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Tissue Analysis Using Mu-Mesic X Rays

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IN VIVO TISSUE ANALYSIS USING MU-MESIC X RAYS

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ABSTRACT

The energies of the mu-mesic x rays emitted when negative muons are captured by atoms of the various elements in tissue are characteristic of the particular element. The yields of x rays can then be used as a measure of the amount of the various elements in the tissue. The x-ray spectra from animal tissues show clearly the spectral series from carbon, nitrogen, and oxygen.

I. INTRODUCTION

It has been pointed out¹ that mu-mesic x rays are potentially useful as a clinical tool to obtain tissue chemical information. The spectrum of x rays emitted when negative muons are captured in tissue provides information about the chemical composition of the tissue.

There are several accelerator laboratories where there will be negative beams of sufficient intensity to be of possible usefulness as a medical diagnostic tool. Those laboratories are LAMPF at Los Alamos, New Mexico; TRIUMF in Vancouver, British Columbia; and SIN near Zurich, Switzerland. Preliminary investigations of chemical analysis with negative muons are being carried out in both Europe and North America.

II. PHYSICAL BACKGROUND

Negative muons are one of the decay products of negative pions which are typically formed as a result of the interaction of protons of energy greater than approximately 300 MeV with nuclei in a stationary solid target. Figure 1 lists the muon mass and lifetime and also illustrates the pion production-pion decay sequence leading to the formation of muons.

Muons have a well-defined range-energy relationship as shown in Fig. 2. For example, a 44-MeV muon has a range of 10 cm in soft tissue. When negative

muons stop in tissue they are captured into a Bohr orbit around a tissue atom as illustrated in Figs. 3 and 4. In this respect the muon acts just as an electron would if it were captured by an atomic nucleus. Figure 4 also illustrates the subsequent process by which the muon cascades down through the energy levels accompanied by emission of mu-mesic x rays whose energies depend on the atomic number of the capturing atom and on the initial and final energy levels involved in the transition.

The Rydberg constant, R , is much larger for muons than for electrons as shown in Fig. 5. For this reason the muonic x-ray energies are typically in the tens to hundreds of keV range. Figure 6 outlines the energy level transition scheme giving rise to the muonic x rays. Figure 7 shows the energies of x rays from selected transitions in some elements commonly found in tissue. A significant fraction of x rays with these energies will be able to escape from the body through several cm of tissue without being absorbed. Figure 8 shows some of the differences between electronic and muonic x rays with regard to their energies and the probability of escape from the body.

The probability that a muon will be captured by a given type of tissue atom, and then undergo a particular energy level transition while cascading down through the Bohr orbits of that atom, is as yet

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incompletely understood, but there is no doubt that it is affected strongly at the atomic number of the atom, by the concentration of the atom, and by the structure of the molecule of which the atom is a part. It is evident then that the spectrum of x rays from transitions in a given type of atom will provide information, although of an indirect nature, about the chemical composition of the tissue, the chemical composition being a measure of the degree of normality or pathology of the tissue. A very simple theory for the probability of capture on a given type of atom is the Fermi-Teller Z-law² which is outlined in Fig. 9. Although this can serve as a guide it is known that in a number of cases it does not correctly predict capture probabilities.

III. FORMATION OF A MUON BEAM

Figure 10 shows the production and subsequent decay of negative pions as an 800-MeV proton beam, such as is available at LAMPF, interacts with a target (typically carbon). At LAMPF the 800-MeV proton beam is produced by the half-mile-long linear accelerator shown in Fig. 11.

The muons produced by pion decay are then collected and transported to and focused at the place where the muons are to be used. This is done with an array of bending and quadrupole magnets. Figure 12 illustrates this process schematically while Fig. 13 shows the layout of magnets for a typical muon channel design. The long straight array of quadrupole magnets is the pion decay section. Figure 14 is a view of the pion decay section of the stopped muon channel at LAMPF.³ Figure 15 is a photograph of an experiment setup at the end of this channel.

IV. EXPERIMENTAL APPARATUS AND TECHNIQUE

Some preliminary work has been done with tissue samples from animals. In these measurements a system of thin scintillation counters is placed in the muon beam to determine when a muon has passed through the counters and stopped in a tissue sample. By recording only those x rays which enter a germanium detector in coincidence with the occurrence of a muon stopping the sample, the x-ray background spectrum is reduced significantly.

Figure 16 shows a proposed system for measuring the muonic x rays from a volume of tissue in the body. The energy characteristics and size of the muon beam are adjusted so that the muons stop in the

organ or volume of tissue of interest. A single germanium detector or a detector array is used to detect the x rays emerging from the body. The spectrum is then recorded for subsequent analysis.

V. RESULTS OF CALCULATIONS AND EXPERIMENTS

Figure 17 lists four groups which have done or are at present involved in measurement of mu-mesic x rays from tissue.

Two spectra from animal tissue measured by Springer et al.⁴ are shown in Fig. 18 (dog liver, normal) and Fig. 19 (dog liver, with tumor). Figure 20 outlines the differences between the spectra from normal dog liver and a liver having tumor tissue. The quantities shown are ratios. For example $[(3 + 1)/(2 + 1)]_p$ stands for the ratio of the number of x rays arising from the $n = 3$ to $n = 1$ muon transition to the number of x rays from the $n = 2$ to the $n = 1$ transition for pathological (p) tissue. It is evident that the ratio of the total number of carbon x rays (ΣC) to the total number of oxygen x rays (ΣO) is significantly different for normal and abnormal tissue.

R. L. Hutson and A. Lundy at LASL took information about the known x-ray response of a 30-cm³ germanium detector, calculated yields from a sample of material whose composition was that of "reference man"⁵ using the Fermi-Teller Z-law, and simulated a measured mu-mesic x-ray spectrum. The resulting spectrum is shown in Fig. 21. Figure 22 outlines the estimated radiation dose delivered to 1 cm³ of soft tissue if enough muons are delivered to that volume to result in 10⁶ oxygen K_α x rays being detected.

Taylor et al.⁶ measured a mu-mesic x-ray spectrum from beef bone. This is shown in Fig. 23. A. Lundy and R. Hutson at LASL calculated the theoretical yields of x rays from several elements in such a sample of bone. Figure 24 shows this calculated spectrum. A quantitative comparison between the measurement and the calculation is shown in Fig. 25. The correspondence between measurement and theory is close enough to lend some credence to the Z-law. However, it is known that the relative yields of x-ray lines from elements can be influenced by the molecular environment of the atom of interest. For example, in Fig. 26, which shows calculated⁷ relative yields of several magnesium

lines both in the metallic form and in MgO, it is seen that the relative yields of x rays arising from the muon transitions from the $n = 3$ to the $n = 2$ level, from the $n = 4$ to the $n = 2$ level, and from the $n = 5$ to the $n = 2$ level differ significantly in the metal and the oxide. Experiments⁸ have also been done with two-element compounds and mixtures and this type of effect has also been observed.

No simple theory exists which can describe the effects on muon transition probabilities of the complex molecular environment in biological systems such as tissue. For this reason it seems evident that much of the useful information which will serve to evaluate the usefulness of mu-mesic x rays as a medical diagnostic tool is going to come from experiment.

At LAMPF the plan is to do initial spectral studies using thin samples of tissue. After the instrumental parameters have been optimized a more systematic study with thin samples will be carried out with the aim of determining whether there are in fact recognizable spectral patterns unique to normal and pathological tissues. After this phase of study animals will be used to start working out the problems of *in vivo* measurements.

Figure 27 shows a pig muscle muonic x-ray spectrum measured recently at LAMPF. This spectrum is the first one taken in the LAMPF program to study the feasibility of the muonic x-ray tissue analysis technique.

VI. DATA ANALYSIS

In order for the mesic x-ray analysis technique to be useful, the spectrum from pathological tissue must be measurably different from a spectrum from normal tissue of the same type. Maximizing the probability of detecting such differences requires that as much information as possible be gotten from a spectrum. One approach is to measure the yield of each of the distinguishable lines in a spectrum and consider these yields, from n lines say, as components of an n -dimensional vector. The spectra from a sample of the normal population would likely define a cluster of points in n -space. A spectrum from an abnormal individual might be expected to fall well outside the normal cluster. In fact, different abnormalities might give rise to separate and unique clusters in n -space, depending on the nature of the abnormality.

VII. POTENTIAL APPLICATIONS

Diagnosis and the monitoring of physiological changes are two broad areas in which mesic x-ray analysis techniques might prove useful. Some suggested diagnostic applications that have been suggested are:

1. Detection of hemochromatosis, a disease involving abnormally high concentrations of iron in the liver.
2. Detection of bone mineral depletion in localized areas that are not amenable to neutron activation or gamma-ray transmission measurements.
3. Detection of abnormally high heavy metal, such as zinc and copper, concentrations which sometimes occur in tumors.

Some physiological changes which might be monitored during the course of disease management include:

1. Chemical changes during wound repair.
2. Early detection of the rejection of tissue transplants.
3. Changes in the amount of calcium phosphate in the heart and lung tissue of people suffering from chronic renal failure.

These potential applications by no means exhaust the possibilities but merely represent a few of the suggestions that have come to our attention.

Several potential advantages of a technique such as mu-mesic x-ray tissue analysis are listed in Fig. 28.

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MUON MASS = 207 m_e

MUON LIFETIME = 2.2 μ s

$P + \text{NUCLEUS} \rightarrow \pi^- + \text{OTHER FRAGMENTS}$

Fig. 1. Properties of muons.

Fig. 2. Muon range in tissue.

Fig. 3. Schematic diagram of a muon stopping in tissue.

Fig. 4. Negative muon capture and energy level transitions in ^{16}O .

$$R_\mu \propto \frac{m_\mu}{1 + \frac{m_\mu}{M_{\text{OXY}}}}$$

$$R_\mu = 204 R_e$$

$$E_{\mu}(2-1)_{\text{OXYGEN}} = 255 E_e(2-1)_{\text{OXYGEN}}$$

Fig. 5. Relationship between electronic and muonic x-ray energies.

Fig. 6. Atomic energy level transitions.

Element	% of Total Body Weight *	$K_{\alpha}(2p-1s)$ Energy (keV)	$L_{\alpha}(3d-2p)$ Energy (keV)
Oxygen	61	133	24.0
Carbon	23	75.9	13.9
Nitrogen	2.6	102	18.9
Calcium	1.4	786	158
Phosphorus	1.1	458	88

* From I.M. Tipton, "Gross and Elemental Content of Reference Man"

Fig. 7. Muonic x-ray energies from the five most abundant elements in tissue.

Fig. 8. Comparison of electronic and muonic Lyman series x-ray energies. The numbers in parentheses are the fractions of x rays which penetrate 10 cm of muscle.

$$P_Z = N_Z Z$$

P_Z - PROBABILITY OF MUON CAPTURE BY ATOM OF ATOMIC NUMBER Z

N_Z - FRACTIONAL NUMBER OF ATOMS OF ATOMIC NUMBER Z

Fig. 9. Fermi-Teller Z-law.

Fig. 10. Pion production by proton-nucleon interaction and muon production by pion decay.

Fig. 11. The Clinton P. Anderson Meson Physics Facility.

Fig. 12. Schematic diagram of the formation of a muon beam.

Fig. 13. Typical muon channel design.

Fig. 14. Pion decay section of the LAMPF stopped muon channel.

Fig. 15. End of LAMPF stopped muon channel with a muonic x-ray experiment in position.

Fig. 16. Schematic diagram of a system for measuring muonic x rays from the human body.

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Fig. 17. List of groups measuring mu-mesic x-ray spectra from tissue.

Fig. 18. Dog liver x-ray spectrum (normal tissue).

Fig. 19. Dog liver x-ray spectrum (with tumor).

Measured ratio of intensity ratios.

Ratio of intensity ratios	carbon (C)	oxygen (O)
1 $\frac{[(3+1)/(2+1)]}{[(3+1)/(2+1)]_n}$	1.01 ± 0.09	0.98 ± 0.03
2 $\frac{[(4+1)/(2+1)]}{[(4+1)/(2+1)]_n}$	1.14 ± 0.17	0.99 ± 0.03
3 $\frac{[(3+1)/(2+1)]}{[(3+1)/(2+1)]_n}$	-	1.03 ± 0.06
4 $\frac{[(2\text{ C})/(2\text{ O})]}{[(2\text{ C})/(2\text{ O})]_n}$	0.75 ± 0.04	

SUBSCRIPT P DENOTES PATHOLOGICAL TISSUE (LIVER TUMOR)

SUBSCRIPT N DENOTES NORMAL TISSUE

DATA OF H. DANIEL, H.-J. FREYER AND K. SPRINGER (PERSONAL COMMUNICATION).

Fig. 20. Comparison of mu-mesic x-ray spectra from normal dog liver and dog liver with a tumor.

Fig. 21. Simulated muonic x-ray spectrum from "standard man."

	QUALITY FACTOR ¹	REMS
DIRECT MUON DOSE = 45 RADS X	3	135
MUON DECAY DOSE = 2.9 RADS X	1	2.9
NUCLEAR EMISSION DOSE = 3.5 RADS X	7	24.5
		162.4 REMS

Fig. 22. Total estimated dose in a 1 cc tissue volume if 10^6 counts are accumulated in the oxygen K_{α} line.

FROM: M. C. TAYLOR, L. COULSON, AND G. C. PHILLIPS
RADIATION RESEARCH 54, 335-342 (1973).

Fig. 23. Mu-mesic x-ray spectrum from cortical bone.

Fig. 24. Simulated muonic x-ray spectrum from cortical bone. (Based on a bone absorption path of 1 cm, soft tissue absorption of 5 cm, and the gamma response of a 30 cc Ge(Li) detector.)

Fig. 26. Calculated mu-mesic x-ray spectrum from magnesium metal.

Fig. 25. Relative mu-mesic x-ray yields from bone.

Fig. 27. Mu-mesic x-ray spectrum from pig muscle.

1. NON-INVASIVE
2. X-RAY SPECTRUM IS SENSITIVE TO BOTH ELEMENTAL COMPOSITION AND MOLECULAR PROPERTIES OF TISSUE
3. CAPABILITY OF STUDY OF SMALL, LOCALIZED TISSUE VOLUME

Fig. 28. Potential advantages and properties of mesic x-ray "tissue analysis" technique.