translating and rotating the sample with respect to the neutron beam.

A High Purity Germanium (HPGe) gamma detector is positioned at 135 degrees from the incident neutron beam orientation and is 20 cm from the sample. A majority of the elements of interest decay by an electric quadrupole transition and this distribution has a maximum intensity at about 45 and 135 degrees. Using the 135 degree orientation helps prevent the gamma detector from being illuminated by either the direct neutron beam or by neutrons that elastically scatter from the target. Lead bricks shield the active area of the detector from the exit area of the collimator. A schematic drawing of this configuration is shown below in fig. 1. Considerable effort has been devoted to optimizing shielding to reduce backgrounds in the gamma detector. Shielding is currently under

development but is continuously being improved as we better understand the sources of background in the detectors. Use of the TUNL nuclear structure laboratory has been provided to this project as part of a collaborative agreement. We have been developing this technology for neutron stimulated spectroscopy since July 2003 as a general imaging technique. The development is very preliminary

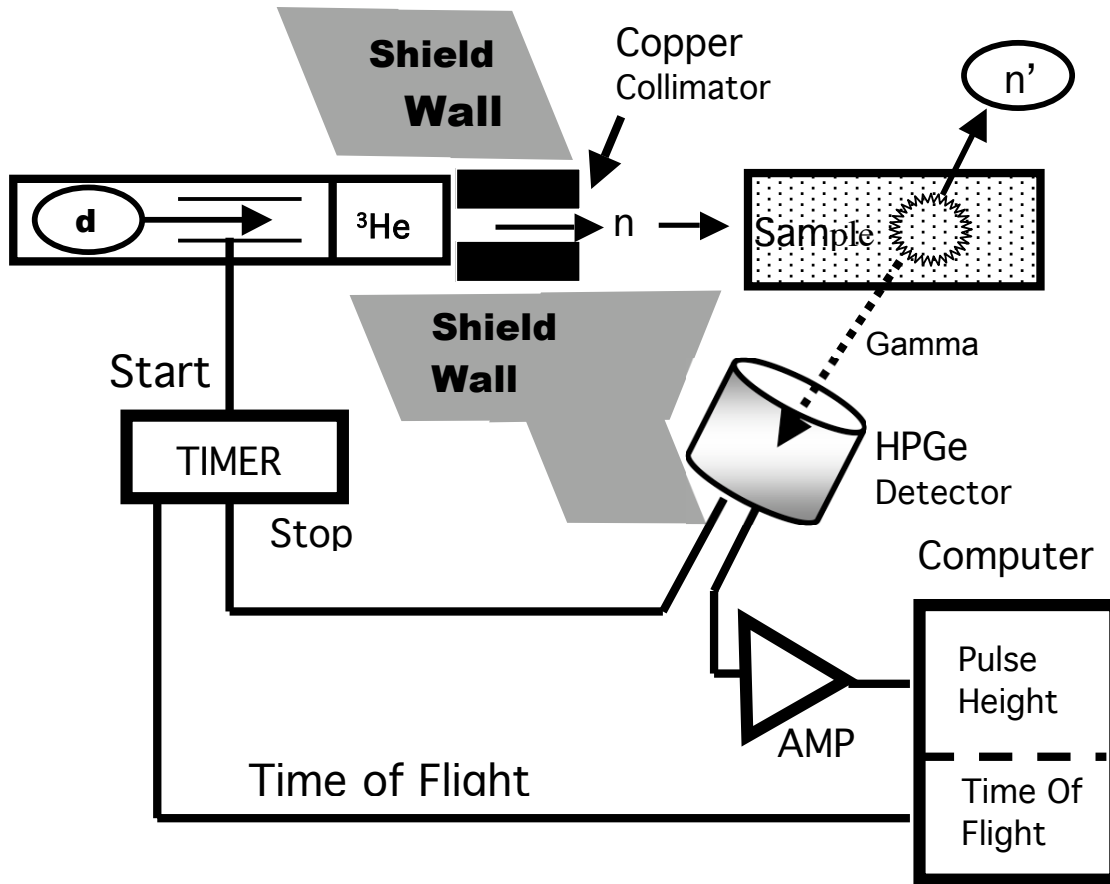


Fig. 1 Schematic of the target area showing a deuteron beam pulse arriving from the accelerator from the left, passing through the beam pick-off tube to generate the start signal for the Time-Of-Flight electronics, traveling into the deuterium gas cell, creating neutrons through the  $d(d,n)$  reaction leaving  $^3\text{He}$  in the gas cell. The neutron travels through the collimator to the sample where it scatters inelastically to produce a neutron of reduced energy  $n'$  and a gamma photon which is collected by the HPGe detector. The signal from the detector stops the timer while the amplified signal from the detector is stored as a pulse height that is proportional to the absorbed gamma energy. The Time-Of-Flight from the deuteron entering the gas cell to the detection of this photon is also stored.

but the results are very encouraging. We have successfully measured gamma spectra from  $^{12}\text{C}$ ,  $^{16}\text{O}$ ,  $^{40}\text{Ca}$ , Fe, Cu, and some combinations. Thus far the samples have been large to provide a strong signal for developing the instrumentation.

### 3.RESULTS

The first experiment was conducted in July 2003. using a small collimator insert. A neutron beam with 2 mm x3 mm extent was produced at 7.5 MeV but with a low flux of about 10 neutrons per second at a large carbon sample. Three gamma detectors were evaluated: a 10in diameter x 10in high cylinder of NaI, 2) a smaller BGO, and 3) a “10%” efficient HPGe. A spectrum was acquired containing 6.4MeV gamma photons from the de-excitation of the first state in  $^{12}\text{C}$ . The low signal in a large background was a difficulty from the beginning starting at a signal-to-background ratio of 1:1000 and ending at 1:5 as we improved the shielding.

The second experiment was conducted over 6 days in Nov 2003. Here we measured spectra from Fe, Cu, Ca, and C. with better shielding and using the BGO detector, the signal to background was improved to 5:1. The greatest increase was achieved by using a time-of-flight gate to allow gammas to be acquired only in a time window that was consistent with the flight of a neutron from the production cell plus the flight of a gamma from the sample to the detector.

In February 2004, a 3rd experiment was conducted with smaller samples but with a HPGe detector with higher efficiency (60%). Here TOF was used with the HPGe detector . The neutron beam was 6cm x 6cm beam at 7.5 MeV. more neutron flux

Neutron stimulated gammas were detected from samples of Fe, Cu, C, combinations of Fe and Cu, Cu and C, as well as with the Fe sample suspended in 500ml of water. Signal to Background: was dramatically improved to 50:1 as can be seen in the spectra shown below in figures 2 and 3.

The spectrum shown in fig. 2 for gammas emitted from Fe, has no background correction. The contribution of the background is obvious particularly at the lower gamma energies. This spectrum is shown in fig 3 corrected for background by subtracting the normalized sample-out spectrum from the sample-in spectrum. The background under the peaks of interest has been reduced by a large factor. In addition, several peaks associated with naturally occurring radioactive elements in the air and target room were almost completely subtracted out. One example is the large peak at 1460keV that is due to the decay of  $^{40}\text{K}$ . The peak corresponding to neutron stimulated gamma emission from the first excited state in  $^{56}\text{Fe}$  is evident at 847keV.

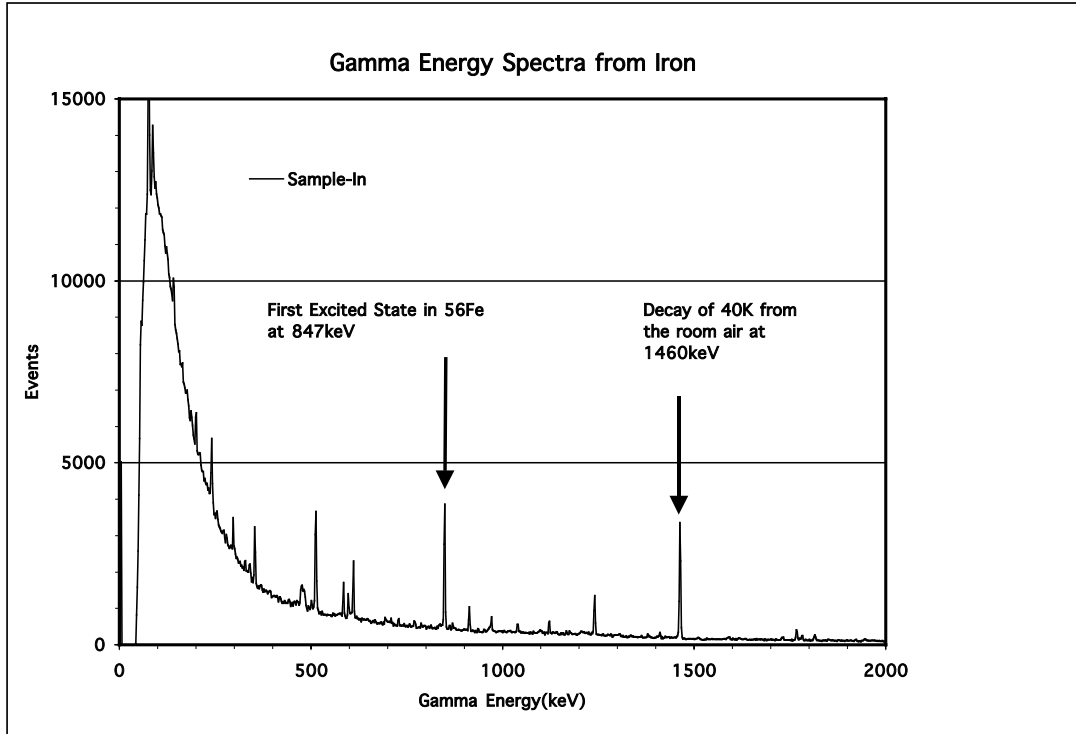


Fig. 2. Spectrum for gamma photons emitted from the iron sample.

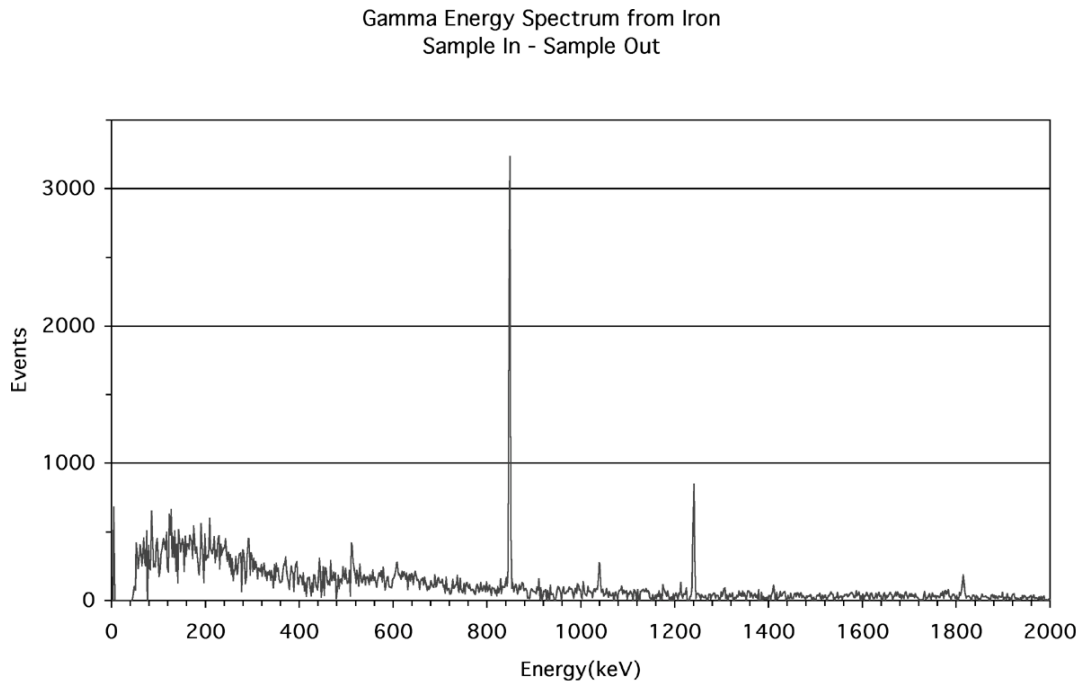


Fig. 3. Spectrum for Fe with the sample-out spectrum subtracted from the sample-in spectrum. Note the dramatic decrease in background especially at lower energies when compared with the non-subtracted spectrum shown in fig. 2 above.

#### 4.DISCUSSION

We have demonstrated a technique for acquiring projection spectra of the decay of excited stable nuclei. By raster scanning the sample and rotation, tomographic projections will be acquired over the spectral range emitted from isotopes of biological interest. While the current state of the technology is not sufficient to support high spatial resolution in such reconstructions, there are no fundamental physical limitations and this resolution can be expected to improve as the process is further developed and refined. Future work will better define the limits of spatial resolution as well as the minimum concentrations of elements that can be formed into an image.

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