Measurement of Blood Flow through Proton Activation of Positron Emitting Tracers

by

Thomas James Miller, Jr.

B.S. with Honors, University of Lowell (1979)

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

June 1981

© Thomas J. Miller, Jr. 1981

The author hereby grants to M.I.T. permission to reproduce and to distribute copies of this thesis document in whole or in part.

Signature of Author

Department of Nuclear Engineering

May 1, 1981

Certified by

Gordon L. Brownell
Thesis Supervisor

Accepted by

Allan F. Henry
Chairman, Departmental Committee on Graduate Students

ARCHIVES

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

JUL 27 1981

LIBRARIES
Measurement of Blood Flow through Proton Activation
Of Positron Emitting Tracers

By
Thomas James Miller, Jr.

Submitted to the Department of Nuclear Engineering
On May 1, 1981 in partial fulfillment of the
Requirements for the Degree of Master of Science

ABSTRACT

The transport of in-vivo proton activated tracers from the thigh of a number of mice has been monitored using a sodium iodide coincidence detection apparatus. A simple biological model was then applied to the wash-out of these tracers from the activated thigh region so that the blood flow in the thigh could be quantified. A number of rudimentary calculations and experiments were performed in order to determine the uncertainties and reproducibility of this technique for the measurement of blood perfusion in a proton irradiated region.

Thesis Supervisor: Dr. Gordon L. Brownell
Title: Professor of Nuclear Engineering
DEDICATION

This thesis is dedicated to my father, Thomas J. Miller, Sr.
ACKNOWLEDGEMENTS

I would like to express my gratitude to all of the people, in both the academic and personal aspects of my life, who helped me to complete this work. My parents, of course, deserve the majority of credit for getting me to this point in my life with my sister Eleanor and friend and advisor Gil Brown unknowingly serving as role models. Dr. Carl von Essen gets credit for introducing me to this exciting field and giving me the opportunity to explore it at SIN with the patient help of Eros Pedroni, Miriam Salzmann and Hans Blattmann.

My main source of inspiration during the time of this work came from Michael Goitein who has provided me with invaluable advice and assistance and whose expectations I hope someday to be able to meet. My thesis supervisor, Gordon Brownell, also provided me with his precious time and advice whenever it was needed.

Danny Doseretz and Sten Gräffman became both friends and advisors during this time and were always successful in persuading me to run more experiments. Richard Abrams assisted me at all hours and at all times and should share equally in any glory, infamy, or obscurity which results from this work.

I must not forget to mention Bengt Bjarngard who performed the most important service of all; finding the money for my support during this time.
My friends deserve mention for always being around when I needed them especially Robert who is always ready to listen and help and Charlie and Gilda for providing me with an impenetrable sanctuary in which I could escape all of science and academia.

Finally, I must thank my wife Susan who deserves sainthood for putting up with me and whose understanding, sympathy, and love were principally responsible for making this work enjoyable.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title Page</td>
<td>1</td>
</tr>
<tr>
<td>Abstract</td>
<td>2</td>
</tr>
<tr>
<td>Dedication</td>
<td>3</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>4</td>
</tr>
<tr>
<td>Table of Contents</td>
<td>6</td>
</tr>
<tr>
<td>List of Figures</td>
<td>8</td>
</tr>
<tr>
<td>List of Tables</td>
<td>10</td>
</tr>
<tr>
<td>Chapter I</td>
<td></td>
</tr>
<tr>
<td>Introduction</td>
<td>12</td>
</tr>
<tr>
<td>I.1 Introduction</td>
<td>12</td>
</tr>
<tr>
<td>I.2 Background and Previous Work</td>
<td>14</td>
</tr>
<tr>
<td>I.3 Rationale</td>
<td>20</td>
</tr>
<tr>
<td>I.4 Objectives</td>
<td>22</td>
</tr>
<tr>
<td>Chapter II</td>
<td></td>
</tr>
<tr>
<td>Biological Considerations</td>
<td>23</td>
</tr>
<tr>
<td>II.1 Standard Blood Flow Measurement Techniques</td>
<td>23</td>
</tr>
<tr>
<td>II.2 Mathematical Model for Clearance of Activated Nuclei</td>
<td>28</td>
</tr>
<tr>
<td>II.3 Discussion of the Limiting Assumptions in the Mathematical Model</td>
<td>35</td>
</tr>
<tr>
<td>Chapter III</td>
<td></td>
</tr>
<tr>
<td>Physical Considerations</td>
<td>42</td>
</tr>
<tr>
<td>III.1 Probable Proton-Tissue Nuclei Reactions</td>
<td>42</td>
</tr>
<tr>
<td>III.2 Theoretical Calculation of Activity Production</td>
<td>46</td>
</tr>
<tr>
<td>III.3 Curve Fitting</td>
<td>49</td>
</tr>
<tr>
<td>III.4 Statistical Error Analysis</td>
<td>55</td>
</tr>
<tr>
<td>III.5 Theoretical Variation of Statistical Error with Dose</td>
<td>58</td>
</tr>
<tr>
<td>III.5.1 Introduction</td>
<td>58</td>
</tr>
</tbody>
</table>
### Chapter IV

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV.1</td>
<td>Introduction</td>
<td>72</td>
</tr>
<tr>
<td>IV.2</td>
<td>Coincidence Detection Apparatus Set-Up</td>
<td>74</td>
</tr>
<tr>
<td>IV.3</td>
<td>Proton Current and Dosimetry Calibrations</td>
<td>82</td>
</tr>
<tr>
<td>IV.3.1</td>
<td>Introduction</td>
<td>82</td>
</tr>
<tr>
<td>IV.3.2</td>
<td>Proton Energy Measurement</td>
<td>84</td>
</tr>
<tr>
<td>IV.3.3</td>
<td>Dose Calibration of Ion Chambers with Faraday Cup</td>
<td>89</td>
</tr>
<tr>
<td>IV.3.4</td>
<td>Estimation of Uncertainties in Dose Measurement</td>
<td>93</td>
</tr>
<tr>
<td>IV.4</td>
<td>Measurement of Activity Produced in Phantoms</td>
<td>96</td>
</tr>
</tbody>
</table>

### Chapter V

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>V.1</td>
<td>Introduction</td>
<td>104</td>
</tr>
<tr>
<td>V.2</td>
<td>Description of Experimental Apparatus and Procedure</td>
<td>106</td>
</tr>
<tr>
<td>V.3</td>
<td>Experiment A - Analysis of Decay in Live vs Dead Mice</td>
<td>112</td>
</tr>
<tr>
<td>V.4</td>
<td>Experiment B - Analysis of Decay in Anesthetized Mice</td>
<td>121</td>
</tr>
<tr>
<td>V.5</td>
<td>Experiment C - Reproducibility of Blood Flow Measurement</td>
<td>131</td>
</tr>
<tr>
<td>V.6</td>
<td>Experiment D - Analysis of Decay in Tourniqueted Mice</td>
<td>138</td>
</tr>
</tbody>
</table>

### Chapter VI

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>VI.1</td>
<td>Introduction</td>
<td>142</td>
</tr>
<tr>
<td>VI.2</td>
<td>Further Work</td>
<td>144</td>
</tr>
</tbody>
</table>

### Appendix

<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Computer Programs</td>
<td>146</td>
</tr>
<tr>
<td>References</td>
<td>186</td>
</tr>
<tr>
<td>Figure</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-------------</td>
</tr>
<tr>
<td>III.5.1</td>
<td>Imaginary Experimental Arrangement Simulated by Program FAKEDATA</td>
</tr>
<tr>
<td>III.5.3.1</td>
<td>Plot of Variation of Statistical Uncertainty with Dose</td>
</tr>
<tr>
<td>IV.2.1</td>
<td>Coincidence Detection Apparatus</td>
</tr>
<tr>
<td>IV.2.2</td>
<td>Diagram of Na-22 Source Movement used to Determine Spatial Sensitivity</td>
</tr>
<tr>
<td>IV.2.3</td>
<td>Plot of Spatial Sensitivity Along the Detector Axis</td>
</tr>
<tr>
<td>IV.2.4</td>
<td>Plot of Spatial Sensitivity Perpendicular to the Detector Axis</td>
</tr>
<tr>
<td>IV.3.1</td>
<td>Proton Scatterer and Aperture Arrangement with Beam Energy Measurement Apparatus in Place</td>
</tr>
<tr>
<td>IV.3.2</td>
<td>Plot of the Results of the Ionization vs Depth Measurement</td>
</tr>
<tr>
<td>IV.3.3</td>
<td>Placement of Faraday Cup and Thimble Ion Chamber</td>
</tr>
<tr>
<td>IV.4.1</td>
<td>Irradiation Set-Up for Measurement of Activity vs Depth</td>
</tr>
<tr>
<td>IV.4.2</td>
<td>Plot of O-15 Activation vs Depth</td>
</tr>
<tr>
<td>IV.4.3</td>
<td>Plot of C-11 Activation vs Depth</td>
</tr>
<tr>
<td>V.2.1</td>
<td>Schematic of Data Collection and Analysis Process</td>
</tr>
<tr>
<td>V.2.2</td>
<td>Mouse Irradiation Apparatus</td>
</tr>
<tr>
<td>V.2.3</td>
<td>X-Ray Positioning Set-Up</td>
</tr>
<tr>
<td>V.3.1</td>
<td>Decay Curve from the Thigh of a Dead Mouse</td>
</tr>
<tr>
<td>Figure</td>
<td>Description</td>
</tr>
<tr>
<td>----------</td>
<td>------------------------------------------------------------------</td>
</tr>
<tr>
<td>V.3.2</td>
<td>Decay Curve from the Thigh of a Live Mouse</td>
</tr>
<tr>
<td>V.3.3</td>
<td>Plot of a Mono-Exponential Wash-Out Curve from a Live Mouse</td>
</tr>
<tr>
<td>V.5.1</td>
<td>Plot of Blood Flow Measurement Reproducibility</td>
</tr>
</tbody>
</table>
LIST OF TABLES

Table III.1.1 Elemental Composition of Standard Man..................43
Table III.1.2 Data for Products of Proton Reactions with
Oxygen and Carbon..............................................44
Table III.5.3.1 Table of the Variation in Statistical Uncertainty
with Changes in Functionally Dependant Parameters...70
Table IV.3.4.1 Estimated Uncertainties in Faraday Cup Dosimetry....95
Table V.3.1 Physical Data from the Activation and Decay
of Dead Mice.........................................................114
Table V.3.2 Physical Data from the Activation and Decay
of Live Mice.........................................................117
Table V.3.3 Results of Blood Flow Analysis in Live Mice........117
Table V.4.1 Physical Data from the Activation and Decay
of Anesthetized Mice (50 rads).................................122
Table V.4.2 Physical Data from the Activation and Decay
of Anesthetized Mice (100 rads)...............................123
Table V.4.3 Physical Data from the Activation and Decay
of Anesthetized Mice (150 rads)................................124
Table V.4.4 Results of Blood Flow Analysis in Anesthetized
Mice (50 rads).....................................................126
Table V.4.5 Results of Blood Flow Analysis in Anesthetized
Mice (100 rads)..................................................127
Table V.4.6 Results of Blood Flow Analysis in Anesthetized
Mice (150 rads)..................................................128
Table V.4.7 Average Blood Flow Measurement Results from
Anesthetized Mice.................................................129
<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>V.5.1</td>
<td>Physical Data from the Activation and Decay of a Stationary Mouse</td>
<td>132</td>
</tr>
<tr>
<td>V.5.2</td>
<td>Results of Blood Flow Analysis in a Stationary Mouse</td>
<td>133</td>
</tr>
<tr>
<td>V.5.3</td>
<td>Physical Data from the Activation and Decay of a Stationary Mouse Irradiated with Different Doses</td>
<td>136</td>
</tr>
<tr>
<td>V.5.4</td>
<td>Results of Blood Flow Analysis in a Stationary Mouse Irradiated with Different Doses</td>
<td>137</td>
</tr>
<tr>
<td>V.6.1</td>
<td>Physical Data from the Activation and Decay of a Tourniquet Mouse</td>
<td>139</td>
</tr>
<tr>
<td>V.6.2</td>
<td>Results of Blood Flow Analysis in a Tourniquet Mouse</td>
<td>140</td>
</tr>
</tbody>
</table>
CHAPTER I: INTRODUCTION

Section I.1 Introduction

Protons have been used in the radiotherapy of solid tumors due to their favorable dose distribution. The interaction of protons with matter produces a characteristic Bragg peak of energy deposition near the end their range. In addition, except for a small discrepancy due to range straggling, all of the protons in a monoenergetic beam will come to a stop at a well defined endpoint. For these reasons, a beam of charged particles such as protons will allow a precise and controllable deposition of dose so as to maximize the radiation dose to the tumor volume and avoid adjacent radiosensitive healthy structures.

Although the majority of protons interact with atomic electrons resulting in ionizations and excitations of the molecular species along their path, a small percentage of protons interact with tissue nuclei producing reactions which result in in-vivo activated positron emitters. A fraction of these positron emitting tracers will be transported away from the region of activation at a rate that is proportional to the rate of blood flow through the region.

A positron that is emitted from an activated tissue nucleus will, within a very short distance, interact with an atomic electron. The result of this interaction is the annihilation of the positron-electron pair producing a pair of photons each with an energy of one rest mass of an electron (0.511 MeV) and traveling away from each other at an angle which is approximately 180 degrees. By placing two detectors facing each other on opposite sides of the activated
volume and counting the pulses which occur in both detectors simultaneously, one can monitor the decay of the positron emitting isotopes.

The time dependence of the number of counts received in the above manner will be a function of two processes; the physical decay half-life of the isotopes involved and, the decrease in counts due to the transport of the activated nuclei out of the area between the two detectors where, if a decay occurs, it will not be observed.

By knowing the decay constants associated with the physical decay of the activated tissue nuclei, one can subtract this component of the decay leaving only the decay due to biological wash-out. This can then be related to the blood flow in the irradiated region.

This method has been used to measure the blood flow in the thigh of a number of mice. The method is reproducible, and gives values for blood flow that are within the range of values measured by other methods.
Section I.2 Background and Previous Work

Charged particle activation analysis was first used in 1938 by Seaborg and Livingood at Berkeley. Since then, charged particle activation has mostly been applied to low Z elements which present some difficulties for neutron activation methods.

The majority of work in the field of activation analysis as a biologic tool has been with the use of neutrons. In vivo activation analysis using neutrons has been and in primarily being used to determine the whole body concentrations of elements such as sodium, chlorine, and calcium.

The use of charged particle activation analysis in vivo has been relatively rare. There are, however, three groups of investigators whose work has provided much of the background material supporting this thesis. The first of these studies is that of Graffman and Jung which was performed at the University of Uppsula in Sweden (Graffman, S., et.al., Acta Radiologica 14: 113-126, 1975). In this study, mice were irradiated with protons to determine the extent of activation of the different radionuclides and the subsequent biochemical fate of some of these radionuclides.

The first finding of the Uppsula study was that the primary activated radionuclides were the positron emitters O-15 and C-11. This was the expected result in view of known reaction cross sections and the elemental composition of the target mice.
A series of physiological studies were then performed in the attempt to quantitate the fraction of induced C-11 which was eliminated by the lungs and the kidneys. The combination of those two sources yielded an elimination fraction of about 3%. The half lives for removal by various physiological means were measured to be between 10 and 17 minutes.

Another important conclusion of this study was the measurement of O-15 activity transported from the irradiation site. By irradiating only the upper or lower half of live mice and killing them after preselected intervals by immersion in liquid nitrogen and then counting both the irradiated and non-irradiated halves, the redistribution of O-15 could be determined. It was found that 60% of the induced O-15 activity was distributed from the irradiation site throughout the body within 5 minutes after irradiation.

The next contribution was a series of studies made by Bennett at Brookhaven National Laboratory in New York (Bennett, G.W., et. al., Nucl. Inst. Methods 125: 333-338, 1975 and Bennett, G.W., et. al., Science 200: 1151-1153, 1978). The goal of this work was to determine if the distribution of activated positron-emitting radionuclides could be used to visualize, with a suitable positron camera, the position of a proton beam being used in therapy. In this case, the redistribution of activated radionuclides posed a problem in that it blurs the visualization of the initial activation distribution. The experiments were designed to determine to what extent biological redistribution would degrade the determination of the position of the proton beam.
From this series of experiments came the supporting conclusion that O-15 and C-11 were the principle components of induced activity by medium energy protons. Measurements of activity vs residual proton range in phantoms and tissue were made as a confirmation of the expected values that could be calculated with a knowledge of elemental composition and cross sections. Much of the initial physical experimental work contained in this thesis was patterned after the experimental procedure of the Brookhaven studies.

In addition to the physical groundwork performed by Bennett and colleagues, some experimentation was accomplished in order to measure the half-life of biologic redistribution in mice. Unfortunately, the quantitation of this half life was impossible due to the time it took for the transportation of the irradiated mice to the counting area and their subsequent immobilization. It could be stated however, that the washout that did occur had a very short lifetime (less than two minutes).

The single work providing the major impetus for this thesis was that of Hughes, Nussbaum, et. al. (Hughes, W.I., Nussbaum, G.H., et. al., Science 204: 1215-1217, 1979). This study, performed at the Tufts New England Medical Center, measured the rate of tissue perfusion from the transport of O-15 activated by 45 million volt x-rays.

Photon activation of positron emitters in tissue as measured by this study was shown to produce primarily the same two nuclei as do protons; namely O-15 and C-11. It was suggested in this study, that the major component of biologic removal of these radioisotopes is due
to the removal of O-15 incorporated into tissue water. This is somewhat supportive of the data received by the Uppsula study.

Assuming the above assumption is correct, the time dependence of positron decay from an irradiated tissue volume should consist of three components: two components due to the physical decays of O-15 and C-11 and the biological wash-out decay due to the removal of O-15 in the form of labeled tissue water. The group at Tufts irradiated the brain of a cat with photons and monitored the region with two NaI crystals in coincidence. The decay curve thus received contained the predicted three components, and the single decay curve due to washout could be isolated by a curve-fitting/curve-peeling technique.

The ability to isolate a single decay component of biologic removal allowed the investigators to use tracer wash-out modeling techniques that were developed for the nuclear medical method of the injected local clearance of a tracer (see section II.2). The decay constant for the wash-out of a single compound is equal to the blood flow divided by the imaged volume multiplied by a constant reflecting the permeability of that compound. For water, the value of this constant is about unity (see section II.3). In this manner, by determining the decay constant of the wash-out of the photon or proton activated nuclei, one may easily quantitate the value of the blood flow through the irradiated and monitored region.

The primary results obtained by Hughes, Nussbaum, et. al. were that about 63% of the induced O-15 activity washed out of the imaged volume which corroborates the findings of the Uppsula study. A value was also obtained for the cerebral blood flow in a cat which was
within the range found by other methods.

Although the method of quantifying blood flow by activation analysis developed by Hughes, Nussbaum, et. al. is that employed in this thesis using protons as the means of activation, there is some evidence that this model may be too simplistic.

It must be remembered that, using the above approach, the implicit assumption is that the form of the removed nuclei is O-15 incorporated into tissue water. There exists some evidence in addition to that uncovered in this thesis that this assumption may not be totally valid.

The first piece of evidence is that, in the Uppsula study, C-11 was shown to be mobile although with a longer half-life than that for mobile O-15. This is supported by work on the wash-out of pion activated positron emitters C-11 and N-13 performed at Los Alamos (Hogstrom, K. R., and Rosen, I. I., Phys. Med. Bio. 25: 927-932, 1980) C-11 was shown to wash out of different tissues with half lives of from 38 to 60 minutes.

The fact that C-11 is indeed mobile will not, however, influence the measured blood flow by O-15 wash-out appreciably if the half-life is relatively slow. The initial decay signal will only be slightly influenced by this smaller component.

Another problem introduced by the measurements of Hughes and Nussbaum is that there was a twenty second interval between completion of activation and the beginning of the counting period. In addition, the counting interval was twenty seconds long. These two factors may
have served to mask the existence of a multi-component 0–15 wash-out. There were no determinations of time or activation rate effects, nor were experimental or statistical uncertainties reported.

In spite of these questions, the use of protons to measure blood flow will be performed in an analogous manner to the technique developed by Hughes, Mussbaum, et al. Certain improvements in counting techniques and statistical analysis should begin to answer many of the questions which were raised in the use of photon activation to measure blood flow.
Section I.3 Rationale

The application of proton activation of positron-emitting tracers as a technique to measure blood flow may be primarily used to study blood flow in proton radiotherapy patients. This may yield some valuable information about tumor physiology which may be useful during the course of treatment.

It is a well known fact in radiation biology that cells existing in hypoxic environments are more radioresistant than cells having a normal oxygen supply. Since blood is the primary route of oxygen supply to tissues, tumors that are in part or in total poorly vascularized may have malignant cells which are living under hypoxic conditions. If these tumors are to be treated with radiation, this fact may have great bearing upon tumor response to treatment. It may be true that the increased radioresistance of a poorly vascularized portion of a tumor requires an increased radiation dosage to that region or possibly treatment by an altogether different modality of cancer therapy.

The knowledge of the blood supply to a tumor is thus seen to be of great import. The question which must now be asked is whether the use of this particular proton activation technique will have any advantages over conventional blood flow measurement techniques (see section II.1).

There are two immediately obvious benefits to be gained through the use of this technique. The first is that this method is both non-invasive and non-perturbing to the tumor system in that the
radiation was already to be delivered for therapeutic reasons. The second apparent benefit is that with the activation analysis technique, it is possible to place a uniform distribution of radioactive tracer in a region where the perfusion may be very low. This is not possible with conventional nuclear medical uptake techniques and limits the ability of conventional techniques to quantitate blood flow in regions of low perfusion in highly perfused surroundings. The signal from the slightly perfused region may be lost with an uptake method but with the activation method, the activity may be placed in the areas of low perfusion alone thus eliminating the noise from any surrounding areas of high perfusion.

Although the proton activation technique will probably be primarily applied to the investigation of the extent of and/or change in tumor perfusion during the course of proton radiotherapy, with further work, it may be possible to improve the technique so that it may be applicable to the measurement of blood flow in inaccessible areas of low perfusion. As a diagnostic tool, proton activation could be very promising if the radiation dose needed for a measurement was acceptable. If more sensitive detectors were used and the geometry optimized, proton activation could become a very powerful procedure for research and diagnosis.
Section I.4 Objectives

The development of the method of proton activation for the quantitation of blood flow into a tool usable in any tissue region and with great accuracy is well beyond the scope of this work. It is our desire only to investigate some of the most rudimentary parameters of importance to the development of this technique and to set up some basic experiments to prove its feasibility. The objectives of this study can thus be summarized:

1) To investigate the ability to detect proton activated positron emitting nuclei in phantoms and tissues with a simple coincidence counting apparatus.

2) To determine if the detection of the transport of these activated nuclei in living tissue is possible with reasonable uncertainty.

3) To apply a simple biological model to the rate of nuclei transport in order to quantitate blood flow within an activated tissue region.

4) To determine the uncertainties in the magnitude of the obtained values of blood flow and the reproducibility of the measurements.
CHAPTER II: BIOLOGICAL CONSIDERATIONS

Section II.1 Standard Blood Flow Measurement Techniques

In order to thoroughly discuss the technique of activation analysis used to measure blood flow, a background of alternate blood flow measurement techniques must first be presented. It should be remembered that, in using this activation analysis technique, blood flow in tissues is to be measured. For this reason, techniques of measuring blood flow in individual vessels will not be mentioned.

In comparing the relative merits of blood flow metering devices, it may be useful to keep in mind some of the following desirable attributes:

1. It should be fairly non-invasive

2. The technique should not be tissue specific

3. Use of the technique should not alter the normal flow of blood

4. It should give an absolute value of volume flow

One commonly used blood flow measuring technique is polarography. Polarography depends on the oxidation of an indicator at a platinum electrode inserted into the tissue where the blood flow is to be measured. The indicator is supplied by the blood stream and thus, the quantity oxidized should be proportional to the blood flow.
Two types of polarograph probes are commonly used. One is based upon the current produced when molecular hydrogen is oxidized to hydrogen ions at the surface of the platinum electrode. The other type of probe uses oxygen as the indicator with the oxidizing electrode being manufactured of platinum with a palladium coating. The currents measured by the probes in either case are linearly related to blood flow.

Problems arise with the polarograph technique when the partial pressure of the indicator (hydrogen or oxygen) is low. In this case, stray potentials from other oxidation-reduction reactions may interfere producing erroneous results. Another limitation of this technique is that the use of a small probe (1-5 microns in diameter) will give only a measure of a very local blood flow rather than an average over some defined tissue volume. This may limit the reproducibility of this technique. It may also be true that the act of inserting the probe perturbs the flow locally (Woodcock, J.P., Theory and Practice of Blood Flow Measurement, Butterworth and Co., London, 1975).

Another method of measuring tissue blood flow is plethysmography. Although there are many types of plethysmography, they are all based upon the technique of occluding the venous return of a limb or organ and measuring the swelling that occurs as a result of arterial inflow. The assumptions and limitations of plethysmography appear to be well known (Woodcock, J.P., Theory and Practice of Blood Flow Measurement, Butterworth and Co., London, 1975). Its main limitation is that, without surgery, it is confined to measuring blood flow in the limbs.
and extremeties or areas of those limbs and extremities where venous occlusion may most easily be affected by the use of a pressure cuff.

Heat clearance probes may also be used to measure tissue blood flow. These probes depend upon changes in thermal conductivities of tissues resulting from changes in blood flow. The primary disadvantage of this technique is that only relative flows, not volume flows can be measured. In addition, accuracy can be effected by the size of the blood vessels located in the vicinity of the probe rather than merely the amount of flow in all vessels near the probe.

The above-mentioned techniques comprise the majority of techniques not using radioactive indicators. All of the radioisotopic indicator techniques may be separated into three categories:

1. Those that measure blood flow by the amount of indicator transported to a region.

2. Those that measure blood flow by the amount of indicator remaining within a region under equilibrium flow conditions.

3. Those that measure blood flow by the clearance rate of indicator from a tissue region.

Each of the radioactive indicator techniques typically use a scintillation counter or an array of such detectors to monitor the change in indicator concentration within the region of interest as a function of time. The indicators are principally injected but sometimes are inhaled or ingested to supply the tissue region.
In order to extract a quantitative estimate of blood flow from the time dependent counting information that is received from the detectors, a model must be constructed of the blood flow dependent transport of the indicators. The basis of a majority of these models will be discussed in the following section. In particular, the transport model that is to be used for the activation analysis technique will be derived.

There have been many problems cited in the literature with the use of conventional radioisotopic indicator techniques. One of the most frequently raised clinical objections is the need to puncture arteries supplying the region, sample venous outflow, or inject indicator directly into the region of interest. In order to overcome these limitations, there has been an increasing interest in using the method of continuous inhalation of $^{15}$-O$_2$, $^{15}$-O, and $^{15}$-O$_2$ (Subramanyam, P., Brownell, G.L., et al., J. Nucl. Med. 19: 48:53, 1978).

There are, however, a few disadvantages to using this positron imaging technique. One disadvantage is that there is an increased complexity in the modeling needed to extract the blood flow information due to the effects of oxygen extraction and metabolism at the site. The need to know oxygen extraction fractions and metabolism parameters has limited this technique primarily to measurements of cerebral blood flow where these parameters are fairly constant for this relatively homogeneous organ.
Another problem common to the intravascular injection or inhalation of radiopharmaceuticals is their inability to quantitate blood flow in areas of poorly perfused tissues. Substantial contamination of the signal from the poorly perfused region of interest by surrounding regions of high blood flow has often limited these techniques (Heymann, M.A., et. al., Prog. in Cardiovas. Diseases 20: 55-79, 1977).

In the case of the local clearance method where an indicator is injected directly into the tissue region of interest, the above stated limitation is not a concern. However, the increased pressure in the extracellular fluid volume resulting from the injection may affect the measured value of blood flow. The role of the volume injected is apparent from the results of Warner (Warner, G.F., et. al., Circulation 8: 732-734, 1965) who, using Na-24 as indicator, found steeper clearance curves with smaller injection volumes in resting muscle.

These effects are not present in the proton activation analysis technique and applying the mathematical treatment of local clearance. Other advantages and disadvantages of activation analysis for the measurement of blood flow will become apparent in later sections.
Section II.2 Mathematical Model for Clearance of Activated Nuclei

In this section, the mathematical model to be used to extract a value of blood flow (in ml/min/100 grams tissue) from the clearance of proton activated nuclei from a tissue region will be derived. The rather simple model which is used is developed from the basic concepts used in modeling almost all of the radioactive tracer transport techniques.

Most of the radioisotopic indicator techniques for the measurement of blood flow rely to some extent upon the Fick principle. Fick, in 1870, stated that cardiac output could be measured from known concentrations of O2 and CO2 in arterial and mixed venous blood and the uptake of O2 and the release of CO2 by the lungs in a fixed period of time. This was a concept which could be applied to any substance carried by the blood stream and for any region in which blood flow is to be measured. Thus, a conservation equation may be written for any indicator transported into and/or away from a region of interest.

The amount of any substance Qi transported into a region in time \( \Delta t \) must be equal to the quantity stored Qi during \( \Delta t \), plus the quantity converted into another substance Qm (if any), plus the amount transported away from the region Qo:

\[
\frac{Q_i}{\Delta t} = \frac{Q_s}{\Delta t} + \frac{Q_m}{\Delta t} + \frac{Q_o}{\Delta t} \tag{II.2.1}
\]
If 02 is the indicator; in steady state the accumulation is zero and blood is the only source of supply and removal. If the arterial and venous flow rates are constant at F ml/min, and if Ca is the concentration of the indicator in the arterial system delivered to the region and Cv is the concentration of the indicator in the venous system leaving the region then:

\[ F(Ca-Cv) = \frac{Qm}{\Delta t} \]  \hspace{1cm} (II.2.2)

The above is known as the Fick equation.

From the single concept of the Fick equation, one may derive the relationships which are used in many of the radioisotopic indicator techniques.

For an equilibrium measurement where samples of arterial and venous blood may be obtained (as in the measurement of cerebral blood flow using the inert indicator Kr-79) the Fick equation may be used almost directly:

\[ \frac{dQr}{dt} = F(Ca-Cv) \] \hspace{1cm} (II.2.3)

where \( dQr/dt \) is the biological component of the decay of the quantity of indicator in the region of interest as measured by a NaI detector.
It may be the case that one wishes to measure blood flow in a small tissue region but cannot sample venous outflow. In this instance, the Fick equation should be rewritten in terms of the concentration of the indicator in the region of interest, Cr, as:

\[
\frac{dQ_r}{V_r dt} = \frac{dCr}{dt} = \frac{Fr}{V_r} (Ca-Cvr)
\]  

(II.2.4)

where \( V_r \) is the volume of the region of interest and \( Cvr \) is the concentration of the indicator in the venous system in the region of interest.

Cvr can be eliminated from the above equation in the following manner: Let D denote the extent to which diffusion equilibrium for a particular inert substance is achieved between blood and tissue during the passage from the arterial to the venous end of the capillary, and let \( Pr \) denote the tissue-blood partition coefficient for the substance, then:

\[
Ca-Cvr = D(Ca-Cr/Pr)
\]  

(II.2.5)

By substitution into equation (II.2.4) we have:

\[
\frac{dCr}{dt} = \frac{FrD}{V_r} (Ca-Cr/P) ; \quad P=Pr=Cr/Cvr
\]  

(II.2.6)
which can be written:

\[
\frac{dCr}{dt} = \frac{FrD}{VRP}(PCa-Cr) \quad (II.2.7)
\]

We may now apply the above differential equation to the local clearance method which is the method applicable to the wash-out of activated tissue nuclei. Conventionally, the local clearance method consists of the injection of a radioactive indicator directly into the region where blood flow is to be measured. The wash-out of the indicator is then monitored by a detector placed over the region. This is quite similar to the proton activation method under study. Instead of injecting the radiopharmaceutical using a hypodermic needle, the indicator is "injected" via the proton beam. The region is then monitored for clearance by the coincidence counting apparatus.

Since there is no arterial supply of indicator in the local clearance method, \( Ca=0 \) in the above expression (II.2.7). If we then say that at time \( T=0 \) the concentration in the region \( Cr \) is known and is equal to \( Cro \) then the solution to the above differential equation is:

\[
Cr(t) = Cro e^{-\lambda rt} \quad (II.2.8)
\]
where:

$$\lambda r = \frac{FrD}{VrP} \quad (I.I.2.9)$$

For other methods, one could have a constant arterial supply in which case:

$$Cr(t) = PCa(1 - e^{-\lambda rt}) \quad (I.I.2.10)$$

If the arterial supply is variable but equal to zero at time T=0 as would be the case if there were much recirculation of a locally injected indicator then:

$$Cr(t) = P\lambda r e^{-\lambda rt} \int_{0}^{t} Ca e^{\lambda rt} dt \quad (I.I.2.11)$$

If equation (I.I.2.8) is the governing equation for the biologic removal of an indicator injected or created in the region of interest, then one can easily write the equation for the total decay of a indicator activated locally. One can see that equation (I.I.2.8) has the same form as an exponential decay due to physical processes. The decay that will be "seen" by the detectors will be the sum of the biological decay or removal process and the physical decay process. As an example, if only one radioisotope is injected into a tissue
region, then, the decay of the number of counts observed by a detector will be given by:

\[ C(t) = C_{bo} \lambda_b t + C_{po} \lambda_p t \]  \hspace{1cm} (II.2.12)

where \( C_{bo} \) is the initial number of counts from the biologic component \( C_{po} \) is the initial number of counts from the physical decay component, \( \lambda_p \) is the decay constant of the biologic wash-out containing the blood flow information as mentioned above, and \( \lambda_p \) is the physical decay constant from the radioisotope.

If there are two radioisotopes being cleared from the region of interest, then another exponential component is added to the sum. As will be shown in a later section, in using protons to "inject" or activate radioisotopes in a tissue volume one activates primarily the two positron emitters O-15 and C-11. Thus, using activation analysis by protons, the governing equation for the number of coincidence counts seen as a function of time is:

\[ C(t) = C_{bo} \lambda_b t + C_{co} \lambda_c t + C_{clc} \lambda_c t \]  \hspace{1cm} (II.2.13)

The two decay constants for O-15 and C-11 are 0.0057762 and 0.00056353 inverse seconds respectively. The first step in finding the value for blood flow from counting decay data is to fit an equation of the above functional form to the data. This should give a
value for the biologic decay constant, \( \lambda_b \). (The curve fitting procedure is described in detail in section III-6) Since \( \lambda_b \) is related to blood flow in the monitored region by equation (II.2.9) then it is obvious that, to extract blood flow, one must know the values for \( D \) and \( P \) governing the diffusion and partition coefficients for the activated nuclei.

In the case of activation by protons, it is assumed that the mobile component is \( 0-15 \) in the form of \( 0-15 \) labeled water. For this assumption, \( D \) and \( P \) both approach unity (Hughes, W.L., et. al., Science 204: 1215-1217, 1979) and thus, from equation (II.2.9):

\[
\lambda_b = \frac{Fr}{Vr} \quad (II.2.14)
\]

If the value of \( F \) is to be known in ml/min/100 grams of tissue, then \( F \) is related to \( \lambda_b \) where \( \lambda_b \) is in inverse minutes by:

\[
Fr = Vr \frac{\lambda_b}{\rho} \times 100 \quad (II.2.15)
\]
Section II.3 Discussion of the Limiting Assumptions in the Mathematical Model

Implicit in the calculation of a value for blood flow from the wash-out of activated nuclei in a proton irradiated tissue region are the following assumptions:

1) The tissue region has a homogeneous blood flow throughout the activated/monitored volume.

2) The mobile radioisotope is O-15.

3) The activated O-15 nuclei which are mobile are incorporated into tissue water.

4) The constant of diffusion equilibrium, D, and the partition coefficient, P, are both equal to unity.

Each of the above assumptions will have some degree of effect on the calculated value of blood flow through the activated region.

The first assumption imposes an intrinsic limitation on the use of this technique. If the tissue region is to have a truly homogeneous perfusion, then this usually has the implication that the region be very small in size. The size of the monitored region, however, will dictate the dose necessary to achieve desirable counting statistics (see section III.5). Although finding a tissue region of a size large enough for a reasonable measurement where the perfusion is constant and uniform might prove to be difficult in theory, it is probably not a major limitation in practice.
The usual desire is not to find the blood flow at a point, but rather the average blood flow to a finite volume of tissue. To within the accuracy of radioisotopic tracer techniques, in general, a tissue volume that may in fact consist of many small volumes of slightly different perfusions will experimentally give a mono-exponential wash-out consistent with a single average perfusion. The consideration of a tissue volume as a single "compartment" with a single value of perfusion will usually give a mono-exponential wash-out as long as the tissue and vasculature within the "compartment" are relatively homogeneous (Lasfèn, N.A. and Perl, W., Tracer Kinetic Methods in Medical Physiology, Raven, New York, 1979).

The second assumption, that O-15 is the mobile radioisotope, should also not prove to be a significant limitation in the face of previous experimental evidence. As mentioned in section 1.2, other investigators have found that C-11 as well as O-15 is removed from the activated tissue volume. However, it is also noted that C-11 is removed with a much longer half-life of wash-out and in lesser relative quantities. Since the value for the calculation of blood flow will be shown to come from the initial decrease in activity during the first minutes of counting, and the majority of activity during this period comes from O-15, the slight additional decrease in activity due to a slowly moving C-11 component should not change the fitted value of O-15 wash-out appreciably. If the half-life of C-11 wash-out is on the order of from 30 to 60 minutes with a fraction of from 0.2 to 0.5 being mobile as has been shown experimentally, the change in total activity during the first five minutes of counting will be negligible.
The third and fourth assumptions are interrelated in that they will limit the accuracy of the technique to the effect of physiological factors or rather capillary permeability factors upon the quantification of blood flow from the rate of wash-out. It can be imagined that if blood flow is very rapid within a volume but the tracer is very impermeable the rate of wash-out observed will be very slow. The reverse situation may also be true. A general discussion of blood-tissue exchange is thus necessary for the continuation of this section.

The exchange of substances across the vascular endothelium takes place by one of three processes: simple diffusion, bulk flow of plasma water, or vesicular transport (Richardson, D.R., Basic Circulatory Physiology, Little, Brown and Co., Boston, 1976). The latter process is of little concern to this thesis as it is insignificant in magnitude and rate as compared to the other two and is primarily the process by which large globular proteins and other such substances are transported across the endothelium.

The majority of blood-tissue exchange of substances takes place by simple diffusion. The rate of diffusion depends upon the blood-interstitial fluid concentration gradient of a substance and the permeability of the vascular endothelium to the substance.

Bulk flow, the second most prominent process, occurs due to the functional behavior of the exchange vessels as highly porous filters that allow a bulk flow of plasma water and all dissolved crystalloids such as electrolytes and glucose but prevents the passage of most suspended colloids such as large proteins. Plasma separated from its
colloids in this manner is called an ultrafiltrate.

Bulk flow or ultrafiltration in the microvasculature is a two-directional process in which the ultrafiltrate shifts back and forth from the blood to the interstitial fluid. The rate of this bulk flow is determined by the permeability of the vascular endothelium and a balance between hydrostatic and colloidal osmotic pressures. The permeability of a naturally occurring substance or indicator is therefore important in both of these processes.

Radioactive indicators commonly used to measure blood flow may be separated into three types: freely diffusible indicators; indicators of restricted diffusibility; and colloidal indicators (Woodcock, J.P., Theory and Practice of Blood Flow Measurement, Butterworth and Co., London, 1975).

The freely diffusible indicators such as Kr-85, Kr-79, I-125, or Xe-133 are small lipophilic molecules which will cross the capillary endothelium over its entire surface area.

Indicators of restricted diffusibility are small hydrophilic molecules or ions such as +Na-24 or +K-42. It is the capillary permeability as well as the flow rate which are the major factors which determine the rate of removal of this type of indicator.

The third group consists of chiefly very large molecules or colloids such as I-131 iodinated human serum albumin.
Water is in a class by itself. Although hydrophilic and not lipophilic, its small size gives it a very high diffusibility. It is therefore transported both by simple diffusion at a high rate and by bulk transport or ultrafiltration (Richardson, D.R., Basic Circulatory Physiology, Little, Brown and Co., Boston, 1976).

The above discussion is crucial to the understanding of how the initial assumption of O-15 being incorporated into tissue water may affect the value of blood flow measured from tracer wash-out. This initial assumption was made on a purely statistical basis. If oxygen is activated randomly and then incorporated randomly into biologic molecules, the existence of such a large relative amount of water in tissues would dictate that the majority of oxygen would be incorporated into water.

If the labeled compound were not water, it would be effected by both the mode of its transport (diffusion or bulk transport) and its permeability. These effects would have to be accounted for in the model.

The use of activation analysis and the assumption of a labeled water tracer gives some rather unique simplifications. In the derivation of the model from the simple Fick equation, the crucial step was made in equation (II.2.5). This was that:

\[ \text{Ca-Cv} = D(\text{Ca-Cr/P}) \]  

(II.2.5)
This later allowed us to relate the blood flow to the wash-out decay constant by:

$$\lambda b = \frac{FrD}{V_Tp} \quad (II.2.9)$$

D is the extent to which diffusion equilibrium for a particular substance is achieved between blood and tissue from the arteriel to the venous end of the capillary. For small molecular tracers in typical local clearance experiments, D is given a value of unity because both bulk transport and diffusion aid in reaching this equilibrium and it occurs very rapidly (Woodcock, J.P., Theory and Practice of Blood Flow Measurement, Butterworth and Co., London, 1975). In activating the tracers homogeneously throughout the tissue rather than injection into the interstitial space in addition to the tracer being in the form of labeled water, diffusion equilibrium should be achieved almost instantaneously. A value of unity for D is therefore not unreasonable.

The definition of P in the above equation is the ratio of the concentration of indicator in the tissue versus the concentration of indicator in the blood. Again, mostly due to the homogeneity of creation of indicator throughout the activated volume and the rapid diffusion and transport of water, the value of P is also most likely to be unity.
If the form of O-15 being transported was simply labeled oxygen or carbon dioxide, the values of P and D being unity would still be a reasonable assumption. Only if the majority of O-15 that is mobile is incorporated into substances with restricted diffusibility would D and P have to be changed appreciably. That this does not occur slightly is improbable, but it is probably not a major factor.

The assumptions made in this simple biological model are thus seen to be reasonable and not extremely limiting. However, they must always be a consideration when a new tissue volume is to be studied that may have a large heterogeneity in composition or perfusion.
CHAPTER III: PHYSICAL CONSIDERATIONS

Section III.1 Probable Proton-Tissue Nuclei Reactions

The Harvard cyclotron produces a beam of protons whose maximum energy is approximately 150 MeV. If such a beam of protons is incident upon a volume of tissue, it is important to know what reactions are likely to occur and in what proportion.

In order to answer the above question, we will first look at the elemental composition of the so-called "standard man". Table III.1.1 gives this elemental composition in weight percent. It is easily seen from this table that, unless there is a very large cross section for isotope production from one of the trace elements, the reactions will be primarily in oxygen, carbon, or hydrogen. Since a hydrogen-proton reaction will not produce an isotope of finite lifetime, the reactions will be proton-oxygen and proton-carbon reactions.

Table III.1.2 gives some data for the products of proton reactions with oxygen and carbon for 100 MeV protons. Close examination of this table will reveal that there are only three principle reactions which produce two positron-emitting isotopes. The three reactions and their cross sections at 100 MeV are:

\[ \text{O}^{16}(p,pn)\text{O}^{15} \quad \sigma = 60 \text{ mb} \]

\[ \text{O}^{16}(p,3p3n)\text{C}^{11} \quad \sigma = 15 \text{ mb} \]

\[ \text{C}^{12}(p,pn)\text{C}^{11} \quad \sigma = 60 \text{ mb} \]
Table III.1.1: Elemental Composition of the Human Body

<table>
<thead>
<tr>
<th>Element</th>
<th>Weight Percent</th>
<th>Approximate Amount in a 70 Kg Man (grams)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen</td>
<td>65.0</td>
<td>45,500</td>
</tr>
<tr>
<td>Carbon</td>
<td>18.0</td>
<td>12,600</td>
</tr>
<tr>
<td>Hydrogen</td>
<td>10.0</td>
<td>7,000</td>
</tr>
<tr>
<td>Nitrogen</td>
<td>3.0</td>
<td>2,100</td>
</tr>
<tr>
<td>Calcium</td>
<td>1.5</td>
<td>1,050</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>1.0</td>
<td>700</td>
</tr>
<tr>
<td>Potassium</td>
<td>0.35</td>
<td>245</td>
</tr>
<tr>
<td>Sulfur</td>
<td>0.25</td>
<td>175</td>
</tr>
<tr>
<td>Sodium</td>
<td>0.15</td>
<td>105</td>
</tr>
<tr>
<td>Chlorine</td>
<td>0.15</td>
<td>105</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.05</td>
<td>35</td>
</tr>
<tr>
<td>Iron</td>
<td>0.004</td>
<td>3</td>
</tr>
<tr>
<td>Zinc</td>
<td>0.0033</td>
<td>2.3</td>
</tr>
<tr>
<td>Rubidium</td>
<td>0.0017</td>
<td>1.2</td>
</tr>
<tr>
<td>Silicon</td>
<td>0.0017</td>
<td>1.2</td>
</tr>
</tbody>
</table>

(Diem, K. and Lentner, C., Scientific Tables, Ciba-Geigy Corp., Basle, Switzerland, 1974)
Table III.1.2

Data for Products of Proton Reactions with Oxygen and Carbon

<table>
<thead>
<tr>
<th>Product Nuclide</th>
<th>$\sigma_o$</th>
<th>$\sigma_c$</th>
<th>Half-Life</th>
<th>Threshold Energy (MeV)</th>
<th>Radiation</th>
<th>Energy, (MeV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{15}_O$</td>
<td>60</td>
<td>0</td>
<td>2 min</td>
<td>20</td>
<td>$\beta^+$</td>
<td>1.74 max</td>
</tr>
<tr>
<td>$^{13}_N$</td>
<td>5</td>
<td>0</td>
<td>10 min</td>
<td>7</td>
<td>$\beta^+$</td>
<td>1.20 max</td>
</tr>
<tr>
<td>$^{14}_C$</td>
<td>2</td>
<td>0</td>
<td>$5.7\times10^3$ y</td>
<td>30</td>
<td>$\beta^-$</td>
<td>0.16 max</td>
</tr>
<tr>
<td>$^{11}_C$</td>
<td>15</td>
<td>60</td>
<td>20.4 min</td>
<td>20</td>
<td>$\beta^+$</td>
<td>0.97 max</td>
</tr>
<tr>
<td>$^{10}_C$</td>
<td>&lt;0.1</td>
<td>2.6</td>
<td>19.5 sec</td>
<td>25</td>
<td>$\beta^+$</td>
<td>1.87 max</td>
</tr>
<tr>
<td>$^{11}_B$</td>
<td>&lt;0.1</td>
<td>66</td>
<td>(stable)</td>
<td>20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$^{10}_B$</td>
<td>0.3</td>
<td>18</td>
<td>(stable)</td>
<td>20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$^{10}_{Be}$</td>
<td>1</td>
<td>1.2</td>
<td>$2.5\times10^6$ y</td>
<td>~30</td>
<td>$\beta^-$</td>
<td>0.55 max</td>
</tr>
<tr>
<td>$^9_{Be}$</td>
<td>6</td>
<td>2.4</td>
<td>(stable)</td>
<td>~35</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$^7_{Be}$</td>
<td>&lt;0.1</td>
<td>18</td>
<td>53.6 d</td>
<td>30</td>
<td>$\gamma$</td>
<td>0.48</td>
</tr>
<tr>
<td>$^9_{Li}$</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>0.18 sec</td>
<td>~300</td>
<td>$\beta^-$</td>
<td>13.6 max</td>
</tr>
<tr>
<td>$^8_{Li}$</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>0.84 sec</td>
<td>100</td>
<td>$\beta^-$</td>
<td>13 max</td>
</tr>
<tr>
<td>$^7_{Li}$</td>
<td>9</td>
<td>15</td>
<td>(stable)</td>
<td>30</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$^6_{Li}$</td>
<td>9</td>
<td>15</td>
<td>(stable)</td>
<td>30</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Cross section for product nuclide production by 100 MeV protons on $^{16}_O$ in millibarns.

** Cross section for product nuclide production by 100 MeV protons on $^{12}_C$ in millibarns.

The two positron emitting isotopes produced, O-15 and C-11 have half-lives of 2 minutes and 20.5 minutes respectively. If the assumptions stated thus far have been correct, a decay curve from a sample of proton-irradiated tissue looking at 0.511 MeV annihilation photons should have only two components with half-lives of 2 and 20.5 minutes.

This decay of proton-irradiated dead tissue has been monitored by two groups of investigators as well as in this study. The two components of decay due to O-15 and C-11 were observed in approximately the predicted proportions given composition and cross sections (Bennett, G.W., et. al., Nucl. Instrum. Methods 125: 333-338, 1975, and Graffman, S. and Jung, B., Acta Radiologica 14: 113-126, 1975).
Section III.2 Theoretical Calculation of Activity Production

In this section, it is desired to calculate the production of C-11 and O-15 per gram-rad or per cc-rad. This will be accomplished for both tissue and lucite at only one proton energy for illustrative purposes only. Measurements of activity production have been made at different proton energies and are reported in section IV.3. This theoretical calculation does not include a calculation of the cross sections. The cross section values used have been experimentally determined and have been reported in the literature (Cumming, J.B., Ann. Rev. Nucl. Sci. 13: 261, 1973, and Valentin, L., et. al., Phys. Lett. 7: 163, 1963).

The first consideration in this calculation are the reaction cross sections for each of the significant reactions producing O-15 and C-11. The three major reactions are O-16(p,pn)O-15, O-16(p,3p3n)C-11, and C-12(p,pn)C-11 which have reaction cross sections at 100 MeV of 60mb, 15mb, and 60mb respectively.

The next consideration is the atomic density of each of the target nuclei in either tissue or lucite. Lucite (\(C_5 \text{H}_8 \text{O}_2\)) has a physical density of 1.18 grams/cc. The atomic density of O-16 in lucite is therefore \(1.2 \times 10^{22}\) atoms/gram or \(1.42 \times 10^{22}\) atoms/cc. The atomic density of C-12 in lucite is \(3.01 \times 10^{22}\) atoms/gram or \(3.55 \times 10^{22}\) atoms/cc.

For tissue, we may take the composition to be that of standard man as 65% by weight oxygen and 18% by weight carbon. This gives the atomic densities of oxygen and carbon in tissue values of \(2.45 \times 10^{22}\).
and $9.03 \times 10^{21}$ atoms/cc respectively.

By referring to range-energy tables (Jannai, J.F., AFWL-TR-65-150, Air Force Weapons Lab, 1966), one may find that for muscle tissue and 100 MeV protons, the stopping power is 7.273 MeV/cm. A simple calculation may be performed to show that this is equivalent to $8.6 \times 10^6$ protons/sq-cm/rad. The value is only slightly different in lucite.

We may now calculate the number of activated nuclei produced from each of the three reactions. In lucite the reaction $^0\text{He}(p,pn)^0\text{He}$ gives:

\[
(8.6 \times 10^6 \text{ cm}^{-2} \text{ rad}^{-1})(3.55 \times 10^{22} \text{ atoms/cc})(6.0 \times 10^{-26} \text{ cm}^2) = 1.83 \times 10^4 \text{ C-15/cc rad}
\]

In lucite the reaction $^0\text{He}(p,3p3n)^0\text{He}$ gives:

\[
(8.6 \times 10^6 \text{ cm}^{-2} \text{ rad}^{-1})(1.42 \times 10^{22} \text{ atoms/cc})(6.0 \times 10^{-26} \text{ cm}^2) = 7.33 \times 10^3 \text{ C-11/cc rad}
\]

And in lucite the reaction $^1\text{H}(p, pn)^1\text{H}$ gives:

\[
(8.6 \times 10^6 \text{ cm}^{-2} \text{ rad}^{-1})(1.42 \times 10^{22} \text{ atoms/cc})(1.5 \times 10^{-26} \text{ cm}^2) = 1.83 \times 10^3 \text{ C-11/cc rad}
\]
The total production of C-11 in lucite is therefore $2.01 \times 10^4$
per cc per rad.

For tissue, similar calculations may be carried out. The results of such calculations give the production of O-15 to be $1.26 \times 10^4$ per cc per rad and C-11 to be $7.82 \times 10^3$ per cc per rad.

This calculation may be repeated for other proton energies as the cross section varies with energy as demonstrated in section IV.3. Dose rate effects were not taken into consideration here, however, they were considered in section III.5 in the computer simulation of activity production.

Section IV.3 contains experimental data from the measurement of the initial O-15 and C-11 produced in lucite. This data will be compared to the results of the calculation performed here as well as the results of cross section measurements performed elsewhere.
Section III.3 Curve Fitting

In order to evaluate the biological decay constant $\lambda b$, one must fit to the coincidence counting data an expression of the form:

$$C(t) = C_b e^{-\lambda b t} + C_{o} e^{-\lambda ot} + C_c e^{-\lambda ct} \quad (III.3.1)$$

where:

- $C(t)$ is the total number of counts registered within a counting interval or channel
- $C_b$, $C_o$, and $C_c$ are the total number of counts per channel at time $t=0$ from the components of biological decay, decay of O-15, and decay of C-11 respectively.
- $\lambda b$, $\lambda o$ and $\lambda c$ are the decay constants of biologic wash-out O-15, and C-11 respectively.

The fitting was performed with the program CHIFIT which is contained in Appendix II.

Program CHIFIT allows the user to fit data with a function of the sum of from one to four exponential decay components. The variable parameters which are adjusted to give the best fit are the counts per channel at $t=0$ for all four components and one of the decay constants if necessary. This allows the program to be used in the irradiation and counting experiments using phantoms where there is no component of
biologic decay and the fitting function takes the form:

\[ C(t) = C_0 e^{-\lambda_0 t} + C_c e^{-\lambda_c t} \quad \text{(III.3.2)} \]

In this case, \( \lambda_0 \) and \( \lambda_c \) are known inputs and \( C_0 \) and \( C_c \) are the variable fitting parameters. In switching to an animal blood-flow measurement, equation (III.3.1) may be used and the variable fitting parameters are \( C_b, C_0, C_c, \) and \( \lambda_b \).

The method used in CHIFIT is simply one of minimizing chi-squared where chi-squared is given by:

\[ \chi^2 = \sum_{i=1}^{N} \frac{1}{\sigma_i^2} (Y_i - Y(X_i))^2 \quad \text{(III.3.3)} \]

and:

\( N \) is the number of counting intervals or channels

\( \sigma_i \) is the standard deviation of the counts in channel \( i \)

\( Y_i \) is the number of counts in channel \( i \)

\( Y(X_i) \) is the function being fit to the data

In explaining the procedure used in minimizing chi-squared and calculating the errors in the adjustable parameters, we will use an example where the fitted function has only two components:
\[ Y(X_i) = C_1 \cdot e^{-\lambda_1 \cdot X_i} + C_2 \cdot e^{-\lambda_2 \cdot X_i} \quad (III.3.4) \]

and the adjustable parameters are \( C_1, C_2, C_3, \) and \( \lambda_1. \) The variable \( X_i \) is, in our case, the time at the midpoint of the \( i^{th} \) channel.

Substituting equation (III.3.4) into the expression for chi-squared gives:

\[
\chi^2 = \sum_{i=1}^{N} \frac{1}{\sigma_i^2} (Y_i - C_1 \cdot e^{-\lambda_1 \cdot X_i} - C_2 \cdot e^{-\lambda_2 \cdot X_i})^2 \quad (III.3.5)
\]

To minimize chi-squared, one takes the partial derivative of the above expression with respect to each of the above adjustable parameters and sets the resulting expressions equal to zero. This gives:

\[
0 = \frac{\partial \chi^2}{\partial C_1} = \sum_{i=1}^{N} \frac{-2 \cdot e^{-\lambda_1 \cdot X_i}}{\sigma_i^2} (Y_i - C_1 \cdot e^{-\lambda_1 \cdot X_i} - C_2 \cdot e^{-\lambda_2 \cdot X_i}) \quad (III.3.6)
\]

\[
0 = \frac{\partial \chi^2}{\partial C_2} = \sum_{i=1}^{N} \frac{-2 \cdot e^{-\lambda_2 \cdot X_i}}{\sigma_i^2} (Y_i - C_1 \cdot e^{-\lambda_1 \cdot X_i} - C_2 \cdot e^{-\lambda_2 \cdot X_i}) \quad (III.3.7)
\]

\[
0 = \frac{\partial \chi^2}{\partial \lambda_1} = \sum_{i=1}^{N} \frac{2 \cdot X_i \cdot e^{-\lambda_1 \cdot X_i}}{\sigma_i^2} (Y_i - C_1 \cdot e^{-\lambda_1 \cdot X_i} - C_2 \cdot e^{-\lambda_2 \cdot X_i}) \quad (III.3.8)
\]
Equations (III.3.6), (III.3.7), and (III.3.8) can be rewritten as:

\[
\sum_{i=1}^{N} \frac{Y_i \cdot e^{-\lambda_1 X_i}}{\sigma i^2} = C_1 \sum_{i=1}^{N} \frac{e^{-2 \cdot \lambda_1 X_i}}{\sigma i^2} + C_2 \sum_{i=1}^{N} \frac{e^{-(\lambda_1 + \lambda_2) X_i}}{\sigma i^2} \tag{III.3.9}
\]

\[
\sum_{i=1}^{N} \frac{Y_i e^{-\lambda_2 X_i}}{\sigma i^2} = C_1 \sum_{i=1}^{N} \frac{e^{-(\lambda_1 + \lambda_2) X_i}}{\sigma i^2} + C_2 \sum_{i=1}^{N} \frac{e^{-2 \cdot \lambda_2 X_i}}{\sigma i^2} \tag{III.3.10}
\]

\[
\sum_{i=1}^{N} \frac{Y_i X_i e^{-\lambda_1 X_i}}{\sigma i^2} = C_1 \sum_{i=1}^{N} \frac{X_i e^{-2 \cdot \lambda_1 X_i}}{\sigma i^2} + C_2 \sum_{i=1}^{N} \frac{X_i e^{-(\lambda_1 + \lambda_2) X_i}}{\sigma i^2} \tag{III.3.11}
\]

It is easily seen that, if \(\lambda_1\) and \(\lambda_2\) are known, equations (III.3.9) and (III.3.10) are simply two equations in two unknowns and can be written in matrix form:

\[
\begin{bmatrix}
\sum_{i=1}^{N} \frac{Y_i \cdot e^{-\lambda_1 X_i}}{\sigma i^2} \\
\sum_{i=1}^{N} \frac{Y_i \cdot e^{-\lambda_2 X_i}}{\sigma i^2}
\end{bmatrix}
= 
\begin{bmatrix}
\sum_{i=1}^{N} \frac{e^{-2 \cdot \lambda_1 X_i}}{\sigma i^2} \\
\sum_{i=1}^{N} \frac{e^{-(\lambda_1 + \lambda_2) X_i}}{\sigma i^2}
\end{bmatrix}
\begin{bmatrix}
C_1 \\
C_2
\end{bmatrix}
\]

\[-(III.3.12)\]
Therefore, the values of the fitted parameters are given by:

\[
C_1 = \frac{1}{\Delta} \cdot \begin{bmatrix}
\sum_{i=1}^{N} \frac{Y_i \cdot e^{-\lambda_1 \cdot X_i}}{\sigma i^2} & \sum_{i=1}^{N} \frac{e^{-(\lambda_1 + \lambda_2) \cdot X_i}}{\sigma i^2} \\
\sum_{i=1}^{N} \frac{Y_i \cdot e^{-\lambda_2 \cdot X_i}}{\sigma i^2} & \sum_{i=1}^{N} \frac{e^{-2 \cdot \lambda_2 \cdot X_i}}{\sigma i^2}
\end{bmatrix}
\]

(III.3.13)

\[
C_2 = \frac{1}{\Delta} \cdot \begin{bmatrix}
\sum_{i=1}^{N} \frac{e^{-2 \cdot \lambda_1 \cdot X_i}}{\sigma i^2} & \sum_{i=1}^{N} \frac{Y_i \cdot e^{-\lambda_1 \cdot X_i}}{\sigma i^2} \\
\sum_{i=1}^{N} \frac{e^{-(\lambda_1 + \lambda_2) \cdot X_i}}{\sigma i^2} & \sum_{i=1}^{N} \frac{Y_i \cdot e^{-\lambda_2 \cdot X_i}}{\sigma i^2}
\end{bmatrix}
\]

(III.3.14)

\[
\Delta = \begin{bmatrix}
\sum_{i=1}^{N} \frac{e^{-2 \cdot \lambda_1 \cdot X_i}}{\sigma i^2} & \sum_{i=1}^{N} \frac{e^{-(\lambda_1 + \lambda_2) \cdot X_i}}{\sigma i^2} \\
\sum_{i=1}^{N} \frac{e^{-(\lambda_1 + \lambda_2) \cdot X_i}}{\sigma i^2} & \sum_{i=1}^{N} \frac{e^{-2 \cdot \lambda_2 \cdot X_i}}{\sigma i^2}
\end{bmatrix}
\]

(III.3.15)

The determinants in (III.3.13), (III.3.14), and (III.3.15) are calculated by diagonalizing the square matrix. This is accomplished in the subroutine DETERM.

If \(\lambda_1\) is also an unknown parameter, the solution becomes iterative. In this process, a value for \(\lambda_1\) is chosen and input to equations (III.3.13) and (III.3.14) to solve for \(C_1\) and \(C_2\). These values are then input to equation (III.3.11). If equation (III.3.11)
is not satisfied by this value of $\lambda_1$, the value is adjusted in an appropriate manner and the process is repeated.
Section III.4 Statistical Error Analysis

Once the fitting parameters have been calculated, it is then necessary to calculate the standard deviation of each of these parameters. This is also accomplished in the program CHIFIT.

The standard deviation of the determination of any fitting parameter \( Z \), is the root sum square of the products of the standard deviation of each data point \( \sigma_i \), multiplied by the effect that that data point has on the determination of \( Z \) (Bevington, P.R., Data Reduction and Error Analysis for the Physical Sciences, McGraw-Hill, New York, 1969). Thus:

\[
\sigma_Z^2 = \sum_{i=1}^{N} \left( \sigma_i^2 \left( \frac{\partial Z}{\partial Y_i} \right)^2 \right)
\]

(III.4.1)

In the example presented in the last section of using a fitted function with two decay components, the evaluation of the standard deviations in \( C_1 \) and \( C_2 \) is straightforward.

\( C_1 \) and \( C_2 \) were given in the preceeding section by equations (III.3.12) and (III.3.13). Taking the partial derivatives of each of these expressions with respect to \( Y_i \) gives:

\[
\frac{\partial C_1}{\partial Y_j} = \frac{1}{\Delta} \left[ \sum_{i=1}^{N} \frac{e^{-\lambda_1 \cdot X_j}}{\sigma_i^2} - \sum_{i=1}^{N} \frac{e^{-\lambda_1 + \lambda_2 \cdot X_i}}{\sigma_i^2} \right]
\]

(III.4.2)
\[
\frac{3C_2}{3Y_j} = \frac{1}{\Delta} \cdot \begin{bmatrix}
\sum_{i=1}^{N} \frac{e^{-2 \cdot \lambda_1 \cdot X_i}}{\sigma_i^2} & \frac{e^{-\lambda_1 \cdot X_j}}{\sigma_j^2} \\
\sum_{i=1}^{N} \frac{e^{-(\lambda_1+\lambda_2)X_i}}{\sigma_i^2}
\end{bmatrix}
\] (III.4.3)

The value of \( \Delta \) in the above expressions is again:

\[
\Delta = \begin{bmatrix}
\sum_{i=1}^{N} \frac{e^{-2 \cdot \lambda_1 \cdot X_i}}{\sigma_i^2} & \sum_{i=1}^{N} \frac{e^{-(\lambda_1+\lambda_2)X_i}}{\sigma_i^2} \\
\sum_{i=1}^{N} \frac{e^{-(\lambda_1+\lambda_2)X_i}}{\sigma_i^2} & \sum_{i=1}^{N} \frac{e^{-2 \cdot \lambda_2 \cdot X_i}}{\sigma_i^2}
\end{bmatrix}
\] (III.4.4)

The calculation of \( \sigma_{C1} \) and \( \sigma_{C2} \) is then given by substituting (III.4.2) and (III.4.3) into (III.4.1). This gives:

\[
\sigma_{C1}^2 = \sum_{j=1}^{N} (\sigma_j^2 \cdot \left( \frac{3C_1}{3Y_j} \right)^2)
\] (III.4.5)

\[
\sigma_{C2}^2 = \sum_{j=1}^{N} (\sigma_j^2 \cdot \left( \frac{3C_2}{3Y_j} \right)^2)
\] (III.4.6)
σi or σj, the standard deviation of the i\textsuperscript{th} or j\textsuperscript{th} data point is usually thought to be governed by Poisson counting statistics. This error is thus given by:

\[ σ_i = \left( C_{\text{total}_i} + C_{\text{background}_i} \right)^{\frac{1}{2}} \]  

(III.4.7)

The next problem is to calculate the error in the half life determined by the fitting program. Since the biological decay constant is determined by an iterative process due to the non-linearity of the equation in \( λ_1 \), the calculation of the standard deviation in \( λ_1 \) is also an iterative process.

The calculation of the standard deviation in \( λ_1 \) is accomplished simply by taking the calculated standard deviations in C1, C2, and C3 and finding the effect that these errors have on the calculation of \( λ \). The magnitude of this effect, calculated using the iterative process used to find \( λ_1 \) initially, then becomes the error in \( λ_1 \).
Section III.5 Theoretical Variation of Statistical Uncertainty with Dose

III.5.1 Introduction

The analysis of how the statistical uncertainty in the determination of blood flow varies with proton dose is probably one of the most crucial to this thesis. It is this variation which will ultimately determine the limitations of this technique. If a therapeutic dose of protons cannot yield a calculated value of blood flow known to a small uncertainty, then subtle changes in tumor physiology with treatment cannot be measured. If, however, a small fraction of a therapeutic dose can be delivered and blood flow can be determined very accurately, then the proton activation analysis technique may be used for diagnostic purposes in other than radiotherapy patients.

The statistical error $\sigma_b$, in the measured value of blood flow varies not only with dose, but also with detection efficiency, dose rate, sampling interval size, the magnitude of the fixed vs mobile nuclei, and the half life of washout. In order to look at the variation in $\sigma_b$ as a function of the above parameters, a computer program was written to simulate the activation and detection of the positron emitting isotopes in tissues. The variable inputs into the program are the proton dose, the detection crystal size and placement, the length of the counting intervals, the fraction of the fixed vs mobile nuclei, the dose rate, and the half life of the biologic wash-out.
The output of this program consists of a set of counts vs time data which might be expected if an experiment was run with the input experimental parameters. This output was then fed into the program CHIFIT which determines, by an iterative process described in the previous sections, the value of the input half-life and its standard deviation. This is also a check upon how well CHIFIT is able to determine a given biologic decay constant.

The program FAKEDATA is the program which creates the artificial experimental data. The set-up of this imaginary experiment is as follows: a sphere of tissue weighing one gram is suspended at the geometric center of two crystals of some input dimensions. The tissue has an elemental composition of a standard man with a weight percent of 65% oxygen and 18% carbon. It is irradiated uniformly with a proton beam whose dose rate is equal to some input value, usually that of the Harvard Cyclotron. The beam is monochromatic and the protons in the beam have an energy of 100 MeV. The tissue has an adjustable blood flow which removes activated nuclei from the active detection area between the detectors. A diagram of this imaginary arrangement is shown in figure III.5.1.

The manner in which each analysis is performed is that all of the experimental variables are held constant and set to some value which is close to the actual value used in the later animal experiments. One variable is then allowed to change its value and a set of data is produced. The relative error is then calculated from this data and is plotted as a function of the changing variable. This gives both an idea as to the expected uncertainties in measurement with changes in
Figure III.5.1.1: Imaginary Experimental Arrangement as Modeled in Program FAKEDATA
experimental set-up as well as a feeling of how one might optimize the experimental variables in order to most accurately ascertain the value of blood flow in a given situation.
Section III.5.2 Computer Simulation of Experimental Data

As mentioned in the previous section, the program FAKEDATA simulates experimental data which might be produced in an activation analysis experiment performed under certain input conditions. The first priority of the program FAKEDATA is to determine the initial number of detected coincidence events after the beam is turned off for each of the activated species. This is calculated by first looking at the rate of production of each isotope.

The dose rate in a typical experiment from the Harvard cyclotron is about 20 rads/sec in tissue from 100 MeV protons. The flux is typically $2.0 \times 10^8$ protons/sq cm-sec thus giving the number of protons per unit area per rad in the beam a value of approximately $1.0 \times 10^7$ protons/sq cm-rad. The two isotopes whose production rate we wish to calculate are C-11 and O-15.

If tissue density is taken to be unity and its composition by weight is 65% oxygen and 18% carbon, then the atomic densities can be calculated to be $2.45 \times 10^{22}$ atoms/cc of oxygen and $9.03 \times 10^{21}$ atoms/cc of carbon.

There are three reactions to be considered. At 100 MeV, the production of O-15 from the reaction O-16(p, pn)O-15 has a cross section of 60 mb. The two reaction which produce C-11, O-16(p, 3p3n)C-11 and C-12(p, pn)C-11, have cross sections of 15 mb and 60 mb respectively. We can now easily calculate the production rate from these three reactions. From O-16(p, pn)O-15 we have:

\[
\frac{2.45 \times 10^{22} \text{ atoms O}}{\text{cc tissue}} \times \frac{1 \times 10^7 \text{ protons}}{\text{cm}^2 \text{ rad}} \times \left(6.0 \times 10^{-26} \text{ cm}^2\right) = 14700 \frac{\text{O-15}}{\text{cc rad}}
\]
Similarly, from $O-16(p,3p3n)C-11$ we produce $73,500$ C-11/sec and from $C-12(p,\alpha n)C-11$ we produce $108,360$ C-11/sec for a total production rate of $181,860$ C-11/sec. It can easily be seen that, if one could vary the dose rate, one could vary the production rate in proportion.

We are now ready to write equation governing the simultaneous production and decay of the radionuclides during the activation period. First, define some variables:

- $R_o$ is the rate of production of $O-15$ in atoms/sec
- $R_c$ is the rate of production of C-11 in atoms/sec
- $F_o$ is the fraction of $O-15$ nuclei that are mobile
- $F_c$ is the fraction of C-11 nuclei that are mobile
- $N_o$ and $N_c$ are the number of $O-15$ and C-11 nuclei
- $\lambda_b$, $\lambda_o$, and $\lambda_c$ are the decay constants for biologic removal, $O-15$, and C-11

The change in the number of $O-15$ nuclei in a short time interval $dt$ during the activation period by protons will be equal to the production rate in $dt$ minus the decay of activated nuclei by physical processes minus the decay by biologic wash-out. This may be written:

$$dN_o = -\lambda_b F_o N_o dt - \lambda_o N_o dt + R_o dt$$  \hspace{1cm} (III.5.2.1)

Since only a fraction of the $O-15$ nuclei may be mobile, it is
necessary to multiply the decay by biologic removal by the appropriate fraction. Similarly for C-11, one may write:

\[ dNc = -\lambda c \cdot Nc \cdot dt + Rc \cdot dt \quad (III.5.2.2) \]

Integrating the above equations and solving for the number of nuclei gives:

\[ N_0 = \frac{Ro}{(\lambda b\cdot Fo + \lambda o)} (1 - e^{-(\lambda b\cdot Fo + \lambda o)t}) \quad (III.5.2.3) \]

\[ Nc = \frac{Rc}{\lambda c} (1 - e^{-\lambda c\cdot t}) \quad (III.5.2.4) \]

The false data set is ready to be created. Using the above equations, the initial number of nuclei of C-11 and C-15 given a production rate and a dose can be found. The decay of only a fraction of these will be detected, however, as the detection efficiency of the apparatus is not 100%. The detection efficiency of a set of cylindrical NaI crystals of given dimensions may be approximated quite easily. If the radius of the crystals is \( r \), and the distance from a point source located along the axis of the crystals to one of the
crystal faces is $d$, then the geometric detection efficiency of the coincidence set-up may be easily shown to be equal to:

$$
\varepsilon_{geo} = 1 - \frac{d}{(d^2 + r^2)^{1/2}} \tag{III.5.2.5}
$$

If it is assumed that the intrinsic detection efficiency including photofraction of the NaI crystals for 0.511 MeV photons is approximately 90% (Knoll, G.F., Radiation Detection and Measurement, Wiley and Sons, New York, 1979), then the total detection efficiency is equal to:

$$
\varepsilon_{total} = (0.9)^2 \cdot \varepsilon_{geo} \tag{III.5.2.6}
$$

To produce the false data set, a set of data is produced that contains the number of detected counts in a time interval vs the mid-point time of that interval. This is done for a total counting time of 15 minutes. The number of counts as a function of time detected in a time interval $\Delta t$, is simply given by:

$$
C_{total} = \varepsilon_{total} \cdot \Delta t \cdot (N_0 \cdot F_0 \cdot \lambda b \cdot e^{-\lambda b \cdot t} + N_0(1-F_0) \cdot \lambda 0 \cdot e^{-\lambda 0 \cdot t} + N_c \cdot \lambda c \cdot e^{-\lambda c \cdot t})
\tag{III.5.2.7}
$$
This data is then written to a file by the program FAKEDATA in order that it be analyzed by the program CHIFIT. The results of this analysis are contained in the next section.
Section III.5.3 Statistical Analysis of Simulated Experimental Data

The statistical analysis of the simulated experimental data was performed in the following manner: Each of the experimental parameters in the program FAKEDATA were allowed to vary one at a time while keeping the other parameters constant. A set of data was produced and analyzed by CHIFIT and the relative error in the determination of blood flow was calculated. In this manner, it could be seen how the error in the determination of blood flow could best be reduced.

In program FAKEDATA, each of the experimental parameters were given default values that most closely resembled common values obtained in the animal experiments. These default values were:

1) Dose = 100 rads
2) Dose Rate = 20 rads/second
3) Crystal Separation = 26 cm
4) Crystal Diameter = 3 inches
5) Counting Intervals = 5 seconds
6) Mobile to Fixed O-15 Fraction = 0.6
7) Blood Flow = 90 ml/min/100 grams of tissue
The primary concern of this analysis is how the uncertainty in blood flow determination varies with dose. By setting the above parameters 2-7 equal to their default values and varying only the dose, this functional dependence could be determined.

The results of the above exercise are plotted in Figure III.5.3.1. As can be seen from this plot, at low doses the uncertainty rises quite rapidly but at very high doses there is not a great gain in the reduction of uncertainty. The plot demonstrates that at reasonably small fractions of a therapeutic dose (i.e. 20 rads), the uncertainty in blood flow determination is acceptable (i.e. approx. 20%).

Changing the other parameters will simply shift the dose-uncertainty curve towards or away from the origin. To best illustrate the magnitude of this shift with changes in each of the parameters, the default dose of 100 rads was chosen and each of the parameters were changed from their default values. The results of this analysis are tabulated in Table III.5.3.1.

As can be seen from Table III.5.3.1, changes in counting interval length and counting rate had the least effect upon the relative uncertainty. Of the parameters that are adjustable by the investigator, improved counting efficiency best reduced the error in blood flow determination.

Also noticed from Table III.5.3.1, is that the relative error in blood flow determination is very dependent upon the blood flow rate itself. This may mean that low blood flow rates will be detected with
Figure III.5.3.1: Plot of the Variation in Uncertainty in Blood Flow Determination as a Function of Proton Dose
<table>
<thead>
<tr>
<th>Parameter Change</th>
<th>Percent Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>all parameters set to the default values</td>
<td>19.9</td>
</tr>
<tr>
<td>high dose (production) rate (1000 rads/sec)</td>
<td>19.3</td>
</tr>
<tr>
<td>improved detection efficiency (10&quot; crystals separated by 5 cm)</td>
<td>1.4</td>
</tr>
<tr>
<td>high blood flow (150 ml/min/100 gr)</td>
<td>11.9</td>
</tr>
<tr>
<td>low blood flow (40 ml/min/100 gr)</td>
<td>36.5</td>
</tr>
<tr>
<td>short counting intervals (1 sec)</td>
<td>18.0</td>
</tr>
<tr>
<td>long counting intervals (10 sec)</td>
<td>19.9</td>
</tr>
<tr>
<td>high mobile to fixed nuclei ratio (0.8)</td>
<td>14.7</td>
</tr>
</tbody>
</table>
difficulty and an associated high uncertainty.

It is important to remember, however, that for this simulated experiment the amount of tissue in which blood flow is being measured is one gram. There is always a trade-off between the sensitivity of the measurement and the spatial resolution. For a much larger tissue mass, the error in the blood flow determination would have to be much smaller. It is also expected that if a very small bit of tissue is to be measured for perfusion, that the relative uncertainty for a given dose will be proportionally larger. One gram was used in this case in order to normalize the other experimental parameters.

Although this exercise is by no means definitive, it provides the ability to optimize the adjustable experimental parameters given a set of biologic conditions and may be a consideration in the design of future blood flow measurement devices using positron detection.
CHAPTER IV: PHYSICAL MEASUREMENTS

Section IV.1 Introduction

A number of measurements were made of physical parameters of importance to this thesis. In order to measure blood flow by proton activation of positron emitters, it is first necessary to be able to detect positrons. To this end, a simple coincidence detection apparatus was used with a number of basic tests being performed to insure its functional operation.

It is also important to be able to measure proton dose to the activated tissue region. Section IV.3 is therefore concerned with proton dosimetry as performed prior to the animal experiments at the Harvard Cyclotron. A short section on the uncertainties in the dose measurement is also included.

After assembling the requisite detection and dose measurement apparatus, it is now possible to measure the spatial distribution of positron activity along the beam axis. This measurement, which is the subject of Section IV.4, is necessary for two reasons. The first, is that the measured activity may be compared to the values calculated in Section III.2 as a check of the assembled experimental apparatus. If the measured values compare favorably to those measured by other investigators in their attempt to measure reaction cross sections, then this gives some degree of assurance that no major errors have been made in either proton dosimetry or positron detection. The second reason for measuring the spatial distribution of activity along the proton beam axis is to provide a means of visualizing the theoretical homogeneity of tracer distribution which may be deposited
within a tissue volume. It is this uniformity of tracer deposition that is one of the major theoretical advantages of this technique over that of injected local clearance.

Although these physical measurements which were made prior to performing the animal experiments are by no means totally complete, they should provide an elementary basis upon which some conclusions may be made as to the performance of proton activation as a blood flow measuring tool.
Section IV.2 Coincidence Detection Apparatus Set-Up

The coincidence counting apparatus used to detect the resulting annihilation radiation from positron decay is shown in Figure IV.2.1. The apparatus consists of an ordinary coincidence counting circuit using two 3"x3" cylindrical NaI(Tl) scintillation detectors. A number of standard tests were performed to insure the functional operation of the detection system.

In order to match the individual detectors, a Na-22 disk source was used. Na-22 decays by positron emission and electron capture and has a half-life of 2.6 years.

All of the components for each detector were identical Ortec components with the exception of the photomultiplier tubes and bases and the high voltage supplies. Both a dual trace oscilloscope and a Canberra multi-channel analyzer were available for calibration.

Using the Na-22 source and with the HV supply set according to the manufacturers specifications, the output pulses from both amplifiers were matched by varying the gain settings. With the pulse height, observed with the oscilloscope, set equal to one volt from each crystal, the pulse width from crystal A equaled 1.2 $\mu$ sec and from crystal B, 1.5 $\mu$ sec. Using the MCA, the 0.511 MeV peak was located in the same channel from each crystal.

The energy resolution for crystals A and B, defined as the full width at half maximum of the full energy peak divided by the mean pulse height of the peak, was measured to be 9.1% and 10.0% respectively. This is approximately the values expected from NaI(Tl)
Figure IV.2.1: Coincidence Detection Apparatus
crystals from 0.511 MeV photons (Knoll, G.F., Radiation Detection and Measurement, Wiley and Sons, New York, 1979).

The stability of the output from the amplifiers was checked over both very short time intervals and also over days and weeks. The equipment would remain stable over the course of a week and would only require slight adjustments over longer time periods.

The windows on the spectroscopy amplifiers were set around the 0.511 MeV peak using the MCA gated with the output of the SCA for each crystal. These settings were then checked using an oscilloscope.

By placing the Na-22 source between the two crystals and looking at the output of the two SCA's on the dual trace oscilloscope, gating the output of one with the output of the other, it could be seen if the logic pulses were truly in coincidence. In this manner, it was found that no delay circuitry was needed to achieve coincidence between the two crystals.

The coincidence unit that was used was an overlap unit and thus the resolving time is equal to the length of the logic pulse which was one μ sec. Although this is relatively long, the singles count rate in this application was low and thus the number of false coincidences (=2·τ·C1·C2 where τ is the resolving time and C1 and C2 are the singles count rates from crystals 1 and 2 respectively) should also be low.
The next determination that was made was of the spatial sensitivity of the coincidence system as it was set up for the phantom and animal experiments. Shielding in the form of lead bricks were placed on five sides of the crystals leaving the faces exposed to each other with a separation distance of 12.5 cm. The Na-22 source was placed in the geometric center of the two crystals and moved both along and perpendicular to the crystal axis as shown in Figure IV.2.2. Counts were taken from the coincidence unit for ten minute intervals at different positions along or perpendicular to the axis at 0.5 cm increments. Plots of the resulting counts versus position data are contained in Figures IV.2.3 and IV.2.4. The FWHM of the spatial sensitivity of this set-up perpendicular to the axis was measured to be 4.8 cm and the FWHM of the spatial sensitivity along the axis was measured to be 3.2 cm.

The FWHM of these plots are then indicative of the sensitive volume between the two crystals without added collimation. This would be a useful parameter if a large volume were to be placed between the crystals and activated. The animal experiments contained within this thesis were collimated, however, and the spatial resolution was thus defined by the proton collimation and the collimation of the activated volume (see Section V.2).

The final check of the equipment was to place the detection system within the beam room with the proton beam passing between the two detectors. Watching the output of the amplifiers from each of the crystals during cyclotron operation and immediately after the beam is shut off gave an indication as to the background levels. During
NaI crystals are 3"x3" right cylinders

Na-22 source is moved both along and perpendicular to the detector axis in order to determine spatial sensitivity

Figure IV.2.2: Na-22 Source Movement to Determine Spatial Sensitivity
Figure IV.2.3: Plot of Spatial Sensitivity along the Detector Axis
Figure IV.2.4: Plot of Spatial Sensitivity Perpendicular to the Detector Axis
operation, the background level was extremely high even with the lead brick shielding in place. Immediately after beam shut-off, the background level dropped to an acceptable level (one or two coincidences per second) and within minutes thereafter the background level decreased to the normal room level (0.2 coincidences per second).

After these initial equipment checks were completed, the only routine check that was necessary prior to running an experiment was to check the location of the 0.511 MeV peak and window from each crystal with the MCA and/or scope. Fine adjustments to the amp gain were sometimes necessary to bring the peaks back into their original channels. No other adjustments were made during the duration of the experiments.
Section IV.3 Proton Current and Dosimetry Calibrations

Section IV.3.1 Introduction

In order to estimate the ultimate usefulness of blood flow measurement by proton activation of positron-emitting tracers, it is necessary to know the magnitude of radiation dose that must be delivered in order that enough nuclei be activated to determine blood flow. If it was found that tens of thousands of rads of dose are necessary in order that the half life of wash-out to be determined within ten percent accuracy, then the use of this technique on human subjects would be unacceptable. It is thus necessary to know the proton current and dose delivered to the phantoms and animals studied in order to assess the feasibility of using activation analysis with doses less than that delivered during radiotherapy.

The measurement of proton current and/or dose during each experiment is performed using a parallel plate nitrogen filled ionization chamber which is an integral part of the beam line. The output from the ionization chamber is input to the cyclotron control panel and the charge collected during the operation of the cyclotron is measured in terms of "monitor units". A digital readout of the number of monitor units collected is continuously displayed on the control panel until a pre-specified number of monitor units and thus charge have been collected at which time the cyclotron automatically shuts off.
It is of course unacceptable to relate the accuracy of blood flow determination in terms of "monitor units delivered" and therefore the parallel plate ionization chamber must be calibrated so that one knows the dose absorbed by tissue at a specific location in the proton beam per monitor unit delivered.

Although the process of measuring the absorbed dose of protons in terms of an upstream ionization chamber may seem indirect, it offers the advantage of being able to measure the dose without perturbing the system being irradiated. If a small thimble ionization chamber or thermoluminescent dosimeter were placed next to the irradiated object during proton bombardment, their presence would have the effect of perturbing the radiation field (although this effect would probably be small). In addition, if the irradiated tissue region is large and the volume in which the dose is to be determined is in the center of the tissue, an ionization chamber, TLD, or diode placed outside the tissue will not accurately reflect the absorbed dose at the center.

The measurement of the dose absorbed by a piece of tissue or a piece of phantom material that will be the subject of the next few subsections. The first measurement that must be performed is that of the energy of the protons in the beam. The knowledge of the incident proton energy is crucial to the calculation of dose.
Section IV.3.2 Proton Energy Measurement

The first step in the calibration of the ion chamber is the measurement of the energy of the protons in the beam. This is accomplished by finding the range of the protons in water and then consulting range energy tables such as those by M. Rich and R. Madey (Rich, M., and Madey, R., University of California Radiation Lab Report, UCRL-2301, USAEC, 1954).

The geometry and aperture arrangement of the incident proton beam are shown in Figure IV.3.1. The protons from the cyclotron are first confronted by a thin metal foil from which they scatter at relatively small angles. The resulting scattered protons are then collimated by collimator (A). Protons which have scattered by the edge of collimator (A) are intercepted by collimator (B) which is placed just outside of the path of protons which have made it through collimator (A) unhindered. Collimator (C) is the next real collimator in line. This collimator further defines the spread of the now diverging beam. Collimator (D) acts as another anti-scatter aperture from the edges of (C).

Also shown in Figure IV.3.1 is the beam energy measurement apparatus. This consists of a water-filled tank placed at a well defined position along the beam axis with a small thimble ionization chamber suspended in the water at some initial position. The rod from which the ionization chamber is suspended is connected to small drive motors and a pulley system which allows the rod and thus the ion chamber to be moved to any position in the water tank. The input to the motors and the output of the ion chamber are connected to a PDP
Figure IV.3.1: Proton Scatterer and Aperture Arrangement with Beam Energy Measurement Apparatus in Place
computer through a CAMAC crate and can thus be controlled and monitored from outside the beam room.

With the ion chamber placed against the wall of the tank nearest the entrance of the proton beam a measurement of relative ionization vs depth in the tank is made. The cyclotron is run for a preset number of parallel plate ionization chamber "monitor units" and charge is collected on the thimble ionization chamber during this time. When the cyclotron stops, the charge collected during the run is recorded by the computer along with position information of the small ion chamber. The motors are then stepped to a new position along the beam axis a few millimeters downstream moving the ion chamber and a new measurement of collected charge is made.

At the end of this process, the thimble ion chamber has traversed the entire depth of the water tank along the path of the incident protons and recorded the relative ionization deposited at many different depths. A plot of a typical ionization vs depth measurement is shown in Figure IV.3.2.

Figure IV.3.2 is, as expected, in the shape of a typical plot of stopping power vs depth for any heavy charged particle. The Bragg peak near the end of range occurs in this measurement due to greater ionization in the ionization chamber which will be collected with increasing energy deposition per unit path length. As can be readily seen, the distal portion of the Bragg peak has a steep but finite slope. Therefore, the end of range of the protons in the water bath is not defined as the position where the ionization curve intersects the x-axis but rather as the mean proton end of range. This "range
Figure IV.3.2: Plot of Relative Ionization Measured as a Function of Depth in Water
straggling° causing the individual protons in the beam to come to rest at slightly different positions is due to the statistical nature of the protons interactions with the atomic electrons in the water. We are only able to determine the average distance where an incident proton of a given energy will stop in a given material.

This mean proton range is good enough to determine to very small uncertainty the energy of the incident beam upon the water tank. By noting the mean range in water and also considering the thickness of the polystyrene wall of the water tank, one can either calculate or more easily look up in the aforementioned range energy tables the energy of the protons in the beam.
Section IV.3.3 Dose Calibration of Ion Chambers with Faraday Cup

After determining the energy of the protons in the beam, the next step is to find the beam current in order to calculate the calibration factor of dose to tissue per parallel plate ionization chamber monitor unit. This measurement is accomplished using both a Faraday cup and a small thimble ionization chamber.

Figure IV.3.3 shows the beam geometry and aperture arrangement with the water bath removed and the Faraday cup and the small thimble ionization chamber placed in the position where the absorbed dose is to be calculated. The initial measurement is made with the thimble ion chamber removed.

The Faraday cup that was used in these experiments has been provided with a guard ring which can be placed at varying potentials and windings which permit the application of a magnetic field within the steel casing. Both of these affect the number of low-energy secondary electrons which enter or leave the collecting volume and may be used to determine the uncertainty in charge collection resulting from these electron secondaries. The Faraday cup is large enough and is placed close enough to the proton beam exit so as to intercept all of the diverging proton beam.

Once the beam is turned on during the calibration process, the charge collected by both the parallel plate ionization chamber, $Q_{pic}$, and the Faraday cup, $Q_{fc}$, is measured by two electrometers. The charge collected by the Faraday cup is of course directly related to the number of protons incident upon the cup during the calibration
Figure IV.3.3: Placement of Faraday Cup and Thimble Ion Chamber in the Proton Beam
period.

Once the absolute value of the number of protons is measured in this manner, this value can be related to the charge collected on the parallel plate ionization chamber.

The next step in the calibration process is the removal of the Faraday cup and the insertion of a small thimble ionization chamber at a point where the proton dose is to be determined. The beam is run again and a charge is measured from both the parallel plate ionization chamber and the thimble ionization chamber.

Since we have just measured the charge collected on the parallel plate ionization chamber per proton in the incident beam, and we now know the unit charge collected on the thimble chamber per charge measured on the parallel plate ionization chamber, we can easily calculate the charge collected on the thimble ionization chamber per proton in the incident beam.

At this point, we can calculate the calibration factor of dose to a volume of tissue placed at the position of the thimble ionization chamber per monitor unit of the parallel plate ionization chamber. The only other piece of information needed is the stopping power of protons of this energy in tissue. A very complete set of tables of stopping powers can be found in in the reference by J. F. Janni (Janni, J.F., AFWL-TR-65-150, Air Force Weapons Lab, 1966).
Knowing the energy of the incident protons, the area of the beam, the charge collected on the thimble ion chamber per proton, the charge collected on the parallel plate ion chamber per unit charge collected on the thimble ion chamber, and the stopping power of the protons in tissue, one can write:

\[
\frac{\text{dose to tissue}}{Q_{\text{pic}}} = \frac{Q_{\text{tic}}}{Q_{\text{pic}}} \cdot \frac{P_+}{Q_{\text{tic}}} \cdot \frac{1}{A} \cdot \frac{1}{\rho} \cdot \frac{dE}{dx} \quad (\text{IV.3.3.1})
\]

After the parallel plate ionization chamber has been calibrated in the above manner, the dose to any material placed in the beam path can be readily measured simply by measuring the charge collected on the thimble ion chamber at the position of the material and knowing the stopping power in that material. Since everything is calibrated back to the original parallel plate ionization chamber, one may easily deliver a predetermined dose to an object by setting the correct number of monitor units to be counted before the cyclotron is shut off.

If the calibration is done carefully in a well collimated high energy monoenergetic proton beam, this produces a calibration factor which may be used in beams of different qualities. The uncertainties and assumptions that are considerations in proton dosimetry in different proton beams are the subject of the next section.
Section IV.3.4 Estimation of Uncertainties in Dose Measurement

In the previous section it was stated that, after calibration of both the parallel plate ion chamber and the thimble ion chamber in a specific well-defined proton beam, one could measure the dose in proton beams which may be polychromatic or of different geometries using the following calibration factor for the thimble ion chamber:

\[
\frac{\text{dose to tissue}}{Q_{\text{pic}}} = \frac{Q_{\text{tic}}}{Q_{\text{pic}}} \cdot \frac{P^{+}}{A} \cdot \frac{1}{\rho} \cdot \frac{dE}{dx}
\]

In order to make the above statement, a number of assumptions implied in the calibration procedure must be analyzed. The most important of these assumptions are:

1) The calibration beam is truly monochromatic and of well known energy.

2) The Faraday cup counts protons with 100% efficiency.

3) The response of the thimble ion chamber varies linearly with deposited energy.

4) The response of the thimble ion chamber is independent of LET.

5) The effects of nuclear interactions on the calibration procedure may be neglected.
Tests of these assumptions and measurements of the uncertainties in the Faraday cup based dosimetry procedure have been made at the Harvard Cyclotron and were reported by Verhey, et al. (Verhey, L.J., et al., Rad. Res. 79: 34–54, 1979). In addition, this dosimetry procedure was compared to a calorimetric measurement of dose.

The results of the estimated uncertainties in Faraday cup dosimetry as measured and calculated by Verhey, et al are contained in Table IV.3.4.1. Most of the entries in this table are self-explanatory. The entries listed under the percentage uncertainties due to general and columnar recombination effect the thimble and parallel plate ion chambers with respect to their response as a function of deposited energy and LET. If recombination occurs, the ion pairs are not collected and the dose estimate is lowered.

The comparison of the Faraday cup dosimetry with the calorimetric measurement gave results in close agreement (about 4% difference). Dosimetry intercomparisons have been carried out with the thimble ion chamber from the Harvard Cyclotron at charged particle facilities throughout the world. As a result of the above measured and calculated uncertainties and these intercomparisons, the total uncertainty in measure dose from the Faraday cup based procedure is taken to be on the order of 5% (personal conversation - L. Verhey).
Table IV.3.4.1: Estimated Uncertainties in Faraday Cup Dosimetry

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficiency of Faraday Cup</td>
<td>1.0</td>
</tr>
<tr>
<td>Range of Calibration Beam</td>
<td>0.3</td>
</tr>
<tr>
<td>dE/dx</td>
<td>2.0</td>
</tr>
<tr>
<td>Low Energy Protons</td>
<td>0.5</td>
</tr>
<tr>
<td>Effective Area</td>
<td>0.5</td>
</tr>
<tr>
<td>General Recombination</td>
<td>0.2</td>
</tr>
<tr>
<td>Columnar Recombination</td>
<td>1.5</td>
</tr>
<tr>
<td>Nuclear Interactions</td>
<td>1.0</td>
</tr>
<tr>
<td>Measurement Precision</td>
<td>2.0</td>
</tr>
</tbody>
</table>

| Total Uncertainty with Individual Errors added in Quadrature | 3.7 |

Section IV.4 Measurement of Activity Produced in Phantoms

It is possible to check the calculation made in Section III.2 by making a measurement of activity production or reaction cross section. Rather than making a single measurement, it is desirable to make measurements along the beam axis as it traverses some absorber material. This will not only allow an actual measurement of the activity distribution from an incident proton beam, but will provide a check of cross section measurements as a function of energy which can be calculated from the residual proton range.

The activated material used in this experiment was lucite or polymethylmethacrylate which has a composition of $C_5H_8O_2$. The lucite material was machined into small cylindrical disks with a radius of 1 cm and a thickness of 0.95 cm. The absorbing material, placed in front of the disks, in this case was water.

The irradiation set-up is shown in schematic in Figure IV.4.1. The protons are collimated into a beam significantly larger than the diameter of the face of the lucite disk. They then traverse a distance of water and impinge upon the lucite disk.

The water is contained in a "water telescope" which may be lengthened or retracted to provide an easily measurable amount of water absorber to be placed in front of the lucite disk. When the telescope is lengthened, water is drawn from the holding bottle so as to completely fill the volume. When retracted, the water is pushed back into the same bottle. The lucite disk was taped to a lucite window at the distal end of the water telescope for irradiation.
Figure IV.4.1: Irradiation Set-Up for Measurement of Activity vs Depth
The activation vs depth experiment was performed in the following manner: The water telescope was retracted fully leaving only 2.6 cm of water absorber between proton entrance and the exit window. A small silicone diode was taped to the front of the lucite window in this position. The cyclotron was operated for a few monitor units and a reading was taken of the charge collected by the diode. The water telescope was lengthened and the process repeated. In this manner, the data for a relative ionization vs depth curve could be taken in the exact configuration of the irradiation of the lucite phantom disks.

The silicone diode was then removed and the water telescope was again fully retracted. A lucite disk was taped to the exit window and irradiated with a fixed number of monitor units and thus a fixed flux of protons (see section IV.3). Immediately after irradiation, the disk was placed in the geometric center of the coincidence counting apparatus, the face of the lucite disk parallel with the face of the crystals. A set of coincidence counts vs time data was then taken for the disk. This procedure was then repeated with the water telescope lengthened to a new position and thus more water absorber placed in front of the lucite disk being activated.

At the end of the experiment, a set of coincidence counting data had been generated for the decay of an activated lucite disk located at different positions along the proton beam axis. This data was then analyzed by the program CHIFIT (see section III.3) by fitting the data with a function of the sum of two exponentials one governing the physical decay of 0-15 and the other governing the physical decay of
C-11. In this manner, the initial activity of each component could be found. By dividing the initial activity by the appropriate decay constant, the initial number of detected activated nuclei of each type could be found.

Figure IV.4.2 shows a plot of the initial number of detected O-15 activated nuclei vs depth of water absorber plotted under the relative ionization curve. Figure IV.4.3 shows the initial number of detected C-11 activated nuclei vs depth of water absorber plotted under the same relative ionization curve.

As can be seen from these figures, the distribution of activation is relatively uniform until the end-of-range of activation when it drops off rapidly. The end of range of activation does not correspond to the end of range of the protons as, after the protons have decreased in energy below reaction threshold, the activation of O-15 and/or C-11 cannot occur. This distribution of activation is similar to that measured by other researchers (Bennett, G.W., et. al., Nucl. Inst. Methods 125: 333-338, 1975).

As a check, the magnitude of the actual number of detected nuclei at a given energy may be checked with that calculated in Section III.2. In section III.2, it was calculated that, at 100 MeV, the initial number of activated O-15 nuclei from lucite would be $7.3 \times 10^3$ O-15/cc/rad and the initial number of activated C-11 nuclei would be $2.0 \times 10^4$ C-11/cc/rad.
Figure IV.4.2: Plot of 0-15 Activation vs Depth
Figure IV.4.3: Plot of C-11 Activation vs Depth
In order to calculate the initial number of activated nuclei, the detection efficiency has to be known. This was done with the aid of a table of detection efficiencies (Grosjean, C.C. and Brosaert, W., Table of Absolute Detection Efficiencies of Cylindrical Scintillation Gamma-Ray Detectors, Computing Laboratory, University of Ghent, Belgium, 1965). These tables allow the user to calculate detection efficiencies of planar sources located at some distance from the face of a NaI crystal of some given dimensions. In order to use the tables, the lucite disk was taken to be a circular planar disk located at a distance from the crystal face that corresponded to the crystal face to disk face distance plus one-half the disk thickness.

The distance from the lucite disk centerline to either of the crystals faces was approximately 6 cm. From the tables mentioned above, this gave an intrinsic detection efficiency of 0.38 and a geometric efficiency of 0.16. Since the intrinsic efficiency is that for a single crystal, the total intrinsic efficiency for the coincidence system is the square of 0.38 or 0.14. The total detection efficiency is thus 0.14x0.16 or 0.022.

Each lucite disk was given 10 monitor units which, at 100 MeV was calibrated to be equal to 39 rads. The volume of the lucite disk was 2.98 cc. The number of detected O-15 nuclei in the disk at the start of counting at 100 MeV was 13842 and the number of detected C-11 at the start of counting was 41739. The transferal time from the irradiation position to the start of counting was 30 seconds so that the number of detected O-15 and C-11 immediately at the end of irradiation was 16478 and 42590 respectively.
The number of activated $^{0-15}$ measured per cc per rad may now be calculated:

\[ \frac{16478}{0.022} \div (2.98 \text{ cc}) \cdot (39 \text{ rad}) = 6.4 \times 10^3 \frac{^{0-15}}{\text{cc rad}} \]

The measured number of $^{C-11}$ activated per cc per rad is:

\[ \frac{42590}{0.022} \div (2.98 \text{ cc}) \cdot (39 \text{ rad}) = 1.7 \times 10^4 \frac{^{C-11}}{\text{cc rad}} \]

Calculating the statistical errors gives the initial activity of $^{0-15}$ a value of $6.4 \times 10^3 \pm 118$ and for $^{C-11} 1.7 \times 10^4 \pm 298$.

Considering the magnitude of the other errors in each of the determinations there is a very close agreement between the calculated activity for $^{0-15}$ and $^{C-11}$ and the measured values. Considering the fact that both of our measurements were low (as were the other measurements at other range/energies as compared to values in the literature), there is a high probability that a systematic error in either or detection efficiency or flux measurement or range measurement was responsible. For an agreement this close, however, it was decided that such errors were of negligible importance in the final goal of blood flow measurement.
CHAPTER V: BLOOD FLOW MEASUREMENTS

Section V.1 Introduction

The measurement of blood flow by activation of O-15 and C-11 with protons was made in the upper leg of a number of mice. There were four set of experiments performed. These experiments were designed in order to attempt to demonstrate a few rudimentary postulates about the behavior of the component of biologic wash-out.

The first experiment consisted of the irradiation and monitoring the leg of four mice at different doses both alive and dead. This was simply to show that dead mice have two decay components, one each for the physical decays of O-15 and C-11, and that live mice have a third component due to perfusion.

The second experiment was an attempt to demonstrate the effect of anesthesia on the measured value of blood flow as well as an attempt to achieve some degree of reproducibility in the results of the blood flow analysis. It was thought that the large variability in the measured values of blood flow in the first experiment was due to the different effects upon the mice of their placement in the mouse positioning apparatus. If the mice were placed under anesthesia, it was thought that the trauma of being placed in the "mouse-holder" would not be a blood flow influencing factor.

The third experiment was an attempt to manipulate the measured value of blood flow through the use of a tourniquet. If the measured value of blood flow was reduced when the tourniquet was applied, then that would substantiate the hypothesis that the wash-out of activated
nuclei was governed by blood flow rate.

The fourth and final experiment was another attempt to demonstrate the reproducibility of the activation analysis technique. Rather than use many different mice, a single mouse was placed in the mouse-holder and was allowed to adjust to his new uncomfortable surroundings for fifteen minutes in position for irradiation and counting. A number of measurements were made without disturbing the position of the mouse in the hope that the blood flow and thus the half-life of biologic removal would remain constant over the series of measurements.

The remainder of this chapter is concerned with the discription, results, and analysis of these experiments as well as a discussion of the assumptions and uncertainties implicit in the measurement of blood flow as calculated in this work.
Section V.2 Description of Experimental Apparatus and Procedure

The coincidence detection apparatus used in the following animal experiments is the same as that described in Section IV.2. The output from the coincidence unit is fed into a CAMAC scaler. The counts versus time information is thus controlled by and entered into a PDP 11 series computer located at the Harvard Cyclotron. A file containing this data may then be sent via telephone modem to a VAX 11-780 computer at the Massachusetts General Hospital. Once at MGH, the decay data may be analyzed by CHIFIT (see Section III.3) and printed on a line printer using specially developed software. A schematic of this process is shown in Figure V.2.1.

The mouse collimator/holder, which was designed and constructed for these experiments is shown in schematic in Figure V.2.2. The material used in its construction is a composite of relatively high Z metals with a low melting point (trade name - Cerrobend) so that molding the collimator was easily accomplished. A special proton collimator was machined from brass to insure uniform proton irradiation over the exposed thigh area. The irradiated area corresponded to a portion of the thigh of the mouse weighing slightly less than one gram (usually between 0.7 and 0.8 grams).

The mouse collimator/holder is placed between the crystals such that the center of the irradiated mouse thigh region corresponds to the geometric center of the two crystals. There is approximately 4mm between the upper and lower edges of the irradiated area and the upper and lower edges of the mouse collimator/holder to allow for height positioning error and some small angle scatter from the edges of the
Figure V.2.1: Schematic of Data Collection and Analysis Process

TO SCA FROM CRYSTAL B

TO SCA FROM CRYSTAL A

COINCIDENCE UNIT

CAMAC TIMER AND COUNTER

TIMING INFORMATION

COUNTING INFORMATION

PDP COMPUTER AT THE CYCLOTRON

FILES CONTAINING COUNTING DATA

CYCLOTRON TELEPHONE MODEM

PHONE LINES

MGH TELEPHONE MODEM

VAX COMPUTER AT THE MGH

LINE PRINTER
Mouse collimator has top removed to show proton path. NaI detectors are housed in lead brick shields.

Cross section of mouse collimator:
The body of the mouse is held in the lower cylinder with the thigh region exposed between the two halves of the collimator. The ankle and foot are tethered within the upper cylinder and are secured to the brass anchor plate bolted to the top of the collimator.

Figure V.2.2: Schematic of Mouse Irradiation Apparatus
final proton collimator. The potential for activating some material other than the desired mouse thigh area was always an important consideration in the design and set-up.

From Figure V.2.2, it is possible to visualize the fate of proton activated nuclei. If an activated nucleus contained in the thigh area is incorporated into some large biologic macromolecule and thus remains stationary, its decay may be observed by the NaI crystals. If, however, the nucleus is mobile and washed out of the thigh region by the blood flow in the thigh, it will be moved into the collimated region of the mouse's body where, when it decays, the resulting annihilation photons will not be detected.

The procedure for each mouse thigh measurement is as follows: After a check of the functional operation of the detection equipment, (see Section IV.2) and a dosimetry calibration, (see Section IV.3) the first mouse is loaded into the mouse collimator/holder. The mouse is then placed into position between the two detectors as shown in Figure V.2.2. In order to check the positioning of the mouse, an x-ray film is taken of the proton beam's view of the mouse leg. This is illustrated in Figure V.2.3.

The x-ray tube is placed down stream of the protons behind the mouse. Film is then placed in the proton beam line behind the proton collimator. The desired x-ray image is that of a centered portion of the mouse's thigh framed by the proton beam collimator with no other portions of the apparatus sticking into view. An illustration of a typical proton beam's view x-ray film is also shown in Figure V.2.3.
Figure V.2.3: X-Ray Positioning Apparatus and Film
Figure 1.2.3: X-ray Positioning Apparatus and Film
After completing the mouse positioning, the CAMAC unit is initialized through a data acquisition program and the mouse is ready for irradiation. The thigh of the mouse is given a pre-set number of "monitor units" and thus rads (again see Section IV.3) and immediately upon completion of the irradiation the CAMAC unit is sent a command to begin counting. The number of coincidences are taken over five second intervals for a total counting duration of fifteen minutes.

When the desired number of mice are irradiated and counted, the files containing the mouse decay data as well as background runs are sent to the VAX at MGH for analysis.
Section V.3 Experiment A: Analysis of Decay in Live and Dead Mice

This first experiment was performed simply to demonstrate the existence of a third decay component in live mice. The experiment used four mice which were irradiated and counted as described in the previous section while alive and then were sacrificed, remounted, and irradiated and counted again. Three different proton doses were used; 50, 100, and 200 rads. The results of the irradiation and counting of the dead mice will be presented first.

A typical decay curve resulting from the decay of the activated portion of a dead mouse thigh is shown in Figure V.3.1. The program CHIFIT when asked to fit the data with a function containing the expected two decay components of O-15 and C-11, was able to do so for each of the dead mice. If asked to fit a third component, CHIFIT would return a value of the fitted decay constant of 0.0057762 or the same as O-15 and would split the two initial decay rates among the two oxygen components. Thus, a separate third component could never be found.

A summary of the data obtained from the analysis of the decays from all of the irradiated dead mice is contained in Table V.3.1. In this table are not only the four mice from experiment A but also five other mice that were killed and irradiated after Experiment B.

By looking at Table V.3.1, one may see that the fitted initial decay rate from these mice had a significant variation when the proton dose was the same. By dividing by the appropriate decay constant, the initial number of detected nuclei of each type may be found. It is
Figure V.3.1: Two Component Decay Curve from the Thigh of a Dead Mouse
Table V.3.1 Experiment A: Physical Data from the Activation and Decay of Dead Mice

<table>
<thead>
<tr>
<th>Mouse</th>
<th>Dose (rads)</th>
<th>Initial Decay Rate (cts/ t)</th>
<th>Initial Number of Nuclei</th>
<th>Ratio of Initial Nuclei</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0-15</td>
<td>C-11</td>
<td>0-15</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>178.9</td>
<td>20.5</td>
<td>6411</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 2.3</td>
<td>± 0.7</td>
<td>± 82</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>365.8</td>
<td>43.3</td>
<td>13085</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 3.2</td>
<td>± 1.0</td>
<td>± 114</td>
</tr>
<tr>
<td>3</td>
<td>200</td>
<td>632.6</td>
<td>75.5</td>
<td>22675</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 4.2</td>
<td>± 1.3</td>
<td>± 151</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>423.2</td>
<td>56.5</td>
<td>15171</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 3.6</td>
<td>± 1.1</td>
<td>± 129</td>
</tr>
<tr>
<td>A1</td>
<td>50</td>
<td>464.3</td>
<td>56.9</td>
<td>8171</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 5.4</td>
<td>± 1.6</td>
<td>± 95</td>
</tr>
<tr>
<td>A2</td>
<td>100</td>
<td>462.7</td>
<td>54.2</td>
<td>16552</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 3.6</td>
<td>± 1.1</td>
<td>± 131</td>
</tr>
<tr>
<td>A3</td>
<td>150</td>
<td>681.6</td>
<td>85.9</td>
<td>24431</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 4.4</td>
<td>± 1.4</td>
<td>± 158</td>
</tr>
<tr>
<td>B1</td>
<td>50</td>
<td>484.5</td>
<td>63.2</td>
<td>8533</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 5.5</td>
<td>± 1.7</td>
<td>± 98</td>
</tr>
<tr>
<td>B2</td>
<td>100</td>
<td>430.6</td>
<td>55.1</td>
<td>15435</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 3.6</td>
<td>± 1.1</td>
<td>± 127</td>
</tr>
</tbody>
</table>

Note: Last five entries are from Experiment B
reasonable to expect that even if the initial number of detected nuclei may vary due to dose or variation in the physical size of the individual mouse's leg, that the ratio of activated O-15 to activated C-11 should be about the same from mouse to mouse. This was found to be the case within statistical error of the measurement. The average value of this ratio was found to be 0.81 with a standard deviation of 0.04. This ratio is low compared with the result which might have been predicted from the theoretical calculation contained in Section III.2. This prediction, for irradiation of a tissue with a composition of standard man, would give a ratio of activated O-15 to C-11 to be 1.6. It is possible that the lower value for the relative amount of oxygen activation found in the mouse thigh may be due to the presence of a large percentage of bone in the tissue with its relatively higher concentration of carbon. That these ratios are consistent should be a more important consideration to this measurement than the predictability of the their absolute values.

The irradiation and decay of the thigh of a live mouse produced a decay curve such as that shown in Figure V.3.2. A very short third component is easily seen and was easily fit by CHIFIT. A fourth component could, in all cases, not be found.

The results of curve fitting all four of the live mice are shown in Table V.3.2. The decay plots and fitted curves of all of the mice may be found in Appendix A. Table V.3.3 shows the initial decay rates transformed to the initial number of each type of nuclei. In addition, Table V.3.3 gives the value of blood flow corresponding to the observed wash-out decay constant calculated by using equation
Figure V.3.2: Decay Curve from the Activation and Decay of a Thigh of a Live Mouse
Table V.3.2 Experiment A: Physical Data from the Activation and Decay of Live Mice

<table>
<thead>
<tr>
<th>Mouse</th>
<th>Dose (rad)</th>
<th>Initial wash-out</th>
<th>Decay Rate (cts/ t)</th>
<th>Half life (secs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0-15</td>
<td>0-11</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>121.2 ±11.1</td>
<td>119.7 ±3.6</td>
<td>10.2 ±0.6</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>342.6 ±16.1</td>
<td>165.4 ±10.3</td>
<td>32.6 ±1.0</td>
</tr>
<tr>
<td>3</td>
<td>200</td>
<td>181.8 ±15.4</td>
<td>241.6 ±9.7</td>
<td>28.8 ±1.0</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>367.7 ±15.3</td>
<td>175.9 ±5.8</td>
<td>42.5 ±1.0</td>
</tr>
</tbody>
</table>

Table V.3.3 Experiment A: Measurement of Blood Flow in Live Mice

<table>
<thead>
<tr>
<th>Mouse</th>
<th>Dose(rad)</th>
<th>Initial wash-out</th>
<th>Number of Nuclei</th>
<th>Blood Flow (ml/min/100 grams)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0-15</td>
<td>0-11</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>811 ±74</td>
<td>4290 ±129</td>
<td>3686 ±216</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>5898 ±277</td>
<td>5930 ±369</td>
<td>11682 ±358</td>
</tr>
<tr>
<td>3</td>
<td>200</td>
<td>2970 ±251</td>
<td>8643 ±347</td>
<td>10314 ±355</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>3036 ±127</td>
<td>5305 ±208</td>
<td>15217 ±360</td>
</tr>
</tbody>
</table>
The first impression of this blood flow data is that the calculated values have a very large variability. The very large value for the blood flow in mouse 1 is relatively unusual in that, in many subsequent measurements in mice performed both during and after the course of this work, a value close to this magnitude was never observed.

The blood flow values calculated in these series of experiments are quite believable. Alternate measurements of blood flow in mouse skeletal muscle found in the literature give values ranging from 40 to 70 ml/min/100 grams (Peterson, H.I., Tumor Blood Circulation, CRC Press, Florida, 1979). The majority of the mouse measurements contained in this thesis lie within this range. A typical value for human resting skeletal muscle is 50 ml/min/100 gr and for exercising skeletal muscle, 100 ml/min/100 gr (Lassen, N.A. and Perl, W., Tracer Kinetic Methods in Medical Physiology, Raven, New York, 1979).

In order to demonstrate that the biologic wash-out is indeed a single exponential, the two physical components were subtracted from the decay data and the resulting data has been plotted in Figure V.3.2. For all of the four mice irradiated in Experiment A, the assumption of the wash-out being a single exponential seems to be valid. In a more heterogeneous tissue region, this may not be the case.
Figure V.3.3: Typical Plot of a Mono-Exponential Wash-Out Curve

from the Activation and Decay of a Live Mouse
Another interesting fact which may be gathered from Table V.3.3, is that the ratio of fixed to mobile nuclei is not a constant from mouse to mouse. This is not an important consideration in terms of the absolute value of blood flow, but the magnitude of this ratio will have an effect upon the uncertainty in the measurement (see Section III.5.3). The inconsistency of this ratio is surprising, however, in light of the expected uniformity of the experimental animals. This phenomena is one which warrents further investigation.
Section V.4 Experiment B: Analysis of Decay in Anesthetized Mice

Due to the large variability in measured blood flow observed in experiment A, it was desired to try and achieve some degree of reproducibility among the measurements by placing the mice under anesthesia. The rationale for this decision, was that the variability in blood flow was due to the different degrees of trauma experienced by the mice while being placed in the mouse collimator/holder apparatus. Since the different mice seemed to respond differently to the mounting procedure, it was reasoned that different levels of physiological stress were being introduced. It was thought that anesthesia would eliminate this variable.

Fifteen mice were irradiated and counted with each mouse being given a dose of sodium barbitate (50 mg/Kg body weight) ten minutes prior to irradiation. A given mouse would normally take two to three minutes to fall asleep and would remain unconscious for about 45 minutes. The counting time was again fifteen minutes.

The mice were numbered and irradiated in the following order: A1, B1, C1, ..... A5, B5, C5 with all A mice receiving 50 rads, the B mice receiving 100 rads, and the C mice receiving 150 rads.

The results of the curve fitting procedure are shown in Tables V.4.1 for the A mice, V.4.2 for the B mice, and V.4.3 for the C mice. The corresponding analysis of the initial numbers of each type of nuclei and the blood flow calculation results are contained in Tables V.4.4, V.4.5, and V.4.6.
Table V.4.1 Experiment B: Physical Data from the Activation and Decay of Anesthetized Mice

<table>
<thead>
<tr>
<th>Mouse</th>
<th>Dose (rad)</th>
<th>Initial Decay Rate (cts/ t)</th>
<th>Half life (secs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>wash-out</td>
<td>0-15</td>
</tr>
<tr>
<td>Al</td>
<td>50</td>
<td>306.4</td>
<td>± 27.8</td>
</tr>
<tr>
<td>Bl</td>
<td>50</td>
<td>322.1</td>
<td>± 28.4</td>
</tr>
<tr>
<td>Cl</td>
<td>50</td>
<td>218.7</td>
<td>± 27.7</td>
</tr>
<tr>
<td>Dl</td>
<td>50</td>
<td>248.9</td>
<td>± 27.8</td>
</tr>
<tr>
<td>El</td>
<td>50</td>
<td>310.7</td>
<td>± 30.8</td>
</tr>
</tbody>
</table>
Table V.4.2 Experiment B: Physical Data from the Activation and Decay of Anesthetized Mice

<table>
<thead>
<tr>
<th>Mouse</th>
<th>Dose (rad)</th>
<th>Initial Decay Rate (cts/t)</th>
<th>Half life (secs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>wash-out</td>
<td>0-15</td>
</tr>
<tr>
<td>A2</td>
<td>100</td>
<td>207.9</td>
<td>351.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 25.7</td>
<td>± 20.4</td>
</tr>
<tr>
<td>B2</td>
<td>100</td>
<td>154.3</td>
<td>395.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 18.1</td>
<td>± 11.7</td>
</tr>
<tr>
<td>C2</td>
<td>100</td>
<td>255.8</td>
<td>343.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 17.1</td>
<td>± 9.6</td>
</tr>
<tr>
<td>D2</td>
<td>100</td>
<td>150.5</td>
<td>323.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 17.2</td>
<td>± 11.4</td>
</tr>
<tr>
<td>E2</td>
<td>100</td>
<td>187.9</td>
<td>373.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 18.8</td>
<td>± 12.6</td>
</tr>
</tbody>
</table>
Table V.4.3 Experiment B: Physical Data from the Activation and Decay of Anesthetized Mice

<table>
<thead>
<tr>
<th>Mouse</th>
<th>Dose (rad)</th>
<th>Initial Decay Rate (cts/t)</th>
<th>Half life (secs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>wash-out</td>
<td>0-15</td>
</tr>
<tr>
<td>A3</td>
<td>150</td>
<td>454.5</td>
<td>332.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>±52.8</td>
<td>±47.1</td>
</tr>
<tr>
<td>B3</td>
<td>150</td>
<td>281.6</td>
<td>637.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>±27.9</td>
<td>±20.6</td>
</tr>
<tr>
<td>C3</td>
<td>150</td>
<td>180.1</td>
<td>393.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>±17.6</td>
<td>±10.7</td>
</tr>
<tr>
<td>D3</td>
<td>150</td>
<td>372.1</td>
<td>196.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>±35.7</td>
<td>±30.7</td>
</tr>
<tr>
<td>E3</td>
<td>150</td>
<td>186.7</td>
<td>657.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>±23.0</td>
<td>±15.0</td>
</tr>
</tbody>
</table>
By looking at Tables V.4.4 thru V.4.6, it is apparent that there was some success in achieving a greater degree of uniformity among measurements. Again, there is very little reproducibility with respect to the ratio of fixed to mobile nuclei.

Table V.4.7 gives the average values of blood flow measured from these three groups of mice and their standard deviation as well as the average of fixed to mobile nuclei. A disturbing result of this tabulation is that there appears to be a dose effect in the measurement. This could be explained by a deviation from a single compartment model. If there were a very fast component, it may be detected by the irradiation with a smaller dose given in a shorter time. This may explain the higher average value for the 50 rad case.

The above explanation is, however, probably not correct. If there were a very fast component that is not found in the case of higher doses (and thus longer irradiations) then this component could be ignored in the shorter/lower dose case by not analyzing the first minute of counts vs time data. Doing this produced no change in the fitted value of wash-out in the 50 rad cases and thus there is only a single exponential present.

There are only a few statements which can be made about the results of this specific experiment. Anesthesia does not appear to greatly reduce the amount of variability in measured blood flow among the different mice although the variability is reduced somewhat. There is not a great difference in average blood flow measured when the animal is placed under anesthesia as opposed to awake. A more rigorous study of this specific effect may, however, show otherwise.
Table V.4.4 Experiment B: Measurement of Blood Flow in Anethetized Mice

<table>
<thead>
<tr>
<th>Mouse</th>
<th>Dose (rad)</th>
<th>Initial wash-out</th>
<th>Number of nuclei</th>
<th>Blood Flow (ml/min/100 grams)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>50</td>
<td>1896 ±172</td>
<td>7519 ±243</td>
<td>7476 ±299</td>
</tr>
<tr>
<td>B1</td>
<td>50</td>
<td>1915 ±168</td>
<td>7820 ±241</td>
<td>8094 ±300</td>
</tr>
<tr>
<td>C1</td>
<td>50</td>
<td>1180 ±149</td>
<td>7984 ±221</td>
<td>7891 ±299</td>
</tr>
<tr>
<td>D1</td>
<td>50</td>
<td>1770 ±197</td>
<td>7221 ±274</td>
<td>8348 ±317</td>
</tr>
<tr>
<td>E1</td>
<td>50</td>
<td>1507 ±149</td>
<td>8981 ±227</td>
<td>9950 ±316</td>
</tr>
</tbody>
</table>
Table V.4.5 Experiment B: Measurement of Blood Flow in Anethetized Mice

<table>
<thead>
<tr>
<th>Mouse</th>
<th>Dose (rad)</th>
<th>Initial wash-out</th>
<th>Number of Nuclei 0-15</th>
<th>Blood Flow (ml/min/100 grams)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A2</td>
<td>100</td>
<td>4824 ± 596</td>
<td>12598 ± 731</td>
<td>13355 ± 465</td>
</tr>
<tr>
<td>B2</td>
<td>100</td>
<td>2627 ± 308</td>
<td>14184 ± 1657</td>
<td>12186 ± 395</td>
</tr>
<tr>
<td>C2</td>
<td>100</td>
<td>3526 ± 235</td>
<td>12318 ± 344</td>
<td>15419 ± 430</td>
</tr>
<tr>
<td>D2</td>
<td>100</td>
<td>2619 ± 300</td>
<td>11584 ± 407</td>
<td>11068 ± 394</td>
</tr>
<tr>
<td>E2</td>
<td>100</td>
<td>3356 ± 336</td>
<td>13379 ± 451</td>
<td>12631 ± 430</td>
</tr>
</tbody>
</table>
Table V.4.6 Experiment B: Measurement of Blood Flow in Anethetized Mice

<table>
<thead>
<tr>
<th>Mouse</th>
<th>Dose (rad)</th>
<th>Initial wash-out</th>
<th>Number of nuclei</th>
<th>Blood Flow (ml/min/100 grams)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>O-15</td>
<td>C-11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A3</td>
<td>150</td>
<td>12920 ± 1501</td>
<td>11888 ± 1680</td>
<td>20795 ± 619</td>
</tr>
<tr>
<td>B3</td>
<td>150</td>
<td>5834 ± 578</td>
<td>22836 ± 738</td>
<td>21859 ± 574</td>
</tr>
<tr>
<td>C3</td>
<td>150</td>
<td>2740 ± 267</td>
<td>14093 ± 382</td>
<td>14336 ± 429</td>
</tr>
<tr>
<td>D3</td>
<td>150</td>
<td>9839 ± 944</td>
<td>7055 ± 1100</td>
<td>18542 ± 538</td>
</tr>
<tr>
<td>E3</td>
<td>150</td>
<td>3145 ± 387</td>
<td>23503 ± 536</td>
<td>22536 ± 536</td>
</tr>
</tbody>
</table>
Table V.4.7: Average Blood Flow Measurement Results for Anesthetized Mice

<table>
<thead>
<tr>
<th>Dose (rad)</th>
<th>Average Ratio of Mobile to Fixed Nuclei</th>
<th>Average Blood Flow (ml/min/100 gr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>0.10 ± 0.02</td>
<td>95.6 ± 23.2</td>
</tr>
<tr>
<td>100</td>
<td>0.13 ± 0.03</td>
<td>60.8 ± 15.0</td>
</tr>
<tr>
<td>150</td>
<td>0.21 ± 0.16</td>
<td>55.6 ± 11.3</td>
</tr>
</tbody>
</table>
There may also be an unexplained dose effect which will be tested in the next section.

The next section contains the results of experiments which were performed in order to answer some of the questions about variability and dose effect raised in this section.
Section V.5 Experiment C: Reproducibility of Blood Flow Measurement

There are two separate experiments to be discussed in this section. In the first, a single mouse was placed in the mouse collimator/holder and placed in position to be counted and irradiated. After sitting in position for 30 minutes, the mouse was irradiated with 100 rads of protons and counted for 15 minutes. After the counting period was over, the mouse was irradiated again and counted for another 15 minutes. In all, the same mouse, without being moved from its original position, was irradiated and counted five times. The mouse was not anesthetized.

The second experiment was performed in a similar manner to the first using another mouse. The only change was that each irradiation was performed at a different proton dose.

By doing these two experiments, it was believed that the reproducibility for this animal and holder situation could most accurately be measured. By varying the dose in the second measurement, it is possible to look at the dose dependence problem hinted at by the last data set performed with anesthetized animals.

The results of the curve fitting analysis for the stationary mouse performed at a single dose may be found in Table V.5.1 and the blood flow analysis results may be found in Table V.5.2. From these two tables, it can be seen that the variability between measurements is greatly reduced. It is expected that some variability will always exist in this type of measurement as it is very likely that the physiology of the mouse hanging upside-down in the mouse
Table V.5.1 Experiment C: Physical Data from the Activation and Decay of a Stationary Mouse

<table>
<thead>
<tr>
<th>Trial</th>
<th>Dose (rad)</th>
<th>Initial Decay Rate (cts/ t)</th>
<th>0-15</th>
<th>C-11</th>
<th>Half life (secs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>wash-out</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>100</td>
<td>103.4 ± 15.5</td>
<td>246.6 ± 10.8</td>
<td>20.3 ± 1.0</td>
<td>63.4 ± 16.2</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>52.2 ± 14.2</td>
<td>279.3 ± 9.0</td>
<td>26.6 ± 1.0</td>
<td>53.4 ± 8.7</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>147.1 ± 23.4</td>
<td>308.2 ± 11.6</td>
<td>37.7 ± 1.1</td>
<td>52.1 ± 13.6</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>81.6 ± 15.7</td>
<td>257.9 ± 10.7</td>
<td>35.1 ± 1.1</td>
<td>58.6 ± 10.1</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>79.6 ± 14.4</td>
<td>277.4 ± 8.3</td>
<td>38.5 ± 1.1</td>
<td>45.1 ± 6.3</td>
</tr>
</tbody>
</table>
Table V.5.2 Experiment C: Measurement of Blood Flow in a Stationary Mouse

<table>
<thead>
<tr>
<th>Trial</th>
<th>Dose(rad)</th>
<th>Initial wash-out</th>
<th>Number of nuclei</th>
<th>Blood Flow (ml/min/100 grams)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>O-15</td>
<td>C-11</td>
</tr>
<tr>
<td>1</td>
<td>100</td>
<td>1958</td>
<td>8839</td>
<td>7286</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 293</td>
<td>± 387</td>
<td>± 323</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>832</td>
<td>9990</td>
<td>9514</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 226</td>
<td>± 322</td>
<td>± 332</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>2287</td>
<td>11046</td>
<td>13513</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 365</td>
<td>± 416</td>
<td>± 394</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>1431</td>
<td>9247</td>
<td>12684</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 275</td>
<td>± 384</td>
<td>± 394</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>1072</td>
<td>9944</td>
<td>13820</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 194</td>
<td>± 298</td>
<td>± 395</td>
</tr>
</tbody>
</table>
collimator/holder will vary with time. This is reflected in the measurements. Figure V.5.1 shows a plot of the measured blood flow for this single mouse and a line representing the mean of the measurements. From the intersection of the error bars with the line representing the mean value it can be seen that the reproducibility of the measurement is quite good and may possibly be improved with the use of a restraining device that induces less trauma.

The results of the curve fitting analysis for the stationary mouse irradiated at different doses may be found in Table V.5.3 and the blood flow analysis results may be found in Table V.5.4. From these tables, it can be seen that the dose dependence alluded to in the last section has dissipated. The variability in the data is probably due to a physiologic effect as there seems to be a trend in the data reducing the value of blood flow.

It is noted that the rather large statistical error in the last measurement may be due to the large carbon activity background from the previous irradiations. The oxygen activity has time to almost completely die away prior to the next irradiation but a rather large fraction of C-11 activity remains in the activated thigh region. Although this large background is easily accounted for in the fitting procedure, it introduces a rather significant statistical error which accumulates from measurement to measurement.

The dependence of the measured blood flow upon proton dose probably does not exist. Before this can be said with certainty, however, it is necessary to perform a large number of additional measurements such as those performed in these last two sections.
Figure V.5.1: Plot of Blood Flow Measurement Reproducibility
<table>
<thead>
<tr>
<th>Trial</th>
<th>Dose (rad)</th>
<th>Initial Decay Rate (cts/ t)</th>
<th>Half life (secs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>wash-out</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>108.9 ± 12.7</td>
<td>51.9 ± 16.1</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>175.5 ± 21.2</td>
<td>65.7 ± 19.8</td>
</tr>
<tr>
<td>3</td>
<td>150</td>
<td>125.4 ± 24.9</td>
<td>63.1 ± 18.3</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>34.3 ± 17.3</td>
<td>74.5 ± 29.0</td>
</tr>
</tbody>
</table>

Table V.5.3 Experiment C: Physical Data from the Activation and Decay of a Stationary Mouse with Different Doses
Table V.5.4 Experiment C: Blood Flow Measurement from a Stationary Mouse with Different Doses

<table>
<thead>
<tr>
<th>Trial</th>
<th>Dose (rad)</th>
<th>Initial Number of Nuclei</th>
<th>Blood Flow (ml/min/100 gr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>wash-out</td>
<td>O-15</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>1687</td>
<td>7341</td>
</tr>
<tr>
<td></td>
<td></td>
<td>±196</td>
<td>± 275</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>3445</td>
<td>13819</td>
</tr>
<tr>
<td></td>
<td></td>
<td>±417</td>
<td>± 545</td>
</tr>
<tr>
<td>3</td>
<td>150</td>
<td>2366</td>
<td>22378</td>
</tr>
<tr>
<td></td>
<td></td>
<td>±471</td>
<td>± 634</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>737</td>
<td>4699</td>
</tr>
<tr>
<td></td>
<td></td>
<td>±368</td>
<td>± 208</td>
</tr>
</tbody>
</table>
Section V.6 Analysis of Decay in Tourniquet Mice

The goal of this experiment was quite simple; to see if the component of biologic wash-out could be reduced or eliminated with the use of a tourniquet. If this could be accomplished, it provides a simple test of the relationship of biologic wash-out of the activated nuclei with blood flow.

The experiment was performed in the following manner: A mouse was placed in the mouse collimator/holder and irradiated with 100 rads and counted. After the 15 minute counting time, a tourniquet, consisting of a tightly wrapped elastic band, was placed around the upper portion of the mouse's thigh. The mouse was irradiated and counted again. The elastic band was removed and the mouse was given 100 rads and counted a third time. This was done with two mice.

The results of the curve fitting procedure upon this data are shown in Table V.6.1 and the blood flow analysis results are contained in Table V.6.2. As can be seen from the tables, the tourniquet succeeded in completely eliminating the third component of biologic wash-out or reducing it to an extent where it could not be found. This result is not surprising in view of the tightness of the elastic band. It is possible that the blood flow was reduced to such a small amount that the component could not be found. Also interesting is the increased blood flow measured after the tourniquet was removed. The third measurement started just seconds after the removal of the tourniquet after completion of the second measurement. The increased blood flow thus measured is expected in an area deprived of an adequate flow of blood for some time.
Table V.6.1 Experiment D: Physical Data from the Activation and Decay of Tourniqueted Mice (Dose = 100 rads)

<table>
<thead>
<tr>
<th>Mouse</th>
<th>Condition</th>
<th>Initial Decay Rate (cts/ t)</th>
<th>Half life (secs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>wash-out                0-15</td>
<td>C-11</td>
</tr>
<tr>
<td></td>
<td>unclamped</td>
<td>290.8 ± 31.3</td>
<td>191.6 ± 26.7</td>
</tr>
<tr>
<td>1</td>
<td>clamped</td>
<td>——</td>
<td>317.6 ± 31.1</td>
</tr>
<tr>
<td></td>
<td>unclamped</td>
<td>225.1 ± 14.4</td>
<td>228.1 ± 6.5</td>
</tr>
<tr>
<td>2</td>
<td>clamped</td>
<td>——</td>
<td>444.7 ± 38.1</td>
</tr>
<tr>
<td></td>
<td>unclamped</td>
<td>224.1 ± 15.2</td>
<td>203.9 ± 9.3</td>
</tr>
</tbody>
</table>
Table V.6.2 Experiment D: Blood Flow Measurements from Tourniqueted Mice (Dose = 100 rads)

<table>
<thead>
<tr>
<th>Mouse</th>
<th>Condition</th>
<th>Initial Number of Nuclei</th>
<th>Blood Flow (ml/min/100 gr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>wash-out</td>
<td>0-15</td>
</tr>
<tr>
<td>unclamped</td>
<td></td>
<td>7707</td>
<td>6866</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 829</td>
<td>± 956</td>
</tr>
<tr>
<td>1</td>
<td>clamped</td>
<td></td>
<td>11533</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 1131</td>
<td>± 361</td>
</tr>
<tr>
<td>unclamped</td>
<td></td>
<td>2230</td>
<td>8191</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 143</td>
<td>± 233</td>
</tr>
<tr>
<td>unclamped</td>
<td></td>
<td>5588</td>
<td>6715</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 456</td>
<td>± 427</td>
</tr>
<tr>
<td>2</td>
<td>clamped</td>
<td></td>
<td>16444</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 1407</td>
<td>± 681</td>
</tr>
<tr>
<td>unclamped</td>
<td></td>
<td>3448</td>
<td>7310</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 234</td>
<td>± 334</td>
</tr>
</tbody>
</table>
A question has been raised by this experiment that has not been answered in this thesis. That question concerns the sensitivity of this blood flow measurement method to changes in the magnitude of blood flow. Although this has been discussed somewhat in Section III.5, only an experimental determination will give truly accurate results. A series of experiments could be performed whereby a tourniquet was applied very slightly and the pressure increased as successive measurements were made. In this manner, it could easily be seen at what point this method becomes inadequate.

This section did show quite clearly that, at least on a very crude level, the activation of positron emitters by protons may be used to measure the effect of a physiological change in the biologic system.
CHAPTER VI: CONCLUSIONS

Section VI.1 Introduction

There were a number of interesting findings revealed during this short exploration into the subject of blood flow measurement by proton activation, the most important of which is that the technique is feasible. The extent of its application is, however, the major question.

One of the most interesting sections which was designed to aid in answering the above question was section III.5 in which a short computer simulation was performed in order to ascertain the variation of the uncertainty in blood flow determination with dose. This section has shown that although fairly high doses are needed to measure blood flow with small uncertainty and reasonable spatial resolution, these doses are on the order of a fraction of a proton therapeutic dose. While this means that this technique will probably not be applicable in common diagnostic situations, it may have application in providing physiologic information in a patient undergoing proton radiation therapy.

Another potential application of positron tracer activation by protons may be in performing experiments in animal physiology. Theoretically, this is probably the least invasive blood flow measurement technique developed to date which will measure tissue perfusion rather than flow in large vessels. Certain refinements of this technique may enable very elegant measurements of blood flow to be made which may be useful in evaluating pharmaceutical agents.
Although seemingly of great promise, this blood flow measurement technique must still be subjected to a number of tests before its efficacy can be assured.
Section VI.2 Further Work

There are four main areas in which further work is obviously needed. These are in the areas of biologic modeling, detection apparatus refinement, further animal experimentation, and blood flow verification.

In terms of modeling, it is obvious that if this technique is to be used in more heterogeneous tissue regions, more complex models will have to be developed. Multi-compartment models will have to be developed especially for this application and are a definite necessity if muti-detector systems are to be used. An entire analysis of the statistical uncertainties will also have to be developed to go along with the more sophisticated models.

Detector modification was seen to be the most important parameter in terms of improving the accuracy of blood flow quantification. Thus, the majority of further work may be concentrated in this area. Different geometries to provide a greater solid angle of detection will have to be explored as well as the possibility of using different detector substances. Multi-detector systems which may be designed to give three dimensional information as to the spatial quantification of blood flow may be desirable. All detector choices will have to be analyzed in terms of the special requirements necessitated by the fact that sensitivity will have to remain high due to the low proton reaction cross sections.
Further animal experiments will have to be performed in order to reduce the trauma of the measurements and make them more precise. Also, physiological and pharmacological manipulation of blood flow in a known way and subsequent measurement will test the use of this technique for future measurements using unknown agents.

It is in the area of blood flow measurement verification that the majority of immediate future work is necessary. Some simple physiological experiments should be designed so that blood flow through an organ or tissue region may be simply and accurately measured by cannulation or some such method. The flow through this same organ or tissue should then be measured by proton activation in much the same conditions to see if the measurements are in agreement. This will provide the ultimate test of almost all of the biological assumptions stated in section II.3.

By performing the above mentioned exercises in a thorough and rigorous fashion, it may be possible to develop this method of blood flow measurement by proton activation into a unique and usable tool which may provide the clinician and experimenter with important diagnostic and experimental information.
APPENDIX: COMPUTER PROGRAMS

This appendix contains the computer programs written for this work. They are contained in the order that they are mentioned in the body of the thesis.

The first program contained herein is CHIFIT which is the curve fitting program using the technique of weighted least squares as described in Section III.3 and III.4.

The next program is CHIPLot which takes the experimental data and the results of CHIFIT and plots a decay curve with the fitted decay components. The output of CHIPLot consists of the plots of the decay data such as those contained in Figures V.3.1 and V.3.2.

The last program contained in this section is Fakedata which produces a set of data given a set of experimental parameters as explained in Section III.5.
PROGRAM FAKEDATA
REAL CTS(1000),TIME(1000)

C
C
C this program simulates a blood flow measurement experiment
producing an imaginary set of data for a given set of
experimental parameters

C

C start by getting some of the experimental parameters

C

PRINT 10
FORMAT(/1X,"DOSE= (default=100 rads): °,"
CALL READREAL(DOSE)
IF(DOSE.EQ.0.)DOSE=100.

C

PRINT 20
FORMAT(/1X,"DOSE RATE = (default=20 rads/sec): °,"
CALL READREAL(DOSE_RATE)
IF(DOSE_RATE.EQ.0.) DOSE_RATE=20.

C

PRINT 30
FORMAT(/1X,"CRYSTAL SEPARATION= (default=20 cm): °,"
CALL READREAL(CRYSTAL_SEPARATION)
IF(CRYSTAL_SEPARATION.EQ.0.) CRYSTAL_SEPARATION=20.

C

PRINT 40
FORMAT(/1X,"CRYSTAL DIAMETER= (default=3 in): °,"
CALL READREAL(CRYSTAL_DIAMETER)
IF(CRYSTAL_DIAMETER.EQ.0.) CRYSTAL_DIAMETER=3.

C

PRINT 50
FORMAT(/1X,"DELTA T= (default=5 sec): °,"
CALL READREAL(DELTA_T)
IF(DELTA_T.EQ.0.) DELTA_T=5.

C

PRINT 60
FORMAT(/1X,"MOBILE TO FIXED 0-15 FRACTION= (default=0.6): °,"
CALL READREAL(F_O)
IF(F_O.EQ.0.) F_O=0.6

C

PRINT 70
FORMAT(/1X,"BLOOD FLOW= (default=90 ml/min/100 gr): °,"
CALL READREAL(BLOOD_FLOW)
IF(BLOOD_FLOW.EQ.0.) BLOOD_FLOW=90.

C

find the crystal radius in cm

C

CRYSTAL_RADIUS=CRYSTAL_DIAMETER*2.54/2.0

C

in tissue, the production of 0-15 by 100 MeV protons per cc
per rad is:

\[
\text{PRODUCTION\_O\_15}=14700.0
\]

and the production of O-15 by 100 MeV protons per cc per rad is:

\[
\text{PRODUCTION\_C\_11}=9093.0
\]

the production rates of O-15 and C-11 per cc per sec is thus:

\[
\begin{align*}
R_{\text{O\_15}} &= \text{PRODUCTION\_O\_15} \times \text{DOSE\_RATE} \\
R_{\text{C\_11}} &= \text{PRODUCTION\_C\_11} \times \text{DOSE\_RATE}
\end{align*}
\]

the decay constants of O-15 and C-11 in inverse seconds are:

\[
\begin{align*}
O_{\text{LAM}} &= 0.0057762 \\
C_{\text{LAM}} &= 0.00056353
\end{align*}
\]

and the decay constant of the biologic wash-out may be calculated from the blood flow by:

\[
\begin{align*}
B_{\text{LAM}} &= \text{BLOOD\_FLOW} \times 0.693/3780.8
\end{align*}
\]

the irradiation time equals:

\[
\begin{align*}
\text{TIME\_IRR} &= \text{DOSE}/\text{DOSE\_RATE}
\end{align*}
\]

we may now calculate the initial number of activated nuclei of each type — first, O-15 which has a mobile component

\[
\begin{align*}
\text{EXP\_TERM} &= 1 - \exp\left(-\left(\left(B_{\text{LAM}}F\_O\right)+O_{\text{LAM}}\right) \times \text{TIME\_IRR}\right) \\
R_{\text{TERM}} &= \left(R_{\text{O\_15}}\right) / \left(\left(B_{\text{LAM}}F\_O\right)+O_{\text{LAM}}\right) \\
O_{\text{NUM\_INIT}} &= R_{\text{TERM}} \times \text{EXP\_TERM}
\end{align*}
\]

now for the initial number of C-11

\[
\begin{align*}
\text{EXP\_TERM} &= 1 - \exp\left(-C_{\text{LAM}} \times \text{TIME\_IRR}\right)
\end{align*}
\]
R_TERM=R_C_11/C_LAM
C_NUM_INIT=R_TERM*EXP_TERM

print the results

PRINT 75,C_NUM_INIT
FORMAT(1X,"INITIAL NUMBER OF O-15 NUCLEI = ",F10.0)
PRINT 76,C_NUM_INIT
FORMAT(1X,"INITIAL NUMBER OF C-11 NUCLEI = ",F10.0)

now, calculate the geometric detection efficiency for
a single crystal

D=CRYSTAL SEPARATION/2.
R=CRYSTAL RADIUS
GEO_EFF=(1-(D/(SQRT((D**2.)+(R**2.))))))

the intrinsic efficiency is about 90% including photofraction
and thus, the total efficiency for the coincidence system is:

TOTAL_EFF=(0.81*GEO_EFF)

print this efficiency

PRINT 77,TOTAL_EFF
FORMAT(1X,"TOTAL DETECTION EFFICIENCY = ",F10.8)

of the initial nuclei created, this limits the number
detected. The initial number of each type of nuclei detected
is therefore:

B_N=(F_0)*Q_NUM_INIT*TOTAL_EFF
O_N=(1-F_0)*Q_NUM_INIT*TOTAL_EFF
C_N=C_NUM_INIT*TOTAL_EFF

print these results

PRINT 81,B_N
PRINT 82,O_N
PRINT 83,C_N
PRINT 84,FORMAT(1X,"DETECTED B NUCLEI = ",F10.2)
PRINT 85,FORMAT(1X,"DETECTED O NUCLEI = ",F10.2)
FORMAT(1X, 'DETECTED C NUCLEI = ',F10.2)

we may now produce the imaginary data, we count for 15 minutes or 900 seconds

NUM CTS=900./DELTA_T
DO 100, I=1,NUM CTS
   T= ((I-1)*DELTA_T)+(DELTA_T/2.)
   COMP1=DELTA_T*(B_LAM*B N*EXP(-B_LAM*T))
   COMP2=DELTA_T*(O_LAM*O N*EXP(-O_LAM*T))
   COMP3=DELTA_T*(C_LAM*C N*EXP(-C_LAM*T))
   CT S(I)=COMP1+COMP2+COMP3
   TIME(I)=T
100 CONTINUE

write this data to a file

T_OFF=1.
BACKGROUND=0.5*DELTA_T
OPEN(UNIT=1,NAME="CHIDATA",TYPE="NEW")
WRITE(1,110)NUM CTS,BACKGROUND,T_OFF
WRITE(1,111)(CTS(I),TIME(I),I=1,NUM_CTS)
110 FORMAT(1X,15,2F10.2)
111 FORMAT(1X,2F10.3)
CLOSE(UNIT=1)
STOP
END
PROGRAM CHIFIT

this program maximizes chi-squared in order to fit data
to a sum of from one to four exponentials

REAL ARRAY(10,10),X(1000),Y(1000),T(1000),C TOTAL(1000),
IP(1000),Q(1000),R(1000),S(1000),C1,C2,C3,LAMBDA1,
1LAMBDA2,LAMBDA3,LAMBDA4,SIGMA_SQRED(1000)

INTEGER N,NUM_COMPONENTS

CHARACTER*1 IANS,STRING*60

LOGICAL KNOW_LAMBDA

first, ask some questions to initialize the fitting routine

KNOW LAMBDA=.FALSE.
PRINT 10
FORMAT(/1X,"NUMBER OF COMPONENTS? (1-4): ",$)
READ(6,11,ERR=9)NUM_COMPONENTS
FORMAT(112)
PRINT 37
FORMAT(/1X,"IS LAMBDA 1 KNOWN? (DEFAULT=NO): ",$)
READ(6,31,ERR=29)IANS
FORMAT(1A1)
IF(IANS.EQ."Y") THEN
   FORMAT(40)
   FORMAT(/1X,"ENTER LAMBDA 1 (DEFAULT=LAMBDAX): ",$)
   READ(6,41,ERR=39)LAMBDA1
   FORMAT(1F15.9)
   IF(LAMBDAX.EQ.0.) LAMBDA1=5.7762E-03
   KNOW_LAMBDA=.TRUE.
ENDIF

IF(KNOW_LAMBDA.EQ..TRUE..AND.NUM_COMPONENTS.EQ.2) THEN
   PRINT 210
   FORMAT(/1X, "LAMBDA 2? (DEFAULT= CARBON) ",$)
   READ(6,41)LAMBDA2
   IF(LAMBDA2.EQ.0.)LAMBDA2=5.6353E-04
ENDIF

IF(KNOW_LAMBDA.EQ..FALSE..AND.NUM_COMPONENTS.EQ.2) THEN
   PRINT 220
   FORMAT(/1X, "LAMBDA 2? (DEFAULT= OXYGEN) ",$)
   READ(6,41)LAMBDA2
   IF(LAMBDA2.EQ.0.)LAMBDA2=5.7762E-03
ENDIF

$
IF(KNOW_LAMBDA.EQ..TRUE..AND.NUM_COMPONENTS.EQ.3) THEN
  PRINT 310
  FORMAT(/1X,"LAMBDA2\? (DEFAULT=NITROGEN) \^\$",$)
  READ(6,41)LAMBDA2
  IF(LAMBDA2.EQ.0) LAMBDA2=1.0E-03
  PRINT 320
  FORMAT(/1X,"LAMBDA 3\? (DEFAULT=CARBON) \^\$",$)
  READ(6,41)LAMBDA3
  IF(LAMBDA3.EQ.0) LAMBDA3=5.6353E-04
ENDIF

C
IF(KNOW_LAMBDA.EQ..FALSE..AND.NUM_COMPONENTS.EQ.3) THEN
  PRINT 220
  READ(6,41)LAMBDA2
  IF(LAMBDA2.EQ.0) LAMBDA2=5.7762E-03
  PRINT 320
  READ(6,41)LAMBDA3
  IF(LAMBDA3.EQ.0) LAMBDA3=5.6353E-04
ENDIF

C
IF(KNOW_LAMBDA.EQ..TRUE..AND.NUM_COMPONENTS.EQ.4) THEN
  PRINT 310
  READ(6,41)LAMBDA2
  IF(LAMBDA2.EQ.0) LAMBDA2=1.0E-03
  PRINT 320
  READ(6,41)LAMBDA3
  IF(LAMBDA3.EQ.0) LAMBDA3=5.6353E-04
  PRINT 440
  FORMAT(/1X,"LAMBDA4\? \^\$",$)
  READ(6,41)LAMBDA4
ENDIF

C
IF(KNOW_LAMBDA.EQ..FALSE..AND.NUM_COMPONENTS.EQ.4) THEN
  PRINT 220
  READ(6,41)LAMBDA2
  IF(LAMBDA2.EQ.0) LAMBDA2=5.7762E-03
  PRINT 460
  FORMAT(/1X,"LAMBDA3\? (DEFAULT=NITROGEN) \^\$",$)
  READ(6,41)LAMBDA3
  IF(LAMBDA3.EQ.0) LAMBDA3=1.0E-03
  PRINT 470
  FORMAT(/1X,"LAMBDA4\? (DEFAULT=CARBON) \^\$",$)
  READ(6,41)LAMBDA4
  IF(LAMBDA4.EQ.0) LAMBDA4=5.6353E-04
ENDIF

C

C

c this section reads the experimental data from a file

C
PRINT 666,LAMBDA1,LAMBDA2,LAMBDA3,LAMBDA4
666 FORMAT(1X,4(1X,G13.6))
OPEN(UNIT=1,NAME="CHIDATA",ERR=9,READONLY,TYpe="OLD")
READ(1,98)N,BACKGROUND,T_OFF

$
READ(1,97)(C_TOTAL(I),T(I),I=1,N)
FORMAT(1X,1S,2F10.2)
FORMAT(1X,2F10.3)
CLOSE(UNIT=1)
OPEN(UNIT=1,NAME="FITDATA",ERR=9,TYPE="NEW")

replace with the variables that you will use in the program

DO 200, I=1,N
  Y(I)=C_TOTAL(I)
  X(I)=T(I)
200 CONTINUE
B2=LAMBDA2
B3=LAMBDA3
B4=LAMBDA4

Calculate SIGMA_SQRED(I)

DO 300, I=1,N
  SIGMA_SQRED(I)=Y(I)+BACKGROUND
300 CONTINUE

Calculate the simplifying coefficients as in the notes

DO 400, I=1,N
  P(I)=Y(I)/SIGMA_SQRED(I)
  R(I)=1./SIGMA_SQRED(I)
  Q(I)=(X(I)*Y(I))/SIGMA_SQRED(I)
  S(I)=X(I)/SIGMA_SQRED(I)
400 CONTINUE

Start by making a guess at the value of LAMBDAL

That is, unless LAMBDAL is known

IF(KNOW_LAMBDAL.EQ..TRUE.) THEN
  B1=LAMBDAL
ELSE
  B1=0.
  DELTA_B1=B2/50.
  IF(NUM_COMPONENTS.EQ.1) THEN
    DELTA_B1=1.0E-04
    B1=1.0E-04
    B1_TOP_GUESS=1.0E-01
  ENDIF
  B1_BEST_TEST=999999999.295
ENDIF
go to the section and do the correct calculation for the number of components that you have

GO TO (1001,1002,1003,1004) NUM_COMPONENTS

for one exponential, the calculation is easy. do it next

1001
SUM1=0.
SUM2=0.
DO 450, I=1,N
   SUM1=SUM1+(R(I)*EXP(-2*B1*X(I)))
   SUM2=SUM2+(P(I)*EXP(-B1*X(I)))
450
CONTINUE

C1=SUM2/SUM1

if LAMBDA1 is not known, use the second equation to iterate for the value of LAMBDA1

IF(KNOW_LAMBDACL.EQ..TRUE.) GO TO 50

TEST1=C1

SUM3=0.
SUM4=0.
DO 451, I=1,N
   SUM3=SUM3+(S(I)*EXP(-2*B1*X(I)))
   SUM4=SUM4+(Q(I)*EXP(-B1*X(I)))
451
CONTINUE

TEST2=SUM4/SUM3
GO TO 80

if there are two components, the next section calculates C1 and C2

1002
PEL1=0.
PEL2=0.
REL1_1=0.
REL1_2=0.
REL2_1=0.
REL2_2=0.
QUEL1=0.
QUEL1_1=0.
QUEL1_2=0.
DO 520, I=1,N
   PEL1=PEL1+(P(I)*EXP(-B1*X(I)))
   PEL2=PEL2+(P(I)*EXP(-B2*X(I)))
$
set up to solve the n equations in n unknowns using
the determinant subroutine

first, solve for C1

ARRAY(1,1)=REL1_1
ARRAY(1,2)=REL1_2
ARRAY(2,1)=REL2_1
ARRAY(2,2)=REL2_2
CALL DETERM(ARRAY,2,DENOMINATOR)
IF(DENOMINATOR.EQ.0.) THEN
    B1=B1+(DELTA_B1/50.)
    GO TO 30
ENDIF
ARRAY(1,1)=PEL1
ARRAY(1,2)=PEL1_2
ARRAY(2,1)=PEL2
ARRAY(2,2)=PEL2_2
CALL DETERM(ARRAY,2,C1_NUMERATOR)
C1=C1_NUMERATOR/DENOMINATOR

calculate the value of C2

ARRAY(1,1)=REL1_1
ARRAY(1,2)=PEL1
ARRAY(2,1)=REL1_2
ARRAY(2,2)=PEL2
CALL DETERM(ARRAY,2,C2_NUMERATOR)
C2=C2_NUMERATOR/DENOMINATOR

if LAMBDA1 is not known, use the third equation to solve for
its value iteratively

IF(KNOW_LAMBDA.EQ..TRUE.) GO TO 50
TEST1=QEL1
TEST2=(C1*SEL1_1)+(C2*SEL1_2)
GO TO 80
calculate C1, C2, and C3 if the number of components is 3

PEL1=0.
PEL2=0.
PEL3=0.
REL1_1=0.
REL1_2=0.
REL1_3=0.
REL2_2=0.
REL2_3=0.
REL3_3=0.
QEL1=0.
SEL1_1=0.
SEL1_2=0.
SEL1_3=0.
DO 530, I=1,N
PEL1=PEL1+(P(I)*EXP(-B1*X(I))
PEL2=PEL2+(P(I)*EXP(-B2*X(I))
PEL3=PEL3+(P(I)*EXP(-B3*X(I))
REL1_1=REL1_1+(R(I)*EXP(-2*B1*X(I))
REL1_2=REL1_2+(R(I)*EXP((-B1+B2)*X(I))
REL1_3=REL1_3+(R(I)*EXP((-B1+B3)*X(I))
REL2_2=REL2_2+(R(I)*EXP(-2*B2*X(I))
REL2_3=REL2_3+(R(I)*EXP((-B2+B3)*X(I))
REL3_3=REL3_3+(R(I)*EXP(-2*B3*X(I))
QEL1=QEL1+(Q(I)*EXP(-B1*X(I))
SEL1_1=SEL1_1+(S(I)*EXP(-2*B1*X(I))
SEL1_2=SEL1_2+(S(I)*EXP((-B1+B2)*X(I))
SEL1_3=SEL1_3+(S(I)*EXP((-B1+B3)*X(I))
CONTINUE

set up to solve the n equations in n unknowns using
the dct main subroutine

first, solve for C1

ARRAY(1,1)=REL1_1
ARRAY(1,2)=REL1_2
ARRAY(1,3)=REL1_3
ARRAY(2,1)=REL2_1
ARRAY(2,2)=REL2_2
ARRAY(2,3)=REL2_3
ARRAY(3,1)=REL3_1
ARRAY(3,2)=REL3_2
ARRAY(3,3)=REL3_3
CALL DETERM(ARRAY,3,DENOMINATOR)
IF(DENOMINATOR.EQ.0.) THEN
   B1=B1+(DELTA_B1/50.)
   GO TO 30
ENDIF
ARRAY(1,1)=PEL1
ARRAY(1,2)=REL1_2
ARRAY(1,3)=REL1_3
ARRAY(2,1)=PEL2
ARRAY(2,2)=REL2_2
ARRAY(2,3)=REL2_3
ARRAY(3,1)=PEL3
ARRAY(3,2)=REL2_3
ARRAY(3,3)=REL3_3
CALL DETERM(ARRAY,3,C1_NUMERATOR)

C1=C1_NUMERATOR/DENOMINATOR

calculate the value of C2

ARRAY(1,1)=REL1_1
ARRAY(1,2)=PEL1
ARRAY(1,3)=REL1_3
ARRAY(2,1)=REL1_2
ARRAY(2,2)=PEL2
ARRAY(2,3)=REL2_3
ARRAY(3,1)=REL1_3
ARRAY(3,2)=PEL3
ARRAY(3,3)=REL3_3
CALL DETERM(ARRAY,3,C2_NUMERATOR)

C2=C2_NUMERATOR/DENOMINATOR

calculate the value of C3

ARRAY(1,1)=REL1_1
ARRAY(1,2)=REL1_2
ARRAY(1,3)=PEL1
ARRAY(2,1)=REL1_2
ARRAY(2,2)=REL2_2
ARRAY(2,3)=PEL2
ARRAY(3,1)=REL1_3
ARRAY(3,2)=REL2_3
ARRAY(3,3)=PEL3
CALL DETERM(ARRAY,3,C3_NUMERATOR)

C3=C3_NUMERATOR/DENOMINATOR

use both sides of equation four to test this value of LAMBDA1
if LAMBDA1 is not known

IF(KNOW_LAMBDA.EQ..TRUE.) GO TO 50

TEST1=QEL1
TEST2=(SEL1_1*C1)+(SEL1_2*C2)+(SEL1_3*C3)
GO TO 80
if the number of components is four, calculate C1, C2, C3, and C4

PELI = 0.
PEL2 = 0.
PEL3 = 0.
PEL4 = 0.
RELI_1 = 0.
RELI_2 = 0.
RELI_3 = 0.
RELI_4 = 0.
RELI_2 = 0.
RELI_3 = 0.
RELI_4 = 0.
QELI = 0.
SELI_1 = 0.
SELI_2 = 0.
SELI_3 = 0.
SELI_4 = 0.
DO 540 I = 1, N
PELI = PELI + (P(I) * EXP(-B1*X(I)))
PEL2 = PEL2 + (P(I) * EXP(-B2*X(I)))
PEL3 = PEL3 + (P(I) * EXP(-B3*X(I)))
PEL4 = PEL4 + (P(I) * EXP(-B4*X(I)))
RELI_1 = RELI_1 + (R(I) * EXP(-2*B1*X(I)))
RELI_2 = RELI_2 + (R(I) * EXP(-(B1+B2)*X(I)))
RELI_3 = RELI_3 + (R(I) * EXP(-(B1+B3)*X(I)))
RELI_4 = RELI_4 + (R(I) * EXP(-(B1+B4)*X(I)))
PEL2 = PEL2 + (R(I) * EXP(-2*B2*X(I)))
RELI_2 = RELI_2 + (R(I) * EXP(-(B2+B3)*X(I)))
RELI_3 = RELI_3 + (R(I) * EXP(-(B2+B4)*X(I)))
RELI_4 = RELI_4 + (R(I) * EXP(-2*B4*X(I)))
QELI = QELI + (Q(I) * EXP(-B1*X(I)))
SELI_1 = SELI_1 + (S(I) * EXP(-2*B1*X(I)))
SELI_2 = SELI_2 + (S(I) * EXP(-(B1+B2)*X(I)))
SELI_3 = SELI_3 + (S(I) * EXP(-(B1+B3)*X(I)))
SELI_4 = SELI_4 + (S(I) * EXP(-(B1+B4)*X(I)))
CONTINUE

set up to solve the n equations in n unknowns using
the determinant subroutine

first, solve for C1

ARRAY(1, 1) = RELI_1

$
ARRAY(1,2) = REL1_2
ARRAY(1,3) = REL1_3
ARRAY(1,4) = REL1_4
ARRAY(2,1) = REL1_2
ARRAY(2,2) = REL2_2
ARRAY(2,3) = REL2_3
ARRAY(2,4) = REL2_4
ARRAY(3,1) = REL1_3
ARRAY(3,2) = REL2_3
ARRAY(3,3) = REL3_3
ARRAY(3,4) = REL3_4
ARRAY(4,1) = REL1_4
ARRAY(4,2) = REL2_4
ARRAY(4,3) = REL3_4
ARRAY(4,4) = REL4_4
CALL DETERM(ARRAY, 4, DENOMINATOR)

IF(DENOMINATOR.EQ.0.) THEN
    B1 = B1 + (DELTAB1/50.)
    GO TO 30
ENDIF

ARRAY(1,1) = PEL1
ARRAY(1,2) = REL1_2
ARRAY(1,3) = REL1_3
ARRAY(1,4) = REL1_4
ARRAY(2,1) = PEL2
ARRAY(2,2) = REL2_2
ARRAY(2,3) = REL2_3
ARRAY(2,4) = REL2_4
ARRAY(3,1) = PEL3
ARRAY(3,2) = REL2_3
ARRAY(3,3) = REL3_3
ARRAY(3,4) = REL3_4
ARRAY(4,1) = PEL4
ARRAY(4,2) = REL2_4
ARRAY(4,3) = REL3_4
ARRAY(4,4) = REL4_4
CALL DETERM(ARRAY, 4, C1_NUMERATOR)

C  
C  
C  
C  
C  
C  
C  
C  

C1 = C1_NUMERATOR/DENOMINATOR

C  
C  
C  
C  
C  
C  
C  
C  

calculate the value of C2

C  
C  
C  
C  
C  
C  
C  
C  

ARRAY(1,1) = REL1_1
ARRAY(1,2) = PEL1
ARRAY(1,3) = REL1_3
ARRAY(1,4) = REL1_4
ARRAY(2,1) = REL1_2
ARRAY(2,2) = PEL2
ARRAY(2,3) = REL2_3
ARRAY(2,4) = REL2_4
ARRAY(3,1) = REL1_3
ARRAY(3,2) = PEL3
ARRAY(3,3) = REL3_3

\$
\texttt{array}(3,4) = \texttt{rel3}_4
\texttt{array}(4,1) = \texttt{rel1}_4
\texttt{array}(4,2) = \texttt{pel4}
\texttt{array}(4,3) = \texttt{rel3}_4
\texttt{array}(4,4) = \texttt{rel4}_4
\texttt{call dete}(\texttt{array},4,\texttt{c2 numerator})

\texttt{c2 = c2 numerator/denominator}

calculate the value of \texttt{c3}

\texttt{array}(1,1) = \texttt{rel1}_1
\texttt{array}(1,2) = \texttt{rel1}_2
\texttt{array}(1,3) = \texttt{pel1}
\texttt{array}(1,4) = \texttt{rel1}_4
\texttt{array}(2,1) = \texttt{rel1}_2
\texttt{array}(2,2) = \texttt{rel2}_2
\texttt{array}(2,3) = \texttt{pel2}
\texttt{array}(2,4) = \texttt{rel2}_4
\texttt{array}(3,1) = \texttt{rel1}_3
\texttt{array}(3,2) = \texttt{rel2}_3
\texttt{array}(3,3) = \texttt{pel3}
\texttt{array}(3,4) = \texttt{rel3}_4
\texttt{array}(4,1) = \texttt{rel1}_4
\texttt{array}(4,2) = \texttt{rel2}_4
\texttt{array}(4,3) = \texttt{pel4}
\texttt{array}(4,4) = \texttt{rel4}_4
\texttt{call dete}(\texttt{array},4,\texttt{c3 numerator})

\texttt{c3 = c3 numerator/denominator}

calculate the value of \texttt{c4}

\texttt{array}(1,1) = \texttt{rel1}_1
\texttt{array}(1,2) = \texttt{rel1}_2
\texttt{array}(1,3) = \texttt{rel1}_3
\texttt{array}(1,4) = \texttt{pel1}
\texttt{array}(2,1) = \texttt{rel1}_2
\texttt{array}(2,2) = \texttt{rel2}_2
\texttt{array}(2,3) = \texttt{rel2}_3
\texttt{array}(2,4) = \texttt{pel2}
\texttt{array}(3,1) = \texttt{rel1}_3
\texttt{array}(3,2) = \texttt{rel2}_3
\texttt{array}(3,3) = \texttt{rel3}_3
\texttt{array}(3,4) = \texttt{pel3}
\texttt{array}(4,1) = \texttt{rel1}_4
\texttt{array}(4,2) = \texttt{rel2}_4
\texttt{array}(4,3) = \texttt{rel3}_4
\texttt{array}(4,4) = \texttt{pel4}

\texttt{call dete}(\texttt{array},4,\texttt{c4 numerator})
C4=C4_NUMERATOR/DENOMINATOR

if LAMBDA1 is not known, use the fifth equation to solve for it iteratively

IF(KNOW_LAMBDA.EQ..TRUE.) GO TO 50
TEST1=QEL1
TEST2=(C1*SEL1_1)+(C2*SEL1_2)+(C3*SEL1_3)+(C4*SEL1_4)
GO TO 80

80 B1_THIS_TEST=ABS(TEST1-TEST2)
D PRINT 1112,B1_THIS_TEST,B1_BEST_TEST
1112 FORMAT(1X,"B1 THIS TEST=",G13.6,1X,"B1_BEST_TEST=",G13.6)
D PRINT 1113, B1,DELTA_B1
1113 FORMAT(1X,"B1=",G13.6,2X,"DELTA_B1=",G13.6,/)  
D PRINT 1114,B1_BEST GUESS
1114 FORMAT(1X,"B1_BEST GUESS=",G13.6)
IF(B1_THIS_TEST.LT.0.001) GO TO 50

this IF is so that the program won't iterate forever on a non-convergent set of data

IF(DELTA_B1.LT.0.00000001)THEN
   PRINT 8222
8222 FORMAT(1X,"NON-CONVERGENCE - EXIT",///)
   GO TO 50
ENDIF
IF(B1.GT.B1_TOP GUESS) THEN
   B1=B1_BEST GUESS-(DELTA_B1*2.)
   IF(B1.LT.0.)B1=0.
   B1_TOP GUESS=B1_BEST GUESS+(DELTA_B1*2.)
   DELTA_B1=DELTA_B1/2.
   B1_BEST TEST=999999999.
   GO TO 30
ENDIF

IF(B1_THIS_TEST.LT.B1_BEST TEST) THEN
   B1_BEST TEST=B1_THIS TEST
   B1_BEST GUESS=B1
   B1=B1+DELTA_B1
   GO TO 30
ENDIF
B1=B1+DELTA_B1
GO TO 30

$
if you get to this point, everything has converged and you just have to report the answers


2001 PRINT 2011,C1 WRITE(1,2011)C1
2011 FORMAT(1X,55X,CEQUALS",C13.6")
   C1_NUCLEI=(C1/(X(3)-X(2)))/B1
   PRINT 22211,C1_NUCLEI
   WRITE(1,22211)C1_NUCLEI
22211 FORMAT(2X,55X,CEQUALS",G13.6,"C1 NUCLEI")
GO TO 2022

2002 PRINT 2011,C1 WRITE(1,2011)C1
   C1_NUCLEI=(C1/(X(3)-X(2)))/B1
   PRINT 22211,C1_NUCLEI
   WRITE(1,22211)C1_NUCLEI
   PRINT 2012,C2
   WRITE(1,2012)C2
2012 FORMAT(1X,55X,CEQUALS",G13.6")
   C2_NUCLEI=(C2/(X(3)-X(2)))/B2
   PRINT 22212,C2_NUCLEI
   WRITE(1,22212)C2_NUCLEI
22212 FORMAT(2X,55X,CEQUALS",G13.6,"C2 NUCLEI")
GO TO 2022

2003 PRINT 2011,C1 WRITE(1,2011)C1
   C1_NUCLEI=(C1/(X(3)-X(2)))/B1
   PRINT 22211,C1_NUCLEI
   WRITE(1,22211)C1_NUCLEI
   PRINT 2012,C2
   WRITE(1,2012)C2
   C2_NUCLEI=(C2/(X(3)-X(2)))/B2
   PRINT 22212,C2_NUCLEI
   WRITE(1,22212)C2_NUCLEI
2013 FORMAT(1X,55X,CEQUALS",G13.6")
   C3_NUCLEI=(C3/(X(3)-X(2)))/B3
   PRINT 22213,C3_NUCLEI
   WRITE(1,22213)C3_NUCLEI
22213 FORMAT(2X,55X,CEQUALS",G13.6,"C3 NUCLEI")
GO TO 2022

2004 PRINT 2011,C1 WRITE(1,2011)C1
   C1_NUCLEI=(C1/(X(3)-X(2)))/B1
   PRINT 22211,C1_NUCLEI
   WRITE(1,22211)C1_NUCLEI
   PRINT 2012,C2
   WRITE(1,2012)C2
   C2_NUCLEI=(C2/(X(3)-X(2)))/B2
   PRINT 2013,C3
   WRITE(1,2013)C3
2013 FORMAT(1X,55X,CEQUALS",G13.6")
   C3_NUCLEI=(C3/(X(3)-X(2)))/B3
   PRINT 22213,C3_NUCLEI
   WRITE(1,22213)C3_NUCLEI
22213 FORMAT(2X,55X,CEQUALS",G13.6,"C3 NUCLEI")
GO TO 2022

$
PRINT 22212,C2 NUCLEI
WRITE(1,22212)C2 NUCLEI
PRINT 2013,C3
WRITE(1,2013)C3
C3 NUCLEI=(C3/(X(3)-X(2)))/B3
PRINT 22213,C3 NUCLEI
WRITE(1,22213)C3 NUCLEI
PRINT 2014,C4
WRITE(1,2014)C4

2014 FORMAT(/1X,"C4=",G13.6)
C4 NUCLEI=(C4/(X(3)-X(2)))/B4
PRINT 22214,C4 NUCLEI
WRITE(1,22214)C4 NUCLEI

22214 FORMAT(2X,"EQUALS",G13.6," C4 NUCLEI")
2222 IF(KNOW_LAMBDA.EQ.FALSE.)THEN
   PRINT 2222,B1
   WRITE(1,2222)B1

2222 FORMAT(/1X,"LAMBDA=",G13.6)

also report the half life of this lambda

HALF LIFE=(LOG(.5))/B1
PRINT 2922,HALF LIFE
WRITE(1,2922)HALF LIFE

2922 FORMAT(/1X,"THE HALF LIFE FOR THIS LAMBDA = ",G13.6)
ENDIF

$
in this section we calculate the error in C1 for the single component case

IF(NUM_COMPONENTS.NE.1) GO TO 4000

calculate delta squared

DENOMINATOR=0.
DO 3100, I=1,N
   DENOMINATOR=DENOMINATOR+(R(I)*EXP(-2*B1*X(I)))
3100 CONTINUE

SIGMA_C1_SQRED=0.
DO 3200, I=1,N
   AAA=SIGMA_SQRED(I)
   BBB=1./((DENOMINATOR)**2.)
   CCC=(R(I)*EXP(-B1*X(I)))**2.
   SIGMA_C1_SQRED=SIGMA_C1_SQRED+(AAA*BBB*CCC)
3200 CONTINUE

SIGMA_C1=SQRT(SIGMA_C1_SQRED)

PRINT 3110,SIGMA_C1
WRITE(1,3110)SIGMA_C1
3110 FORMAT(/1X, "ERROR IN C1 IS +/-", G13.6)

for two components, calculate the errors in C1 and C2

IF(NUM_COMPONENTS.NE.2) GO TO 5000

SIGMA_C1_SQRED=0.
SIGMA_C2_SQRED=0.
DO 4100, I=1,N
   AAA=SIGMA_SQRED(I)
   BBB=1./((DENOMINATOR)**2.)
   CCC=-(CC CC-CCC CCC)**2.
   SIGMA_C1_SQRED=SIGMA_C1_SQRED+(AAA*BBB*CCC)
   CCC=-(CC CC-CCC CCC)**2.
   SIGMA_C2_SQRED=SIGMA_C2_SQRED+(AAA*BBB*CCC)
4100 CONTINUE

SIGMA_C1=SQRT(SIGMA_C1_SQRED)
SIGMA_C2=SQRT(SIGMA_C2_SQRED)

$
PRINT 3110, SIGMA_C1
WRITE(1,3110) SIGMA_C1
PRINT 4222, SIGMA_C2
WRITE(1,4222) SIGMA_C2

FORMAT(/(1X,'ERROR IN C2 IS +/- °,G13.6)
for the three component case, calculate the errors in C1, C2, and C3

IF(NUM_COMPONENTS.NE.3) GO TO 3000

SIGMA_C1_SQRED=0.
SIGMA_C2_SQRED=0.
SIGMA_C3_SQRED=0.

DO 5100, I=1,N
AAA=SIGMA_SQRED(I)
BBB=1/(DENOMINATOR**2.)
F1=(REL1 1*REL2 3*R(I)*EXP(-B1*X(I)))-
1 (REL1 1*REL3 3*R(I)*EXP(-B1*X(I)))
F2=(REL1 2*REL2 3*R(I)*EXP(-B2*X(I)))-
1 (REL1 2*REL3 3*R(I)*EXP(-B2*X(I)))
F3=(REL1 3*REL2 3*R(I)*EXP(-B3*X(I)))-
1 (REL1 3*REL3 3*R(I)*EXP(-B3*X(I)))
FFF=F1+F2+F3
SIGMA_C1_SQRED=SIGMA_C1_SQRED+(AAA*BBB*(FFF**2.))

F1=(REL1 1*REL3 3*R(I)*EXP(-B2*X(I)))-
1 (REL1 1*REL2 3*R(I)*EXP(-B3*X(I)))
F2=(REL2 3*REL1 3*R(I)*EXP(-B1*X(I)))-
1 (REL1 2*REL3 3*R(I)*EXP(-B1*X(I)))
F3=(REL1 3*REL1 2*R(I)*EXP(-B2*X(I)))-
1 (REL1 3*REL2 3*R(I)*EXP(-B3*X(I)))
FFF=F1+F2+F3
SIGMA_C2_SQRED=SIGMA_C2_SQRED+(AAA*BBB*(FFF**2.))

F1=(REL1 1*REL2 2*R(I)*EXP(-B3*X(I)))-
1 (REL1 1*REL3 3*R(I)*EXP(-B2*X(I)))
F2=(REL1 2*REL2 3*R(I)*EXP(-B1*X(I)))-
1 (REL1 2*REL3 3*R(I)*EXP(-B2*X(I)))
F3=(REL2 2*REL1 3*R(I)*EXP(-B1*X(I)))-
1 (REL2 2*REL3 3*R(I)*EXP(-B3*X(I)))
FFF=F1+F2+F3
SIGMA_C3_SQRED=SIGMA_C3_SQRED+(AAA*BBB*(FFF**2.))

CONTINUE

SIGMA_C1=SQRT(SIGMA_C1_SQRED)
SIGMA_C2=SQRT(SIGMA_C2_SQRED)
SIGMA_C3=SQRT(SIGMA_C3_SQRED)

PRINT 5111, SIGMA_C1
WRITE(1,5111) SIGMA_C1
PRINT 5112, SIGMA C2
WRITE(1,5112) SIGMA C2
PRINT 5113, SIGMA C3
WRITE(1,5113) SIGMA C3

5111 FORMAT(/1X,'ERROR IN C1 IS +/- ',G13.6)
5112 FORMAT(/1X,'ERROR IN C2 IS +/- ',G13.6)
5113 FORMAT(/1X,'ERROR IN C3 IS +/- ',G13.6)

C

3000 CONTINUE

now, calculate chi-squared so that you may compare fits

first, make sure components that are not used are zeroed

IF(NUM COMPONENTS.EQ.1) THEN
   C2=0.
   C3=0.
   C4=0.
ENDIF

IF(NUM COMPONENTS.EQ.2) THEN
   C3=0.
   C4=0.
ENDIF

IF(NUM COMPONENTS.EQ.3) THEN
   C4=0.
ENDIF

now, calculate chi-squared

CHI_SQUARED=0.
DO 11111, I=1,N
   COMP1=C1*EXP(-B1*X(I))
   COMP2=C2*EXP(-B2*X(I))
   COMP3=C3*EXP(-B3*X(I))
   COMP4=C4*EXP(-B4*X(I))
   DIFF=(Y(I)-COMP1-COMP2-COMP3-COMP4)**2.
   CHI_SQUARED=CHI_SQUARED+(R(I)*DIFF)
11111 CONTINUE

PRINT 11112, CHI_SQUARED
WRITE(1,11112) CHI_SQUARED
11112 FORMAT(/1X,'CHI_SQUARED= ',G13.6)

this section calculates the error in lambda 1 (B1) if it had to be found
IF(KNOW_LAMBDA.EQ..TRUE.) GO TO 99999

the way this calculation is done is to see how the errors in calculating C1, C2, ... could effect the calculated value of 

lambda

start with the one component case

IF(NUM_COMPONENTS.EQ.1) THEN

set C1 to its highest value in uncertainty

C1_UNCERTAIN=C1+SIGMA_C1

find the best fit lambda for this case

CALL FIND_LAMBDA(N,X,Y,NUM_COMPONENTS,B1,B2,B3,
1 C1_UNCERTAIN,C2_UNCERTAIN,C3_UNCERTAIN,R,
1 UNCERTAIN_LAMBDA)

calculate the difference between this lambda and the real one

DIFF_LAMBDA=ABS(UNCERTAIN_LAMBDA-B1)

do the same thing with C1 having its lowest value in uncertainty

C1_UNCERTAIN=C1-SIGMA_C1
CALL FIND_LAMBDA(N,X,Y,NUM_COMPONENTS,B1,B2,B3,
1 C1_UNCERTAIN,C2_UNCERTAIN,C3_UNCERTAIN,R,
1 UNCERTAIN_LAMBDA)

find the greatest uncertainty in lambda

IF((ABS(UNCERTAIN_LAMBDA-B1)).GT.DIFF_LAMBDA) THEN
  DIFF_LAMBDA=ABS(UNCERTAIN_LAMBDA-B1)
ENDIF

report the results

GO TO 88888

ENDIF
now, take care of the two component case in a similar manner

IF(NUM_COMPONENTS.EQ.2) THEN

C1_UNCERTAIN=C1+SIGMA_C1
C2_UNCERTAIN=C2+SIGMA_C2
CALL FIND_LAMBDA(N,X,Y,NUM_COMPONENTS,B1,B2,B3,
1       C1_UNCERTAIN,C2_UNCERTAIN,C3_UNCERTAIN,R,
1       UNCERTAIN_LAMBDA)
DIFF_LAMBDA=ABS(UNCERTAIN_LAMBDA-B1)

C1_UNCERTAIN=C1-SIGMA_C1
C2_UNCERTAIN=C2-SIGMA_C2
CALL FIND_LAMBDA(N,X,Y,NUM_COMPONENTS,B1,B2,B3,
1       C1_UNCERTAIN,C2_UNCERTAIN,C3_UNCERTAIN,R,
1       UNCERTAIN_LAMBDA)
IF((ABS(UNCERTAIN_LAMBDA-B1)).GT.DIFF_LAMBDA) THEN
   DIFF_LAMBDA=ABS(UNCERTAIN_LAMBDA-B1)
ENDIF

C1_UNCERTAIN=C1-SIGMA_C1
C2_UNCERTAIN=C2-SIGMA_C2
CALL FIND_LAMBDA(N,X,Y,NUM_COMPONENTS,B1,B2,B3,
1       C1_UNCERTAIN,C2_UNCERTAIN,C3_UNCERTAIN,R,
1       UNCERTAIN_LAMBDA)
IF((ABS(UNCERTAIN_LAMBDA-B1)).GT.DIFF_LAMBDA) THEN
   DIFF_LAMBDA=ABS(UNCERTAIN_LAMBDA-B1)
ENDIF

GO TO 888888

ENDIF

now, take care of the three component case in a similar manner

IF(NUM_COMPONENTS.EQ.3) THEN

C1_UNCERTAIN=C1+SIGMA_C1
C2_UNCERTAIN=C2+SIGMA_C2
C3_UNCERTAIN=C3+SIGMA_C3
CALL FIND_LAMBDA(N,X,Y,NUM_COMPONENTS,B1,B2,B3,
C1 UNCERTAIN, C2 UNCERTAIN, C3 UNCERTAIN, R, UNCERTAIN LAMBDA)
DIFF_LAMBDA = ABS(UNCERTAIN_LAMBDA - B1)

C1 UNCERTAIN = C1 + SIGMA C1
C2 UNCERTAIN = C2 + SIGMA C2
C3 UNCERTAIN = C3 + SIGMA C3
CALL FIND_LAMBDA(N, X, Y, NUM COMPONENTS, B1, B2, B3,
C1 UNCERTAIN, C2 UNCERTAIN, C3 UNCERTAIN, R,
UNCERTAIN LAMBDA)

IF((ABS(UNCERTAIN_LAMBDA - B1)) .GT. DIFF_LAMBDA) THEN
DIFF_LAMBDA = ABS(UNCERTAIN_LAMBDA - B1)
ENDIF

C1 UNCERTAIN = C1 + SIGMA C1
C2 UNCERTAIN = C2 - SIGMA C2
C3 UNCERTAIN = C3 + SIGMA C3
CALL FIND_LAMBDA(N, X, Y, NUM COMPONENTS, B1, B2, B3,
C1 UNCERTAIN, C2 UNCERTAIN, C3 UNCERTAIN, R,
UNCERTAIN LAMBDA)

IF((ABS(UNCERTAIN_LAMBDA - B1)) .GT. DIFF_LAMBDA) THEN
DIFF_LAMBDA = ABS(UNCERTAIN_LAMBDA - B1)
ENDIF

C1 UNCERTAIN = C1 - SIGMA C1
C2 UNCERTAIN = C2 + SIGMA C2
C3 UNCERTAIN = C3 + SIGMA C3
CALL FIND_LAMBDA(N, X, Y, NUM COMPONENTS, B1, B2, B3,
C1 UNCERTAIN, C2 UNCERTAIN, C3 UNCERTAIN, R,
UNCERTAIN LAMBDA)

IF((ABS(UNCERTAIN_LAMBDA - B1)) .GT. DIFF_LAMBDA) THEN
DIFF_LAMBDA = ABS(UNCERTAIN_LAMBDA - B1)
ENDIF

C1 UNCERTAIN = C1 - SIGMA C1
C2 UNCERTAIN = C2 - SIGMA C2
C3 UNCERTAIN = C3 + SIGMA C3
CALL FIND_LAMBDA(N, X, Y, NUM COMPONENTS, B1, B2, B3,
C1 UNCERTAIN, C2 UNCERTAIN, C3 UNCERTAIN, R,
UNCERTAIN LAMBDA)

IF((ABS(UNCERTAIN_LAMBDA - B1)) .GT. DIFF_LAMBDA) THEN
DIFF_LAMBDA = ABS(UNCERTAIN_LAMBDA - B1)
ENDIF

C1 UNCERTAIN = C1 - SIGMA C1
$
C2_UNCERTAIN=C2+SIGMA_C2
C3_UNCERTAIN=C3-SIGMA_C3
CALL FIND_LAMBDA(N,X,Y,NUM_COMPONENTS,B1,B2,B3,
  C1_UNCERTAIN,C2_UNCERTAIN,C3_UNCERTAIN,R,
  UNCERTAIN_LAMBDA)

IF((ABS(UNCERTAIN_LAMBDA-B1)).GT.DIFF_LAMBDA) THEN
  DIFF_LAMBDA=ABS(UNCERTAIN_LAMBDA-B1)
ENDIF

C

C1_UNCERTAIN=C1-SIGMA_C1
C2_UNCERTAIN=C2-SIGMA_C2
C3_UNCERTAIN=C3-SIGMA_C3
CALL FIND_LAMBDA(N,X,Y,NUM_COMPONENTS,B1,B2,B3,
  C1_UNCERTAIN,C2_UNCERTAIN,C3_UNCERTAIN,R,
  UNCERTAIN_LAMBDA)

IF((ABS(UNCERTAIN_LAMBDA-B1)).GT.DIFF_LAMBDA) THEN
  DIFF_LAMBDA=ABS(UNCERTAIN_LAMBDA-B1)
ENDIF

C

GO TO 88888

C

ENDIF

C

C

now that you have the highest difference in lambda,
report this uncertainty

C

88888

PRINT 11131,DIFF_LAMBDA

11131

FORMAT(/IX,"ERROR IN LAMBDA IS +/- °,G13.6)

WRITE(1,11131)DIFF_LAMBDA

C

C

calculate the resulting difference in the half life

C

SIGMA_HALF_LIFE=((DIFF_LAMBDA)**2.)*(((LOG(0.5))/(B1**2.))**2.)

SIGMA_HALF_LIFE=SQRT(SIGMA_HALF_LIFE)

PRINT 11133,SIGMA_HALF_LIFE

11133

FORMAT(/IX,"ERROR IN THE HALF LIFE IS +/- °,G13.6)

WRITE(1,11133)SIGMA_HALF_LIFE

C

C

since everything is written out to a file, enter some
comments to label it

C

99999

PRINT 11122

11122

FORMAT(/IX,"ENTER COMMENT STRING FOR FITDATA FILE °,//)

READ(6,11123)STRING

11123

FORMAT(1A60)

WRITE(1,11123)STRING

CLOSE(UNIT=1)

END
SUBROUTINE FIND_LAMBDA(N,X,Y,NUM_COMPONENTS,B1,B2,B3,
   C1_UNCERTAIN,C2_UNCERTAIN,C3_UNCERTAIN,R,UNCERTAIN_LAMBDA)

   REAL X(1000),Y(1000),R(1000)
   LOGICAL FIRST_TRY

   This subroutine finds an uncertain lambda by minimizing
   chi-squared

   Make sure the components that are not used are zeroed

   IF(NUM_COMPONENTS.EQ.1) THEN
      C2_UNCERTAIN=0.
      C3_UNCERTAIN=0.
   ENDIF

   IF(NUM_COMPONENTS.EQ.2) THEN
      C3_UNCERTAIN=0.
   ENDIF

   Start by picking a lambda

   UNCERTAIN_LAMBDA=0.
   FIRST_TRY=.TRUE.
   DELTA_LAMBDA=B1/10.

   Now, calculate chi-squared

   CHI_SQUARED=0.
   DO 11111, I=1,N
      COMP1=C1_UNCERTAIN*EXP(-UNCERTAIN_LAMBDA*X(I))
      COMP2=C2_UNCERTAIN*EXP(-B2*X(I))
      COMP3=C3_UNCERTAIN*EXP(-B3*X(I))
      DIFF=(Y(I)-COMP1-COMP2-COMP3-COMP4)**2.
      CHI_SQUARED=CHI_SQUARED+(R(I)*DIFF)
   11111 CONTINUE
IF(FIRST_TRY.EQ..TRUE.) THEN
    CHI_SQUARED LOWEST=CHI_SQUARED
    UNCERTAIN LAMBDA=UNCERTAIN LAMBDA+DELTA LAMBDA
    FIRST_TRY=.FALSE.
    GO TO 10
ENDIF

C
C IF(CHI_SQUARED.LT.CHISQUARED LOWEST) THEN
    BEST LAMBDA=UNCERTAIN LAMBDA
    CHI_SQUARED LOWEST=CHI_SQUARED
ENDIF

C IF(DELTA LAMBDA.LT.0.000001) THEN
    UNCERTAIN LAMBDA=BEST LAMBDA
    RETURN
ENDIF

C IF(UNCERTAIN LAMBDA.GT.AMAX LAMBDA) THEN
    UNCERTAIN LAMBDA=BEST LAMBDA-DELTA LAMBDA
    DELTA LAMBDA=DELTA LAMBDA/3.
    AMAX LAMBDA=BEST LAMBDA+DELTA LAMBDA
ENDIF

C UNCERTAIN LAMBDA=UNCERTAIN LAMBDA+DELTA LAMBDA
GO TO 10
END
PROGRAM CHIPLT

REAL XLL, YLL, XUR, YUR, X, Y, POINT(2,1000), X_SCALE, Y_SCALE, 1
   X_ORIGIN, Y_ORIGIN

INTEGER NUM_POINTS

CHARACTER IANS*1, COMMENT*60, CHAR X_HASH3*3, CHAR X_HASH4*4,
   1 CHAR Y_HASH2*2, CHAR Y_HASH3*3, CHAR Y_HASH4*4, CHAR Y_HASH5*5

this program plots the decay data for the blood flow
and phantom experiments as well as a fitted curve as
calculated by CHIFIT through the points

get the plot limits

PRINT 40
FORMAT(/'X', 'MINIMUM X= ', )
CALL READREAL(XLL)

PRINT 50
FORMAT(/'X', 'MAXIMUM X= ', )
CALL READREAL(XUR)

PRINT 60
FORMAT(/'Y', 'MINIMUM Y= ', )
CALL READREAL(YLL)

PRINT 70
FORMAT(/'Y', 'MAXIMUM Y= ', )
CALL READREAL(YUR)

if you wish, read the data points from a file

PRINT 114
FORMAT(/'READ FROM CHIDATA FILE? ', )
CALL READCHAR(IANS)
IF(IANS.EQ.'Y') THEN
   OPEN(UNIT=1, NAME='CHIDATA', READONLY, TYPE='OLD')
   READ(1,111)NUM_POINTS, ANULL, BNULL
   FORMAT(1X, I5, 2F10.2)
   GO TO 112
ENDIF

otherwise, type in the data by hand

$
PRINT 110
FORMAT(/1X,"HOW MANY POINTS? ",$)
CALL READINT(NUM_POINTS)

DO 100, I=1,NUM_POINTS
C
IF(IANS.EQ."Y") THEN
  READ(1,211)Y,X
  FORMAT(1X,2F10.3)
ELSE
  PRINT 115
  FORMAT(/1X,"X= ",$)
  CALL READREAL(X)
  PRINT 120
  FORMAT(1X,"Y= ",$)
  CALL READREAL(Y)
ENDIF

C
C do a coordinate transformation for the semi-log plot
C
Y=LOG(Y)

POINT(1,I)=X
POINT(2,I)=Y

CONTINUE
IF(IANS.EQ."Y") THEN
  CLOSE(UNIT=1)
ENDIF

make sure the limits of the plot are in the correct system

YLL=LOG(YLL)
YUR=LOG(YUR)

now get the hard copy of the points

initialize plotter

CALL PLOTTST("CM")

get a scale factor to produce a 20cm X 20cm plot

X_SCALE=20./(XUR-XLL)
Y_SCALE=20./(YUR-YLL)

$
draw a border around the plot

CALL MOVE(5.,5.)
CALL PLOT(5.,25.)
CALL PLOT(25.,25.)
CALL PLOT(25.,5.)
CALL PLOT(5.,5.)

label the axies of the plot

CALL GETSTRING("TIME IN SECONDS",20.5,3.8,15,"CM")
CALL GETSTRING("COUNTS",0.1,18.0,6,"CM")
CALL GETSTRING("PER",0.6,17.0,3,"CM")
CALL GETSTRING("CHANNEL",0.1,16.0,7,"CM")

enter a comment string which will be printed below the plot

PRINT 220
FORMAT(/1X,"ENTER PLOT LABEL (60 CHARACTERS MAX)"//)
READ(6,230)LEN,COMMENT
FORMAT(Q,A)

plot the comment string

CALL GETSTRING(COMMENT,5.0,2.0,LEN,"CM")

ask if you wish to plot a fitted curve to the data

PRINT 240
FORMAT(/1X,"PLOT A FITTED CURVE TO THE DATA? °,$)
CALL READCHAR(IANS)
IF(IANS.EQ."N") GO TO 290

find out how many decay components in the fitted curve

PRINT 250
FORMAT(/1X,"NUMBER OF COMPONENTS? °,$)
CALL READINT(NUM_COMPONENTS)

zero all the fitted parameters

$
C

C  C1=0.
C  C2=0.
C  C3=0.
C  C4=0.
C  ALAMBDA1=0.
C  ALAMBDA2=0.
C  ALAMBDA3=0.
C  ALAMBDA4=0.
C  GO TO (251,252,253,254)NUM_COMPONENTS

C

C  get the decay constant and the initial counts for each component
C  for one component:
C
C
C  251  PRINT 261
C  261  FORMAT(1X,"ENTER C1 \,\,\$,S)
C  CALL READREAL(C1)
C  PRINT 271
C  271  FORMAT(1X,"ENTER LAMBDA1 \,\,\$,S)
C  CALL READREAL(ALAMBDA1)
C  GO TO 269

C

C  for two components:
C
C
C  252  PRINT 261
C  CALL READREAL(C1)
C  PRINT 262
C  262  FORMAT(1X,"ENTER C2 \,\,\$,S)
C  CALL READREAL(C2)
C  PRINT 271
C  CALL READREAL(ALAMBDA1)
C  PRINT 272
C  272  FORMAT(1X,"ENTER LAMBDA2 \,\,\$,S)
C  CALL READREAL(ALAMBDA2)
C  GO TO 269

C

C  for three components:
C
C
C  253  PRINT 261
C  CALL READREAL(C1)
C  PRINT 262
C  CALL READREAL(C2)
C  PRINT 263
C  263  FORMAT(1X,"ENTER C3 \,\,\$,S)
C  CALL READREAL(C3)
C  PRINT 271
C  CALL READREAL(ALAMBDA1)

S
PRINT 272
CALL READREAL(ALAMDBA2)
PRINT 273
FORMAT(1X,"ENTER LAMDBA3 °,"
CALL READREAL(ALAMDBA3)
GO TO 269

for four components:

PRINT 261
CALL READREAL(C1)
PRINT 262
CALL READREAL(C2)
PRINT 263
CALL READREAL(C3)
PRINT 264
FORMAT(1X,"ENTER C4 °,"
CALL READREAL(C4)
PRINT 271
CALL READREAL(ALAMDBA1)
PRINT 272
CALL READREAL(ALAMDBA2)
PRINT 273
CALL READREAL(ALAMDBA3)
PRINT 274
FORMAT(1X,"ENTER LAMDBA4 °,"
CALL READREAL(ALAMDBA4)

now that you have the equation parameters, get set up to
plot a curve. the curve consists of a thousand vectors so
first get their x length

DELTA_X=(XUR-XLL)/1000.

get the position of the endpoint of the first vector

Y_CURVE=C1+C2+C3+C4
X_CURVE=0.
\_Y_CURVE=LOG(Y_CURVE)
X_CURVE_PLOT=((X_CURVE-XLL)*X_SCALE)+5.0
\_Y_CURVE_PLOT=((\_Y_CURVE-YLL)*Y_SCALE)+5.0
CALL MOVE(X_CURVE_PLOT,\_Y_CURVE_PLOT)

plot the remainder of the curve

DO 290, I=1,999 /
   X_CURVE=X_CURVE+DELTA_X
$
COMP_1=C1*EXP(-ALAMBDAL*X_CURVE)  
COMP_2=C2*EXP(-ALAMBDAL2*X_CURVE)  
COMP_3=C3*EXP(-ALAMBDAL3*X_CURVE)  
COMP_4=C4*EXP(-ALAMBDAL4*X_CURVE)  
Y_CURVE=COMP_1+COMP_2+COMP_3+COMP_4  
Y_CURVE=LOG(Y_CURVE)  
X_CURVE_PLOT=+(X_CURVE-XLL)*X_SCALE)+5.0  
Y_CURVE_PLOT=+(Y_CURVE-YLL)*Y_SCALE)+5.0  
CALL PLOT(X_CURVE_PLOT,Y_CURVE_PLOT)  
CONTINUE  

now, provide the ability to plot the individual components  

PRINT 301  
FORMAT(/IX,°.PLOT THE INDIVIDUAL COMPONENTS? (DEFAULT=YES) °,§)  
CALL READCHAR(IANS)  
IF(IANS.EQ.°.N°) GO TO 290  

plot the first component line  

X_START=5.  
Y_START=((LOG(C1)-YLL)*Y_SCALE)+5.0  
CALL MOVE(X_START,Y_START)  

we have just moved the cursor to th beginning of the  
line, now find where the line exits the limits of the graph  

Y_LOW=EXP(YLL)  
Y_HIGH=EXP(YUR)  
Y_EXIT=C1*EXP(-ALAMBDAL*XUR)  

if this y intersection point is greater than the minimum y then  
the line exits by intersecting the right axis, calculate the  
extit point and draw the line  

IF(Y_EXIT.GT.Y_LOW) THEN  
  X_END=25.  
  Y_END=(((LOG(Y_EXIT))-YLL)*Y_SCALE)+5.0  
  CALL PLOT(X_END,Y_END)  
ELSE  

otherwise, the intersection is with the x axis, calculate the  
x intersection point and plot the line  

X_INTERSECT=((LOG(Y_LOW/C1))/(-ALAMBDAL))
X_END=((X_INTERSECT-XLL)*X_SCALE)+5.0
Y_END=5.0
CALL PLOT(X_END,Y_END)
ENDIF

plot the second component line if there is one

IF(NUM_COMPONENTS.LT.2) GO TO 290

X_START=5.
Y_START=((LOG(C2)-YLL)*Y_SCALE)+5.0
CALL MOVE(X_START,Y_START)

we have just moved the cursor to the beginning of the line, now find where the line exits the limits of the graph

Y_LOW=EXP(YLL)
Y_HIGH=EXP(YUR)
Y_EXIT=C2*EXP(-ALAMBDA2*XUR)

if this y intersection point is greater than the minimum y then the line exits by intersecting the right axis, calculate the exit point and draw the line

IF(Y_EXIT.GT.Y_LOW) THEN
  X_END=25.
  Y_END=((LOG(Y_EXIT))-YLL)*Y_SCALE)+5.0
  CALL PLOT(X_END,Y_END)
ELSE

otherwise, the intersection is with the x axis, calculate the x intersection point and plot the line

  X_INTERSECT=(LOG(Y_LOW/C2))/(-ALAMBDA2)
  X_END=((X_INTERSECT-XLL)*X_SCALE)+5.0
  Y_END=5.0
  CALL PLOT(X_END,Y_END)
ENDIF

plot the third component line if any

IF(NUM_COMPONENTS.LT.3) GO TO 290

X_START=5.
Y_START=((LOG(C3)-YLL)*Y_SCALE)+5.0

CALL MOVE(X_START, Y_START)

we have just moved the cursor to the beginning of the line, now find where the line exits the limits of the graph

Y_LOW=EXP(YLL)
Y_HIGH=EXP(YUR)
Y_EXIT=C3*EXP(-ALAMBDA3*XUR)

if this y intersection point is greater than the minimum y then the line exits by intersecting the right axis, calculate the exit point and draw the line

IF(Y_EXIT.GT.Y_LOW) THEN
  X_END=25.
  Y_END=((LOG(Y_EXIT))-YLL)*Y_SCALE+5.0
  CALL PLOT(X_END, Y_END)
ELSE

otherwise, the intersection is with the x axis, calculate the x intersection point and plot the line

X_INTERSECT=(LOG(Y_LOW/C3))/(-ALAMBDA3)
X_END=((X_INTERSECT-XLL)*X_SCALE)+5.0
Y_END=5.0
CALL PLOT(X_END, Y_END)
ENDIF

plot the fourth component line if any

IF(NUM_COMPONENTS.LT.4) GO TO 290

X_START=5.
Y_START=((LOG(C4)-YLL)*Y_SCALE)+5.0
CALL MOVE(X_START, Y_START)

we have just moved the cursor to the beginning of the line, now find where the line exits the limits of the graph

Y_LOW=EXP(YLL)
Y_HIGH=EXP(YUR)
Y_EXIT=C4*EXP(-ALAMBDA4*XUR)

if this y intersection point is greater than the minimum y then
the line exits by intersecting the right axis, calculate the
exit point and draw the line

IF(Y_EXIT.GT.Y_LOW) THEN
  X_END=Z5.
  Y_END=((LOG(Y_EXIT)-YLL)*Y_SCALE)+5.0
  CALL PLOT(X_END,Y_END)
ELSE

  otherwise, the intersection is with the x axis, calculate the
  x intersection point and plot the line

  X_INTERSECT=(LOG(Y_LOW/C4))/(-ALAMBDA4)
  X_END=((X_INTERSECT-XLL)*X_SCALE)+5.0
  Y_END=5.0
  CALL PLOT(X_END,Y_END)
ENDIF
plot the points

DO 200, I=1,NUM_POINTS

  X=((POINT(1,I)-XLL)*X_SCALE)+4.9
  Y=((POINT(2,I)-YLL)*Y_SCALE)+4.9

  CALL GETSTRING("°",X,Y,1,"°CM")
200 CONTINUE
plot hash marks on the x and y axis

PRINT 410
FORMAT(1X,"ENTER NUMBER OF LARGE X HASHES °",S)
CALL READINT(NO_X_HASH)
PRINT 420
FORMAT(1X,"ENTER NUMBER OF LARGE Y HASHES °",S)
CALL READINT(NO_Y_HASH)
DO 430, IXH=1,NO_X_HASH
PRINT 440
FORMAT(1X,"X HASH = °",S)
CALL READREAL(X_HASH)

each time you plot a hash mark, label it
IX_HASH=IFIX(X_HASH)

encode the x hash mark to a character string

IF(IX_HASH.GT.999) THEN
  ENCODE(4,441,CHAR_X_HASH4)IX_HASH
  FORMAT(114)
ELSE
  ENCODE(3,442,CHAR_X_HASH3)IX_HASH
  FORMAT(113)
ENDIF

find the position of the x hash mark and plot it

X_HASH=((X_HASH-XLL)*X_SCALE)+5.
CALL MOVE(X_HASH,5.)
CALL PLOT(X_HASH,5.5)
CALL MOVE(X_HASH,24.5)
CALL PLOT(X_HASH,25.)

plot the encoded label of the x hash mark

IF(IX_HASH.GT.999) THEN
  CALL GETSTRING(CHAR_X_HASH4,X_HASH-0.37,4.6,4,"CM")
ELSE
  CALL GETSTRING(CHAR_X_HASH3,X_HASH-0.35,4.6,4,"CM")
ENDIF

CONTINUE

now for the y hash marks

DO 450, IYH=1,NO_Y_HASH
PRINT 460
FORMAT(/1X,"Y HASH = ",$)
CALL READREAL(Y_HASH)
IY_HASH=IFIX(Y_HASH)
encode the y hash mark to a character string

IF(IY_HASH.GT.9999) THEN
  ENCODE(5,465,CHAR_Y_HASH5)IY_HASH
  FORMAT(115)
  GO TO 466
ENDIF

$
IF(IY_HASH.GT.999) THEN
   ENCODE(4,464,CHAR_Y_HASH4)IY_HASH
   FORMAT(114)
   GO TO 466
ENDIF
C
C IF(IY_HASH.GT.99) THEN
   ENCODE(3,463,CHAR_Y_HASH3)IY_HASH
   FORMAT(113)
   GO TO 466
ENDIF
C
C IF(IY_HASH.GT.9) THEN
   ENCODE(2,462,CHAR_Y_HASH2)IY_HASH
   FORMAT(112)
   GO TO 466
ENDIF
C
C
C find the position of the y hash mark and plot it
C
C
466
Y_HASH=LOG(Y_HASH)
Y_HASH=((Y_HASH-YLL)*Y_SCALE)+5.
CALL MOVE(5.,Y_HASH)
CALL PLOT(5.5,Y_HASH)
CALL MOVE(24.5,Y_HASH)
CALL PLOT(25.,Y_HASH)
C
C plot the encoded label of the y hash mark
C
C
C IF(IY_HASH.GT.9999) THEN
   CALL GETSTRING(CHAR_Y_HASH5,3.5,Y_HASH-0.1,5,"CM")
   GO TO 469
ENDIF
C
C IF(IY_HASH.GT.999) THEN
   CALL GETSTRING(CHAR_Y_HASH4,3.9,Y_HASH-0.1,4,"CM")
   GO TO 469
ENDIF
C
C IF(IY_HASH.GT.99) THEN
   CALL GETSTRING(CHAR_Y_HASH3,4.1,Y_HASH-0.1,3,"CM")
   GO TO 469
ENDIF
C
C IF(IY_HASH.GT.9) THEN
   CALL GETSTRING(CHAR_Y_HASH2,4.4,Y_HASH-0.1,2,"CM")
   GO TO 469
ENDIF
C
469 CONTINUE
450 CONTINUE
$
now, label the x axis origin

CALL GETSTRING("0\degree, 4.95, 4.6, 1\degree CM")

produce a file for output

CALL FILPRINT("LTEST.DAT", 2)

STOP
END
SUBROUTINE DETERM(ARRAY,NORDER,DETERM_VAL)

this subroutine calculates the determinant of a square matrix

ARRAY contains the matrix
NORDER is the order of the determinant or the degree of the matrix
DETERM_VAL is the value of the determinant

REAL ARRAY(10,10),SAVE
DETERM_VAL=1.
DO 50, K=1,NORDER

interchange columns if diagonal element is zero

IF(ARRAY(K,K)) 41,21,41
DO 23, J=K,NORDER
IF(ARRAY(K,J)) 31,23,31
CONTINUE
DETERM_VAL=0.
GO TO 60

DO 34, I=K,NORDER
SAVE=ARRAY(I,J)
ARRAY(I,J)=ARRAY(I,K)
ARRAY(I,K)=SAVE
DETERM_VAL=-DETERM_VAL

subtract row k from lower rows to get diagonal matrix

DETERM_VAL=DETERM_VAL*ARRAY(K,K)
IF(K-NORDER) 43,50,50
K1=K+1
DO 46, I=K1,NORDER
DO 46, J=K1,NORDER
ARRAY(I,J)=ARRAY(I,J)-ARRAY(I,K)*ARRAY(K,J)/ARRAY(K,K)
CONTINUE
RETURN
END
$
REFERENCES


5. Grosjean, C.C. and Bossaert, W., Table of Absolute Detection Efficiencies of Cylindrical Scintillation Gamma-Ray Detectors, Computing Laboratory, University of Ghent, Belgium, 1965


