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MEASUREMENT OF REGIONAL MYOCARDIAL BLOOD FLOW BY
COMPARTMENT MODELING

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ABSTRACT

The purpose of this research was to improve quantitative Positron Emission Tomography (PET). This involved the development of software to analyze PET scan data, validation of a two-compartment model and characterization of a detector that measures the input function to the model.

Validation of the two compartment modeling method to obtain the regional myocardial blood flow (RMBF) was accomplished by comparing results from analyses of dynamic PET scans with data from tissue samples. The calculation of RMBF in a heart may aid in the determination of cardiac muscle viability in patients with coronary artery disease and should assist the therapist in a decision for high cost bypass surgery.

A PET scanner can measure the concentration of positron emitting radioisotopes within an object. After injection of radioactive tracer into human body, the amount of activity measured in tissue depends on the kinetics of the metabolic process and on the transport properties between the blood and cells. The metabolic process kinetics are obtained by measuring the tracer dynamics. The two compartment modeling method is used to represent the tracer dynamics. The parameters in the model are directly associated with

physiological or biochemical meaningful information such as RMBF in the heart.

The validation of the model shows that the two compartment modeling method can be used to calculate RMBF. It overcomes clinical difficulties of previous methods. A maximum likelihood method is used in the model identification and is performed by a software package. A comparison of the result obtained by this method and the previously used "first-pass" method shows that this method provides more accurate results.

The evaluation of the detector system for measurement of the model input function indicates that the detector studied has an acceptable efficiency for data acquisition.

(Keywords: myocardial blood flow, positron emission tomography, compartmental modeling, parameter identification, beta detector)

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CHAPTER 1

INTRODUCTION

1.1 Scope of the Project

Medical care has been greatly enhanced by the invention of advanced medical imaging techniques such as x-ray computed tomography (CT), and magnetic resonance imaging (MRI). These techniques can provide cross-sectional images of the anatomy of an internal body organ, e.g. heart and brain. These images can provide useful diagnostic information. Some diseases may be directly reflected by the images. However, in order to give chemical and metabolic information about tissue and to identify patterns of chemical changes in diseases, rather than only show morphology, a new technique needs to be developed.

Positron emission tomography (PET) is a newly developed imaging technique. It has similarities to CT and MRI. Because PET uses organic compounds which incorporate positron emitting isotopes as tracers, it can provide unique biochemical and physiologic information not obtainable through other imaging techniques. Therefore, PET shows promise in diagnosing and treating a multitude of different diseases.

Until recently, only a few university medical research centers in the United States had performed PET imaging research. Due to the complex technical difficulties with routine PET imaging, such as the requirement of an on-site cyclotron, the clinical utility of PET is just beginning to be realized. In January 1988, The University of Tennessee Medical Center at Knoxville (UTMCK) established a clinical PET facility. The intent of the center has been to provide clinical PET imaging for routine diagnosis and treatment and to conduct research for quantitative PET.

One of goals of UTMCK in clinical PET is the measurement of regional myocardial blood flow (RMBF) by modeling. The major accomplishment of this work is in two areas. One is the development of a software package that can be used to calculate the RMBF. The other area is the development of a detector to measure radioactivity in blood.

1.2 Statement of the Problem

The calculation of the regional myocardial blood flow in a heart may aid in the determination of cardiac muscle viability in patients with coronary artery disease. Interest in calculating the RMBF has been on the increase in recent years. Various techniques have been developed to measure regional myocardial blood flow in organs. These include:

Fick's principle [1], the Kety-Schmidt method [1] and the microsphere technique [2]. Later, Mullani developed a "first-pass" technique based on Fick's principle [3]. These methods have all been based on the principle of conservation of mass within the system. However, it has been indicated that some of these methods may have difficulty in obtaining necessary information to perform the RMBF calculation, some others can only give an estimation of RMBF.

Fick's principle requires a direct measurement of venous radioactivity concentration from the heart. This is difficult to obtain in a routine diagnostic study [4].

The problem with the Kety-Schmidt method is that it is hard to estimate the partition coefficient used to describe its mass-balance equations because it depends on both the tissue being examined and on the radiotracer used. It also requires measurement of venous radioactivity concentration directly from the coronary sinus.

The microsphere technique, which can provide very accurate measurement of RMBF, is difficult in clinical applications. This is because microspheres used must be injected directly into the left ventricle of the heart to prevent it from sticking into the lung. This requires a catheter to be inserted into the left ventricle through the

artery. In addition, microspheres have the potential for brain and kidney embolization. Therefore, it is mostly used as a research tool in animals [4].

The problem with Mullani's technique is that it assumes a uniform extraction fraction from the material. Schelbert has shown that this assumption may be inaccurate, especially for high blood flow rates [5]. This may result in underestimation of perfusion at high blood flow rates. Another problem with this technique is that it assumes that the time needed for making the blood-flow measurement is short enough such that none of the radiotracer has left the region of interest during the period of data acquisition. However, for many tracers, the minimum tissue time delay is too short to accurately measure the myocardial time activity curve given the count rate limitations of PET.

Another method which has also been mentioned is the "three compartment model method" by Hutchins [6]. Although this method is similar to our model, there has been no independent validation of the method, and no error sensitivity analysis.

The two compartment model evaluated in this thesis is clinically noninvasive, an advantage over other methods which require measurement of coronary sinus radioactivity

concentration and the injection of microspheres. This model describes the physiological and biochemical processes in the heart using known physiologic parameters. A maximum likelihood algorithm can be used to calculate the RMBF. Other methods such as the least-square algorithm may also be used to calculate RMBF.

1.3 Development of the Analysis Methodology

1.3.1 Compartment Model Development

Mathematical models are used to incorporate known physiologic and biochemical information about a process into a mathematical description of that process. A compartment model is represented by a number of compartments linked together by arrows that indicate tracer transport between compartments. A compartment is defined as a space in which the tracer is distributed uniformly [7]. Therefore, the tracer kinetics of a compartment model can be described in terms of a set of linear, first-order, ordinary differential equations [7]. In this research, a two-compartment model is used to represent the tracer dynamics of NH_3 ammonia in the heart for estimating the RMBF. One of these compartments represents the freely diffusible NH_3 volume and the other the trapped NH_3 space.

The inputs for the two compartment model are radioactivity in the region of interest of the heart muscle and the radioactivity concentration in the blood. Radioactivity in a region of interest in the heart can be measured with PET as a function of time, and the radioactivity concentration in blood can be measured by a scintillation probe.

1.3.2 Mathematical Model Identification

The maximum likelihood method is used to identify the parameters of the two compartment model by fitting the analytical model activity curve to the experimental data. One of these parameters is the RMBF. A software package [8] is used to perform this model identification.

1.4 Description of Detector

The measurement of radioactivity concentration in blood, which determines the input function, is obtained by setting up an instrument system that contains a plastic scintillation probe, single channel analyzer, multichannel analyzer, preamplifier, timer and counter. The blood is withdrawn at a constant rate through a pump and fed into the plastic scintillation probe coupled to a photo-multiplier tube. The input function is obtained from the MCA output.

1.5 Outline of the Thesis

The purpose of Chapter 1 is to provide the background for this research, the problem definition, and the general approach taken in the research. In Chapter 2, a review of the basic principles of tracer kinetic techniques and modeling theory is followed by the methodology used in this study. This includes the set up of a myocardium mathematical model and definition of model parameters and variables.

Chapter 3 is devoted to the model characterization which includes the analytical solution of the model, synthetic data generation and model response to the variation of several parameters in the model.

The detector system set up and evaluation are described in Chapter 4. Several major validations of the detector including calibration, deadtime, and sensitivity analysis are illustrated.

Chapter 5 outlines clinical application of the model and compares the results obtained by this method for a dog study with the "first-pass" technique.

Conclusions and suggestions for future work are given in Chapter 6.

CHAPTER 2

METHODOLOGY

2.1 Literature Review

2.1.1 Basic Principle of Quantitative PET

Positron emission tomography is a technique for measuring the concentration of positron emitting radioisotopes within an object. Each positron combines with an electron and produces a pair of 511 keV gamma annihilation photons in opposite directions. This gamma ray is penetrating and can be measured externally. The isotope location can be presented as a gray scale image of a cross-sectional of the object with the intensity of each picture element or pixel proportional to the isotope concentration at that position in the object. The quantity that is measured in PET is tissue concentration of positron emitter.

As an imaging tool, PET has the same function as CT and MRI which can provide a cross-section image of an object. The development of quantitative PET is based on the fact that the amount of activity measured in an organ depends on the kinetics of the metabolic process, the transport properties

between the blood and the site of the process in the cell, and the activity delivered over time.

Analysis of the cross-sectional images for determining true tracer concentration in tissue requires correction of the data obtained by the PET scanner due to the physical properties of the detectors needed in a PET system. One correction is the detector partial volume effect. If the objective tissue size is less than two times the spacial resolution of the detector system, tissue concentration will be underestimated. The other correction is radioactivity spillover. Due to the spacial resolution of the PET detector, the observed activity from a small size tissue volume may include activity from surrounding tissue.

The thickness of the left ventricular myocardium is usually 8 to 12 mm whereas the spacial resolution of the image device in PET is from 5 to 10 mm. This results in an underestimation of myocardial tissue concentration. Corrections for this underestimation can be made by using the relationship between count recovery and object size. This relationship is defined as the recovery coefficient (ratio of observed counts to true counts), and it can be established with a bar phantom technique [9].

The characteristics of spatial resolution determine the magnitude of activity spillover. In a heart study, this is the cross contamination of activity between the blood pools and the myocardium tissue. Counts derived from a region of interest in the myocardium represent not only activity in myocardium but also the spillover activity from the blood pool and vice-versa. The approach of correcting activity spillover between the blood pool and myocardium has been developed by Henze et al. [10].

2.1.2 Tracer Kinetic Technique

Tracer kinetic techniques are generally used to trace the physiological and biochemical dynamic processes. They require that measurable tracers be introduced into the tissue being analyzed. In PET studies, commonly used tracers are organic compounds which are chemically incorporated with positron emitting isotopes. This is because organic compounds can be easily extracted or metabolized by tissue. N-13, O-15, C-11, F-18 are mostly used as positron emitting isotopes.

Measurements of the tracer in tissue are taken as a function of time. Thus, tracer dynamic processes can be obtained from the measurements. If structural information about the tissue dynamic process is known, the tracer kinetics can be interpreted from the measurements. Incorporation of

tissue structural information with tracer kinetics can be accomplished by modeling.

A comprehensive model configuration for tissue can be formulated according to known tissue physiological and biochemical information. The model is then simplified using certain assumptions to obtain a more "workable" form, and operational mathematical equations describing the tracer kinetics are developed. The parameters in these equations give physiological or biochemical meaning of the tissue such as blood flow. They can be estimated using many known mathematical methods.

Tracers used in PET are usually introduced into the body by intravenous injection or inhalation. In either method, tracers are well mixed in the blood after going through the heart chambers. Therefore, all arterial blood should have the same concentration. The concentration of tracer delivered to the tissue capillaries can be obtained from any peripheral artery, and the amount of tracer delivered to tissue is proportional to the blood flow.

2.1.3 Mathematical Model Theory

Mathematical models can be used to describe the dynamic behavior of the tracer. A compartment in a mathematical model

can represent either a space physically separated by membranes or chemically different forms of the tracer in tissue. The parameters in the model can be directly associated with physiologically and biochemically meaningful information about the tissue. The link between different compartments is formed by the tracer delivery and extraction into the tissue.

A compartment model describing tissue tracer kinetics is usually represented by a number of compartments linked together by arrows indicating tracer transport between compartments. A compartment is defined as a space in which the tracer is distributed uniformly. The amount of tracer leaving a compartment is assumed to be proportional to the total amount in the compartment. Based on the definition of the compartment, the tracer kinetics can be described in terms of a set of linear, first-order ordinary differential equations. These provide the description of that compartment model. Generally, not very many physiological processes or biochemical reactions can be considered linear. However, as far as the tracer is concerned, linearity is usually valid for its transport [7].

2.2 Two Compartment Model for the Heart

2.2.1 Model Set Up

The myocardial tissue consists of vascular capillary, extracellular space, and cells as shown in Figure 2.1. As described in the previous section, a compartment is defined as a space in which the tracer is distributed uniformly. In calculating RMBF by an NH_3 tracer, a two compartment model is appropriate for describing its tracer dynamics in the heart tissue. One compartment represents the freely diffusible NH_3 space which is a combination of vascular volume and extracellular space. This combination is defined due to the fact that NH_3 flux between these two spaces is extremely rapid [5]. The other compartment represents the trapped NH_3 space which is the intracellular space. The tracer in the heart is uniformly distributed in each compartment space respectively. Each pixel of a PET image represents total activity concentration contained within the vascular volume, extracellular space, and intracellular space.

As shown in Figure 2.2, F is the RMBF by which the tracer is delivered into freely diffusible space. $Q_1(t)$ and $Q_2(t)$ are the radioactivity as a function of time in each compartment. Since both compartments occupy the same image space, the total measured activity $Q(t)$ in the myocardium at

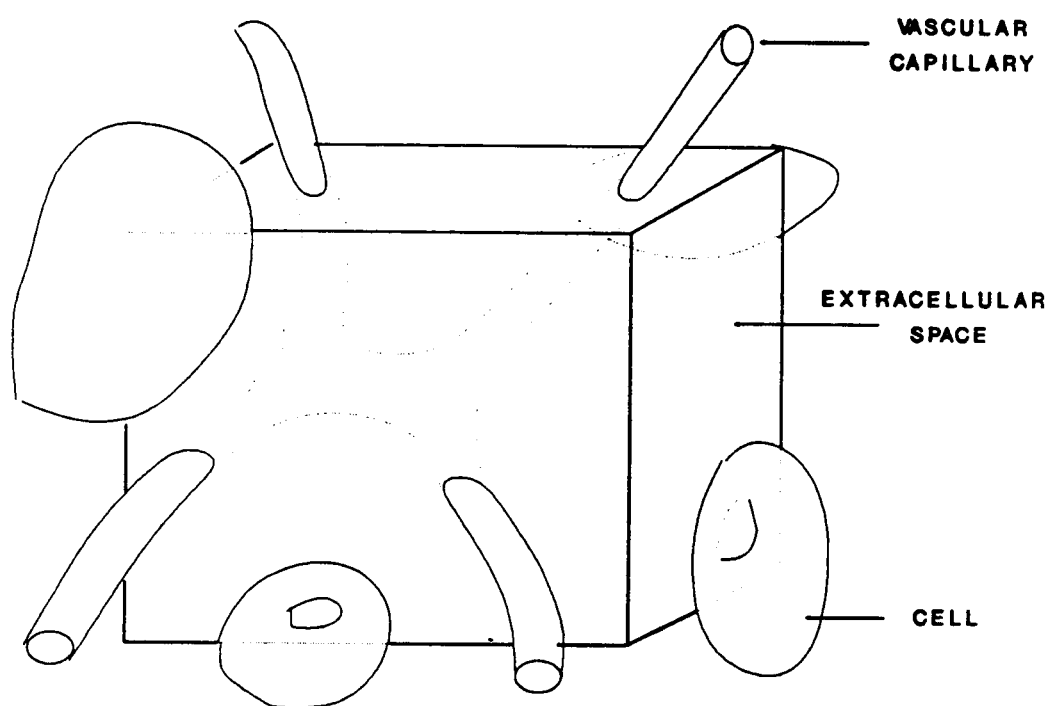


Figure 2.1. Tissue Structure

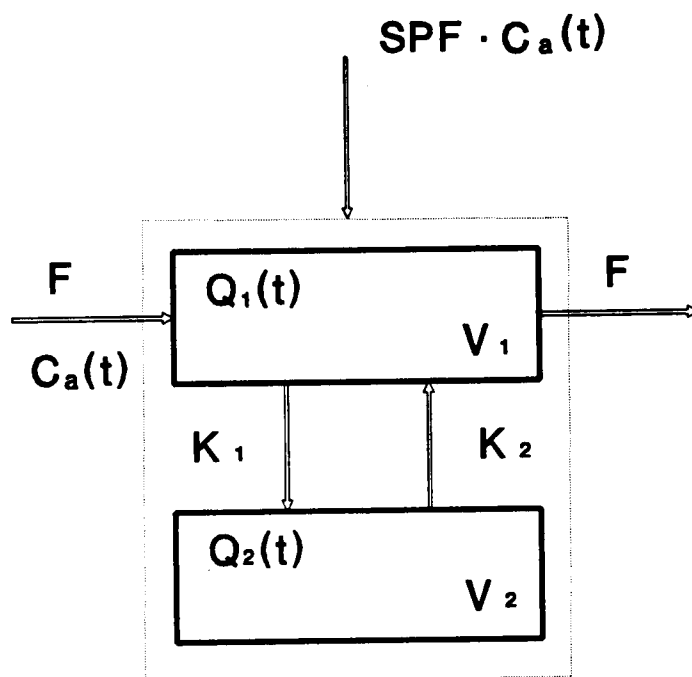


Figure 2.2 Two Compartment Model for Heart Tissue

a region of interest in the PET image is the sum of $Q_1(t)$ and $Q_2(t)$. $C_a(t)$ is the tracer activity concentration as a function of time through the input artery. V_1 and V_2 are the effective distribution volumes of each compartment. K_1 and K_2 represent the forward and reverse rate constants for tracer flux between these compartments. The blood to myocardial spillover factor SPF, is discussed in section 2.2.2.

Utilizing the principle that the rate of change in concentration of a system equal to its gains minus losses, two differential equations are developed to describe the system dynamics [4]:

$$\frac{dQ_1(t)}{dt} = FC_a(t) + \frac{Q_2(t)}{V_2} K_2 - \frac{Q_1(t)}{V_1} K_1 - \frac{Q_1(t)}{V_1} F \quad 2.1$$

$$\frac{dQ_2(t)}{dt} = \frac{Q_1(t)}{V_1} K_1 - \frac{Q_2(t)}{V_2} K_2 \quad 2.2$$

where $Q_1(t)$, $Q_2(t)$ and $C_a(t)$ are variables and F , K_1 , K_2 , V_1 , V_2 are parameters. The variables and parameters used are defined in Table 1. This system of dynamics can also be described in state space matrix form:

Table 1. Symbols Used in the Model Equations

Symbol	Description	Units
F	regional myocardial blood flow	ml/min/gm
$C_a(t)$	the imposed tracer activity	$\mu\text{Ci/ml}$
$Q_1(t)$	tracer activity in first compartment	$\mu\text{Ci/gm}$
$Q_2(t)$	tracer activity in second compartment	$\mu\text{Ci/gm}$
K_1	tracer washout rate	ml/min/gm
K_2	tracer uptake rate	ml/min/gm
V_1 V_2	volume of distribution	ml/gm
SPF	blood pool to myocardium spillover factor	-
t	time	min

$$\dot{X}(t) = AX(t) + B_u U(t) \quad 2.3$$

$$Y = CX(t) + D_u U(t) \quad 2.4$$

where $X(t)$ is the state variable, $U(t)$ is system input or excitation, Y is system output and A , B_u , C and D_u are coefficient matrices. The model dynamics can therefore be described as:

$$\begin{pmatrix} \dot{Q}_1(t) \\ \dot{Q}_2(t) \end{pmatrix} = \begin{pmatrix} -\frac{(F+K_1)}{V_1} & \frac{K_2}{V_2} \\ \frac{K_1}{V_1} & -\frac{K_2}{V_2} \end{pmatrix} \begin{pmatrix} Q_1(t) \\ Q_2(t) \end{pmatrix} + \begin{pmatrix} F \\ 0 \end{pmatrix} C_a(t) \quad 2.5$$

$$Y = [1 \ 1] \begin{pmatrix} Q_1(t) \\ Q_2(t) \end{pmatrix} + [SPF] * C_a(t). \quad 2.6$$

The state variable $X(t)$ is defined as $[Q_1(t), Q_2(t)]^T$, the system input $U(t)$ is $C_a(t)$, and the system output Y is the detected total activity in the tissue. The coefficient matrices of the system are $B_u = [F, 0]^T$, $C = [1 \ 1]$ and $D_u = [SPF]$. The system matrix is

$$A = \begin{pmatrix} -\frac{(F+K_1)}{V_1} & \frac{K_2}{V_2} \\ \frac{K_1}{V_1} & -\frac{K_2}{V_2} \end{pmatrix} \quad 2.7$$

All model parameters are defined in Table 1.

The total tracer activity $Q(t)$ at a region of interest in the heart is obtained from the PET scanner, whereas, the imposed activity concentration $C_a(t)$, can be determined by the detector system. This is described in the following chapter. In the heart study, the arterial input activity concentration can also be determined from the left ventricular blood pool with PET as shown by Weinberg et al. [11].

2.2.2 Model Development

The data representing tracer activity $Q(t)$ in myocardium tissue obtained from a PET scan is corrected for both partial volume and spillover effects from blood pool activity. These corrections are based on relative dimensions of the volume of the blood pool and the myocardium [12]. Figure 2.3 shows the activity curve for a dog myocardium study. The amount of activity in the myocardium is negative at the beginning of data acquisition due to overcorrection for spillover using a geometric algorithm [13]. To compensate for spillover effects, the spillover factor (SPF) is introduced into the myocardial model system as shown in equation 2.6. The SPF is an adjustable weighing factor in the model.

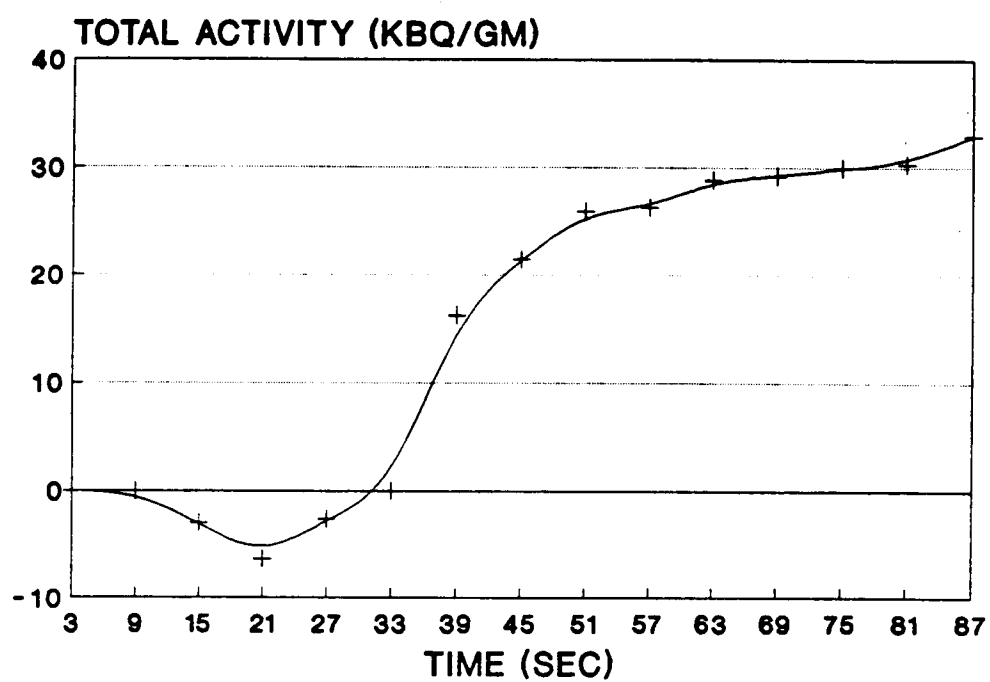


Figure 2.3. The Activity Curve from Dog Myocardium

Another model consideration is the myocardial NH_3 extraction. A factor E is defined to represent the extraction fraction of NH_3 . This factor has been determined to be inversely related to F according to the following equation

$$E = 1 - 0.607e^{(-1.25/F)} \quad 2.8$$

This equation was derived by Schelbert et al. [5] in the metabolism study of dog myocardia.

The extraction fraction factor, E, is also defined as the ratio of the trapped activity to total activity delivered to the system by Crone [14]:

$$E = \frac{K_1}{K_1 + F} \quad 2.9$$

Equation 2.8 and 2.9 are combined to give the relationship between K_1 and F, where

$$K_1 = [1.65e^{1.25/F} - 1] F. \quad 2.10$$

This reduces the number of independent parameters to be estimated by the model.

2.3 Model Identification

The constants appearing in the model discussed in the previous section are F, K_1 , V_1 , K_2 , V_2 and SPF. They are also parameters which have special physiological significance, and

can be identified by comparison of a best fit model to test data. Using the excitation function $C_a(t)$ and the model response output data (shown in Figure 2.4), parameters can be identified.

For an n th order system, $2n-1$ parameters can be identified [15]. However, for an increased number of parameters involved, the greater is the degree of model complexity. Independent parameters can be reduced by either utilizing relationships obtained from other tests or calculations or specifying known values for one or more parameters from other sources [16].

The rate constant K_1 is obtained utilizing the relationship of Equation 2.10. $V_1=0.8$ (ml/gm) is selected as an estimation. It is shown in the following chapter that F is not sensitive to variation in V_1 . As a corollary, there has been no effective identification of V_1 . A new factor Z is defined as $Z=K_2/V_2$. Because of the short time in this study, Z is assumed to be negligible, i.e. $Z=0$ in this analysis. Validation of this assumption is shown in Chapter 3.

Three commonly used methods for model parameter identification are least squares, analogy, and maximum likelihood algorithms. In the myocardial model, the parameters F and SPF (which represent the value of $RMBF$ and spillover

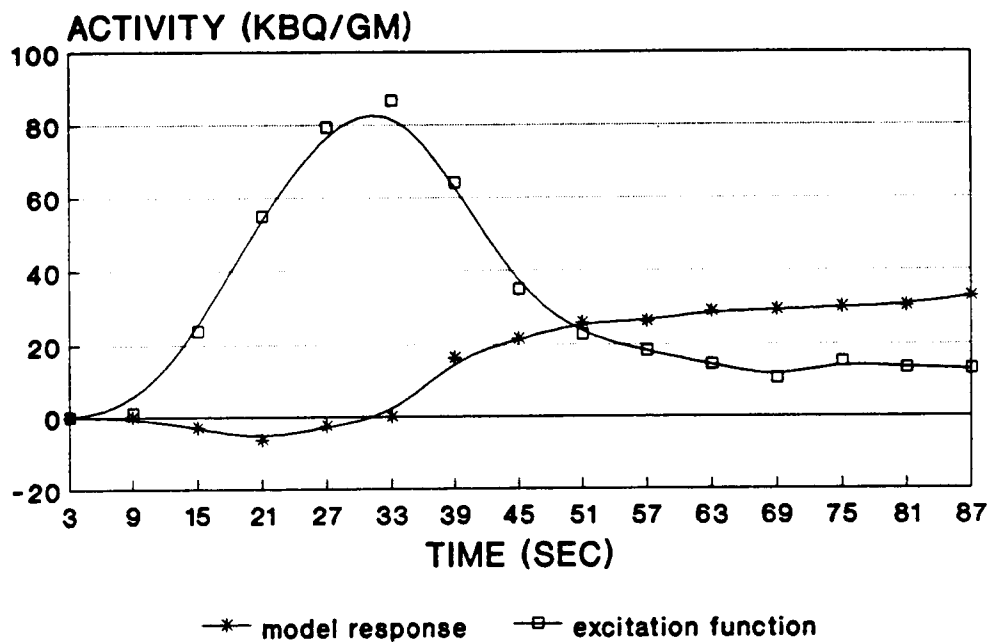
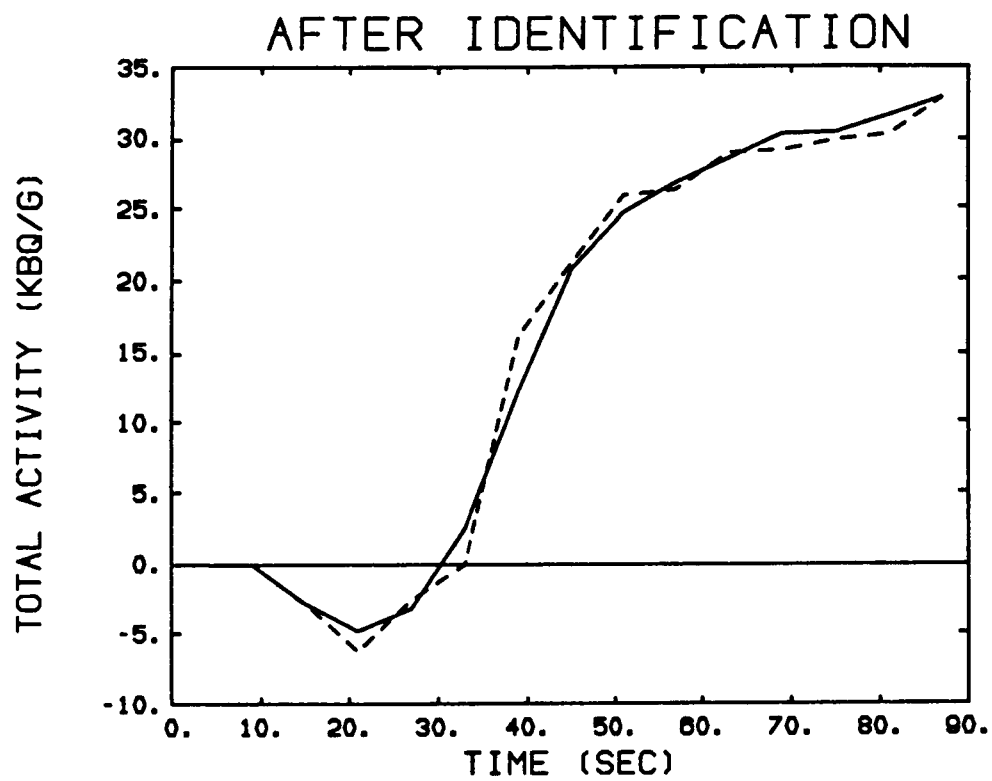


Figure 2.4. Myocardial Tissue Model Excitation
Function and Response

factor) are identified using the maximum likelihood algorithm approach. These parameters are identified using "Ctrl-C" (System Control Technology, Palo Alto, CA) [8] implemented on a SUN 3/280 computer. A curve indicating the best fit of the model to the test data obtained from a dog myocardium is shown in Figure 2.5. A manual describing "Ctrl-C" in the myocardial model identification is given in Appendix A. The computer code used in this identification is given in Appendix B. Table 2 shows the result of RMBF identification for 8 regions of interest (ROI) in a single dog study.



Dashed Line: Test data

Solid Line: Model Response

Figure 2.5. Model Best Fit to Test Data

Table 2. Results of Model Identification for Dog RMBF

ROI	RMBF (ml/min/gm)
1	0.924
2	0.693
3	0.638
4	0.590
5	0.481
6	0.695
7	0.624
8	0.737

CHAPTER 3

MODEL EVALUATION

3.1 Introduction

After a working model is developed, it should be validated. The first step in model validation is examining the qualitative characteristic of its response function to see if it is consistent with experimental kinetic data. This is accomplished by checking the goodness-of-fit of the curves generated by the model and experimental kinetic data. Figure 2.5 shows the best fit curve for this model in a dog experiment. The model response shows good agreement with the experimental data. However, in model validation, there is a possibility that a mathematical best fit could ascribe artificial values to unimportant parameters in the model and thus give inaccurate values for important parameters. Of two alternative models that fit the data equally well, the one with the smaller number of free parameters gives smaller standard errors of estimation [7].

3.2 Analytical Solution of Model and Synthetic Data Generation

In order to test the model sensitivity to different parameters, synthetic data is generated by solving the model differential equations. The model input function, the

arterial input $C_a(t)$, is assumed to be a gamma variate function, $C_a(t) = ate^{-\beta t}$ in which a is equal to 0.65, and β is 0.1 [4] which gives a close approximation to the excitation function in Figure 2.4. The model differential equations are derived as:

$$\frac{dQ_1(t)}{dt} = -\frac{(F+K_1)}{V_1} Q_1(t) + FC_a(t) \quad 3.1$$

$$\frac{dQ_2(t)}{dt} = \frac{K_1}{V_1} Q_1(t) \quad 3.2$$

Assuming $C_a(t) = ate^{-\beta t}$, equation 3.1 becomes

$$\frac{dQ_1(t)}{dt} + \frac{(F+K_1)}{V_1} Q_1(t) = Fate^{-\beta t} \quad 3.3$$

Equation 3.8 is derived from equation 3.3 by letting $K = (F+K_1)/V_1$, this is shown below:

$$\frac{dQ_1(t)}{dt} + KQ_1(t) = Fate^{-\beta t} \quad 3.4$$

$$e^{kt} Q_1(t) = \int e^{kt} Fate^{-\beta t} dt + C_1$$

$$= -\frac{Fa}{(K-\beta)} \int t de^{(K-\beta)t} + C_1$$

$$= -\frac{Fa}{(K-\beta)} \left[te^{(K-\beta)t} - \frac{1}{(K-\beta)} e^{(K-\beta)t} \right] + C_1 \quad 3.5$$

$$Q_1(t) = -\frac{Fa}{(K-\beta)} te^{-\beta t} - \frac{Fa}{(K-\beta)^2} e^{-\beta t} + C_1 e^{-\beta t}. \quad 3.6$$

Using the initial condition $Q_1(0)=0$, the constant C_1 is obtained as

$$C_1 = \frac{Fa}{(K-\beta)^2}. \quad 3.7$$

Substituting this value for C_1 into equation 3.6 gives

$$Q_1(t) = -\frac{Fa}{(K-\beta)} \left[te^{-\beta t} - \frac{1}{(K-\beta)} e^{-\beta t} + \frac{1}{(K-\beta)} e^{-\beta t} \right]. \quad 3.8$$

Letting $C=K_1/V_1$ and integrating both sides of equation 3.2 gives

$$Q_2(t) = \int C Q_1(t) dt + C_2$$

$$= -\frac{FaC}{(K-\beta)} \left[-\frac{1}{\beta} (te^{-\beta t} + \frac{1}{\beta} e^{-\beta t}) + \frac{1}{(K-\beta)\beta} e^{-\beta t} - \frac{1}{(K-\beta)K} e^{-\beta t} \right] + C_2. \quad 3.9$$

The constant, C_2 , is determined by using the initial condition, $Q_2(0)=0$, and is given by the following equation:

$$C_2 = -\frac{FaC}{(K-\beta)} \left[-\frac{1}{\beta^2} + \frac{1}{(K-\beta)\beta} - \frac{1}{(K-\beta)K} \right] \quad 3.10$$

Substituting this value for C_2 in equation 3.9 gives

$$Q_2(t) = -\frac{FaC}{(K-\beta)} \left[-\frac{1}{\beta} (te^{-\beta t} + \frac{1}{\beta} e^{-\beta t}) + \frac{1}{(K-\beta)\beta} e^{-\beta t} - \frac{1}{(K-\beta)K} e^{-Kt} - \left(-\frac{1}{\beta^2} + \frac{1}{(K-\beta)\beta} - \frac{1}{(K-\beta)K} \right) \right]. \quad 3.11$$

The synthetic data representing the activity of a PET scan region of interest is obtained by averaging the integral of the activity observed within the scan time. A typical scan time is 6-8 seconds [4]. The tissue activity concentration at the time between t_1 and t_2 is obtained from the equation,

$$Q(t) = \frac{1}{(t_2-t_1)} \int_{t_1}^{t_2} [Q_1(t) + Q_2(t)] dt \quad 3.12$$

Table 3 shows 90 seconds of synthetic data, simulating all scan acquisition period of 6 seconds per time frame. The average value of each interval was assigned to the time frame midpoint. The values assumed for F and V_1 , in this model, were 1 (ml/min/gm) and 0.8 (ml/gm), respectively. The listing for the computer code which generated this data is shown in Appendix C.

Table 3. Synthetic Data of the Model with
 $F=1$ (ml/min/gm), $V_1=0.8$ (ml/gm)

Time (sec)	Total Activity ($\mu\text{Ci/gm}$)	$C_a(t)$ ($\mu\text{Ci/ml}$)
3	0.047	1.445
9	0.233	2.378
15	0.437	2.176
21	0.598	1.672
27	0.710	1.179
33	0.783	0.791
39	0.828	0.513
45	0.856	0.325
51	0.872	0.202
57	0.882	0.124
63	0.888	0.075
69	0.891	0.045
75	0.893	0.027
81	0.894	0.016
87	0.894	0.009

3.3 Model Response to the Variation of Parameters

3.3.1 Model Response to Flow

The synthetic data for this model was generated using F values ranging from 0.1 to 100 (ml/min/gm) to test the linearity of the model relative to F and to validate the software. The actual range of the F value found in clinical situations is 0.1 to 6 (ml/min/gm). The model was then used to determine the value of F for each synthetic data set and these values are compared to the true F values. Figure 3.1 shows a sample plot of the identification curve fitting. Figure 3.2 shows the relationship between the synthetic value of F and the estimated F using the model. As expected, this relationship is linear with a slope of 0.985 ($r=0.99$) up to an actual flow of 100 (ml/min/gm).

3.3.2 Model Response to the Volume of Distribution

The model was tested for sensitivity of RMBF to errors in the assumed volume of distribution, V_1 . Synthetic data sets were generated with V_1 -values of 0.2, 0.8, 1.5 and 3.0 (ml/gm), respectively. Then, the parameter, F , is estimated for these data sets using arbitrary values of V_1 (0.2 to 3.0 (ml/gm)). The error between the estimated F -values was less than 10% for all values of V_1 , as shown in Figure 3.3. This

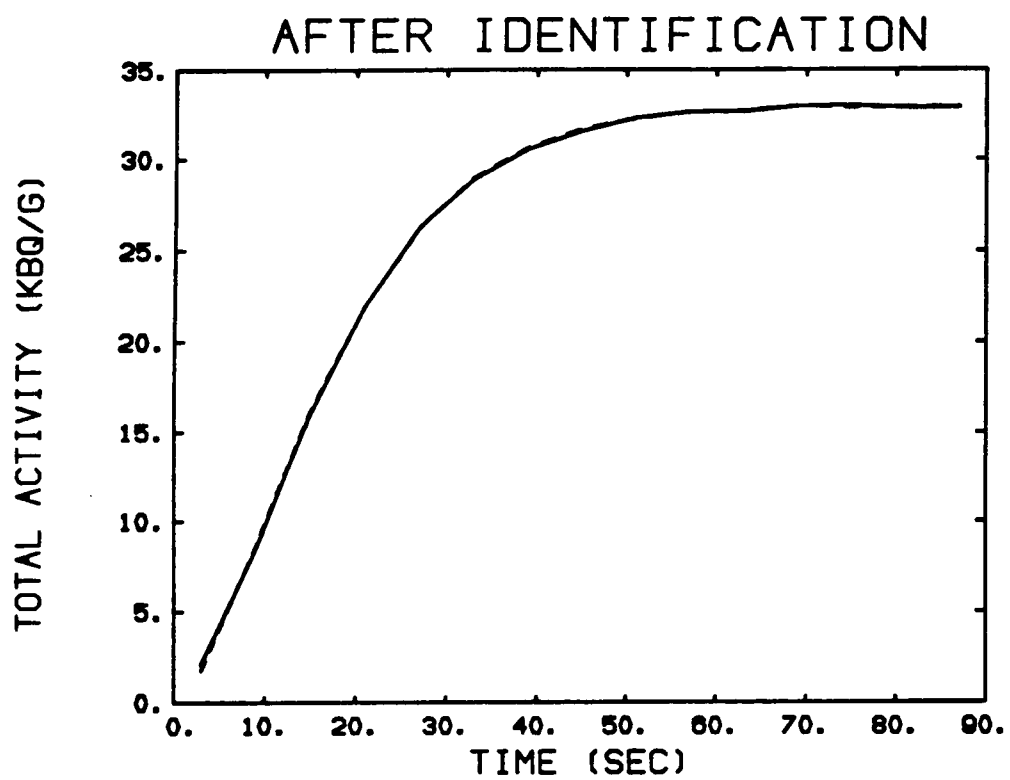


Figure 3.1. Model Response Curve Fitting to the
Synthetic Data

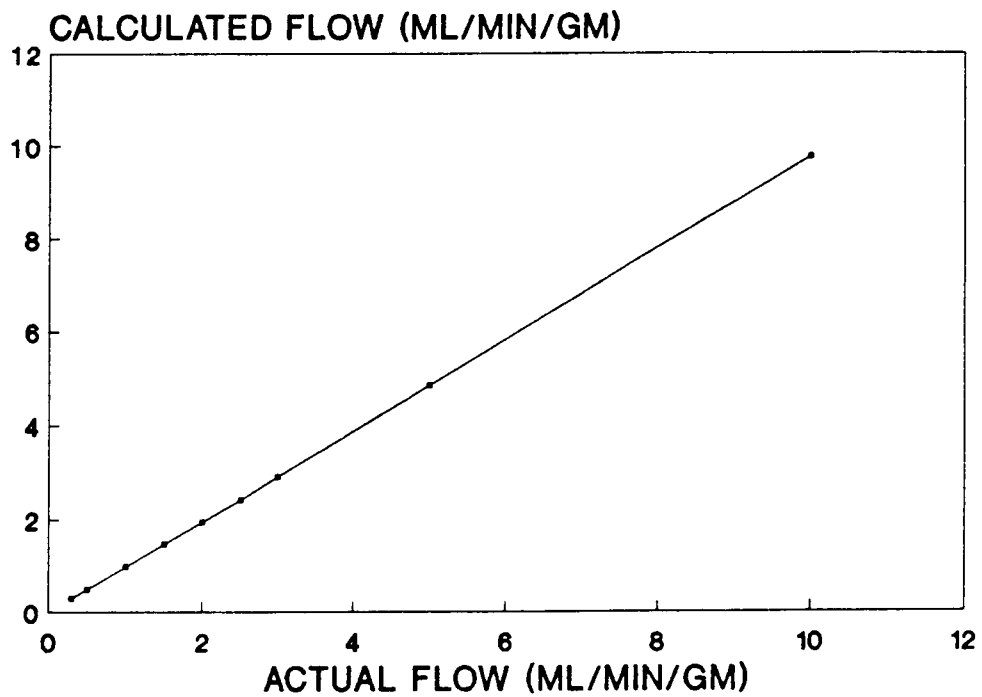


Figure 3.2. Comparison of the Calculated Blood Flow with the Actual Value Used to Generate Synthetic Data

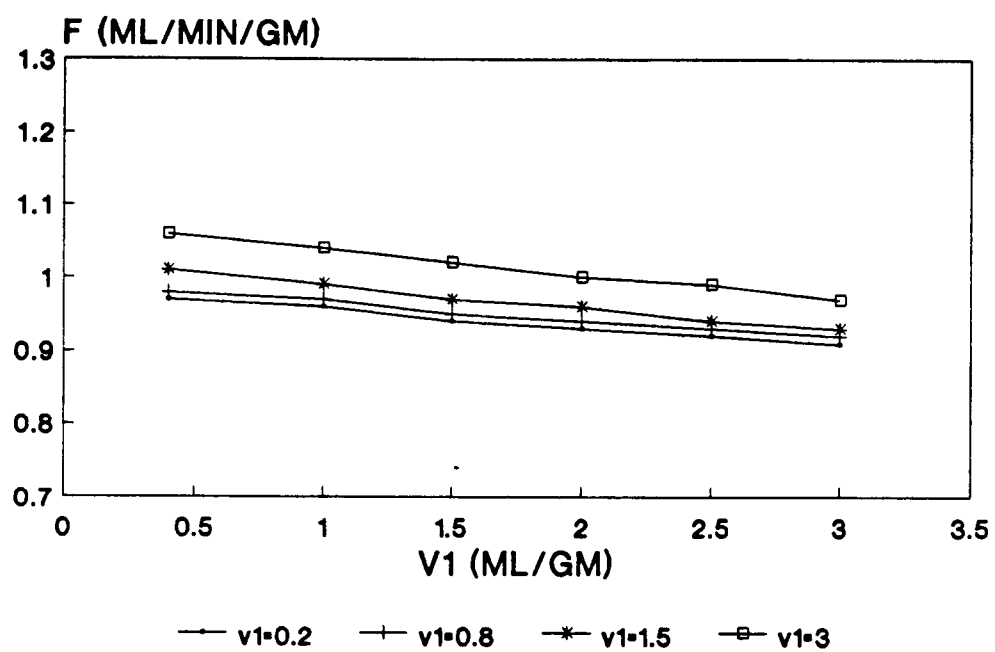


Figure 3.3. Model Response to the Variation of V_1

illustrates that estimated model values of F are insensitive to variations in the volume of distribution, V_1 . Therefore, RMBF error in patient studies due to inaccurate assumption of V_1 are expected to be minimal.

3.3.3 Model Response to Tracer Flux Z

The model response to the variation of Z ($Z=k_2/V_2$) is shown in Figure 3.4. The slope of the line obtained by linear regression is only 0.08 which indicate the calculated F is insensitive to Z . Also, as expected, the calculated values of F varied by only 6% when Z was between 0 and 1.0 min^{-1} . This indicates that the NH_3 release or metabolism from the trapped space is small during the first 90 seconds [4]. This is confirmed by the observation that the estimated F -value changes by only 1.6% when Z varies between 0 and 0.2 min^{-1} for the dog myocardium example [17].

3.3.4 Model Response to Noise

The scan obtained from a PET scan is usually noisy. This may be due to scanner detector noise or noise generated during image reconstruction and processing. The model sensitivity to noise was tested by applying the model to simulated noisy data. These data were obtained by adding Gaussian distributed noise with a standard deviation equal to

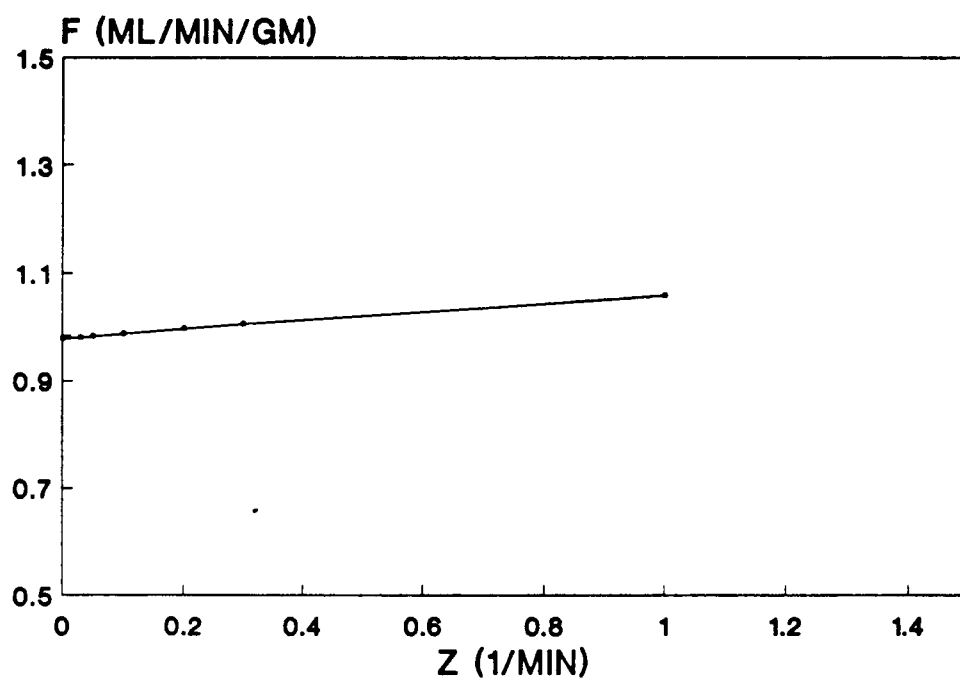
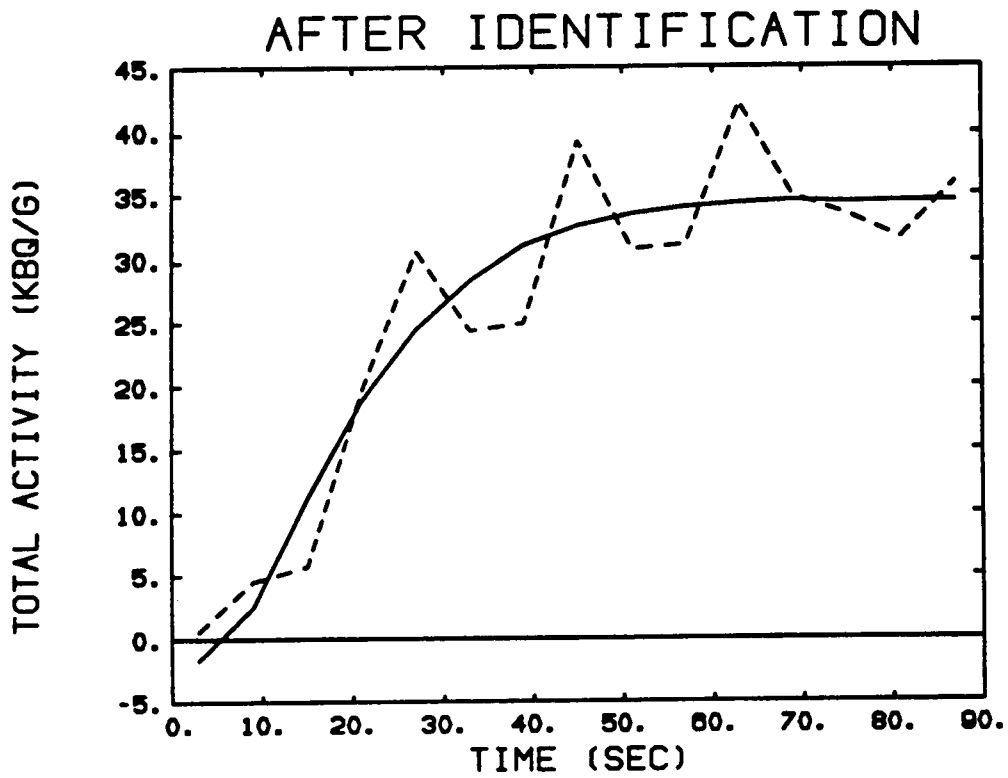


Figure 3.4. Model Response to the Variation of Z

a percent level of the maximum input data value to the ideal synthetic data as shown in Figure 3.5. A scatter plot of the calculated F values with respect to noise level is shown in Figure 3.6. At a noise level of 20%, the calculated F shows less than a 10% coefficient of variation. At a 40% noise level, twice that expected in clinical studies, the calculated F has a 16% coefficient of variation.

3.3.5 Model Response to Integration Interval

It has been stated in the previous section that PET image data are given by activity per unit time averaged over the scan duration. The scan interval corresponds to the integration interval in equation 3.13. Due to noise limitations in patient studies, it appears that PET can only give activity data with a minimum integration interval of 6-10 seconds. The model response to the integration interval was tested with synthetic data based on a discretized rather than integral input function. As shown in Figure 3.7, an underestimation of F is found by increasing the integration interval of synthetic data. With a level of integration interval of 10 seconds, the model response of F value is 0.95 (ml/min/gm) whereas the true value of F is 1.0 (ml/min/gm). The model underestimates the true value of F by 5%. It is also indicated by the curve that smaller integration intervals reduce this error for ideal data. The amount of noise in each



Dashed Line: Synthetic Noise Data

Solid Line: Fitting of the Model to the
Test Data

Figure 3.5. Synthetic Noise Data

Calculated Flow vs. Noise Level

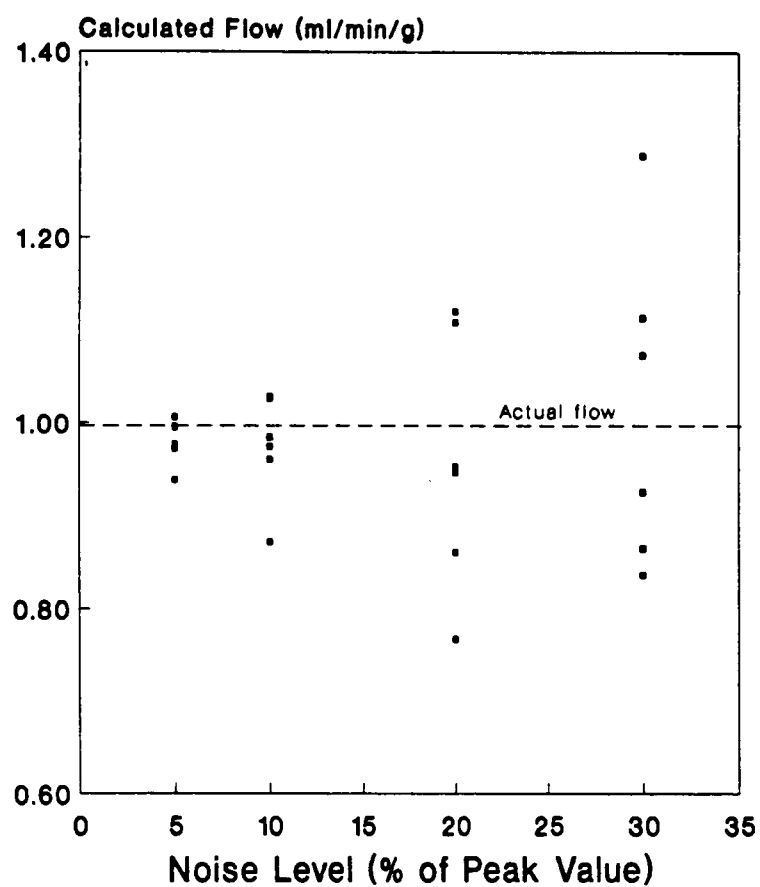


Figure 3.6. Model Response to Noise

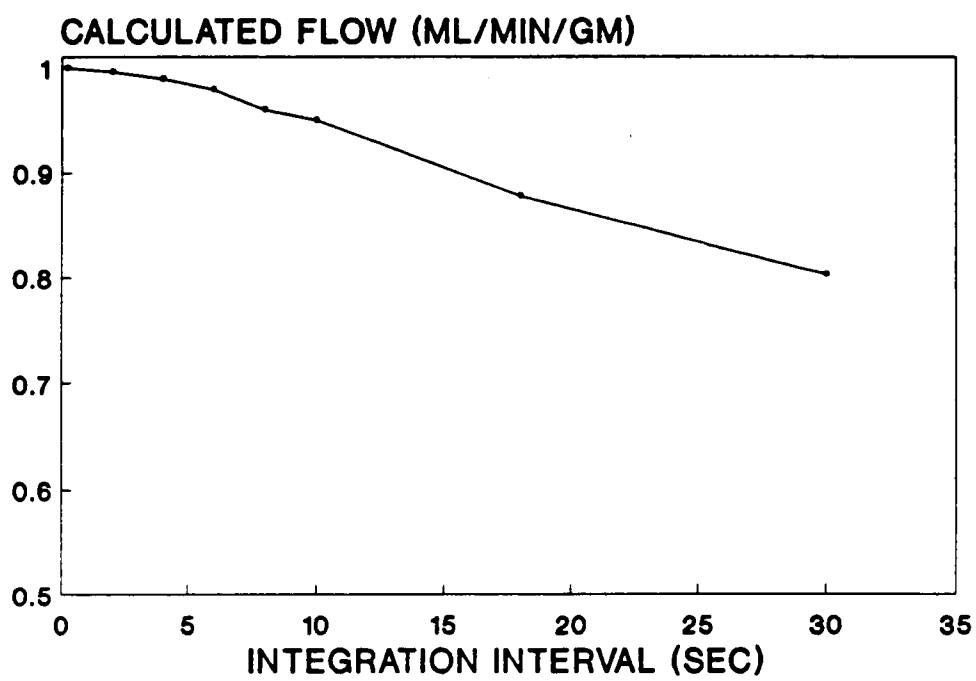


Figure 3.7. Model Response to Integration Interval

image is decreased by using long frame integration intervals in the dynamic scan, but the accuracy of the calculated F is degraded because tissue curve dynamics is lost. Note that with a 6 second interval, the calculated F is 0.985 (ml/min/gm) corresponding to the slope described in Figure 3.2.

CHAPTER 4

DETECTOR SYSTEM

4.1 Introduction

The purpose of developing a blood probe scintillation detector system is to get the activity of the blood as a function of time. This activity is the input function of the compartment models used to quantify physiological parameters with PET. In the study of the heart, this input function can be obtained from the PET images by selecting a region of interest in the blood pool. Compartment models can be used to quantify the function of other organs with PET, other organs do not contain large blood pool images. These images can't be used to determine the arterial input activity. Therefore, a blood probe is also needed to simultaneously ascertain this data from peripheral arteries.

A blood probe detector system has been designed to fulfill this requirement [18]. Figure 4.1 shows a block diagram of this system. Arterial tubing connects the radial artery of the patient to a plastic scintillation probe which is contained inside a photomultiplier (PM) tube. A pump is placed between the artery and the detector to keep the blood flowing at a constant rate.

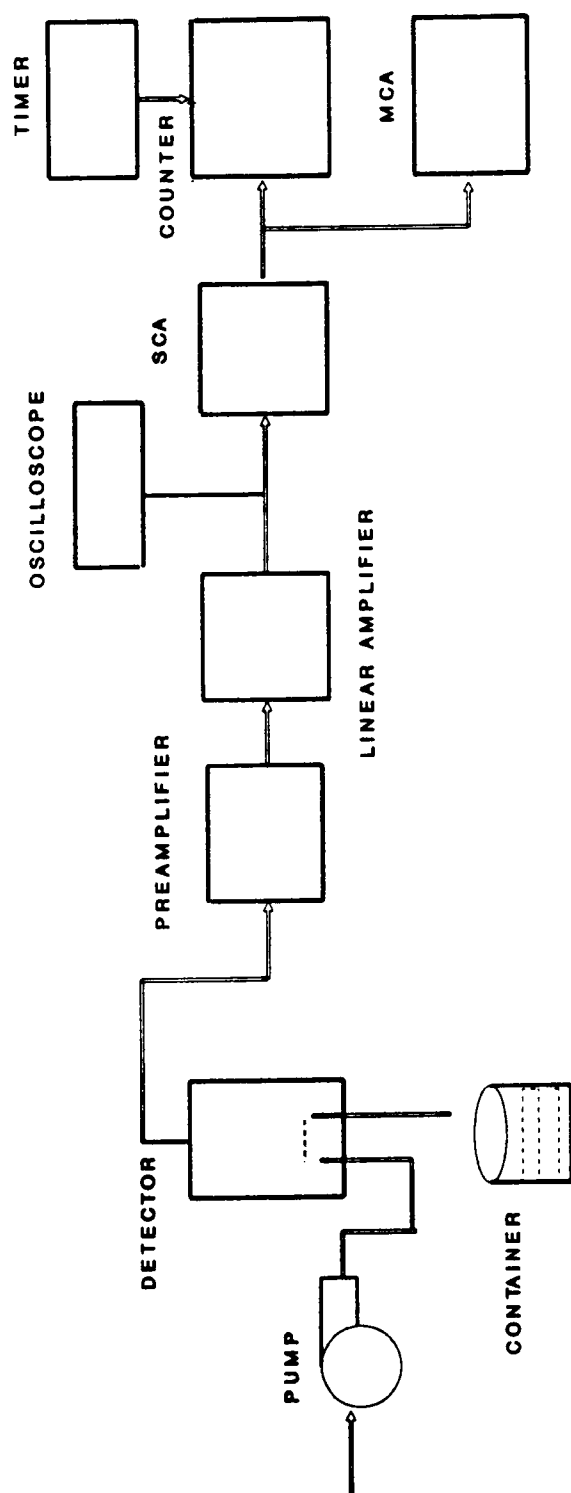


Figure 4.1. Block Diagram of Detector System

The activity in the blood can be determined by injecting a positron emitter into a patient and then withdrawing the blood from the patient's artery into the scintillation probe. Light produced by positrons that deposit their energy in the scintillator is converted into a serial pulse output by the photomultiplier tube. The pulse rate is proportional to the positron activity in the blood. Individual pulses are amplified by a preamplifier and a linear amplifier and then analyzed in a single channel analyzer (SCA). Finally, the instantaneous count rate with respect to time is recorded on a multi-channel analyzer.

4.2 Detector System Set Up

4.2.1 Plastic Scintillation Detector and Photomultiplier Tube

A housing is designed to couple a PM tube and a plastic scintillation probe. It holds the two parts tightly together, thus preventing light from entering. This system is shown in Figure 4.2.

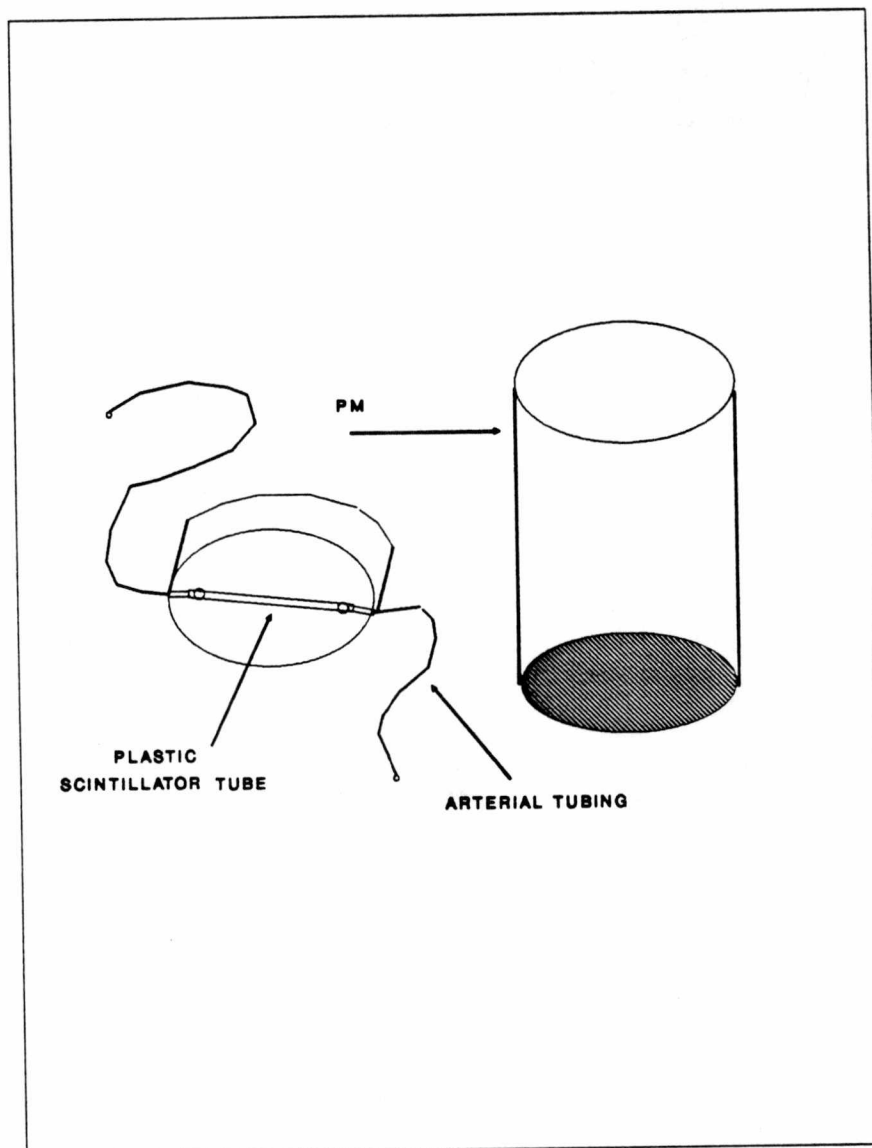


Figure 4.2. Plastic Scintillator Probe

A 2 cm segment of BC-400 plastic scintillation tubing with 0.7 mm inside diameter and 1.5 mm outside diameter is used as the scintillator. It is rolled when cutting from a long segment to avoid splintering. The tubing used to connect this plastic scintillation probe has an inside diameter slightly smaller than the outside diameter of the probe and an outside diameter slightly larger than the inside diameter of arterial tubing. In this way, the plastic scintillator and arterial tubing are well adapted to each other (The tubing used for this purpose is connected to the arterial butterfly needle).

A standard photomultiplier (PM) tube is coupled with the probe. A 1000 volt power supply cable is connected to the PM tube dynode to provide the working environment of PM tube.

4.2.2 Preamplifier and Linear Amplifier

A TC145 scintillation preamplifier from TENNELEC is used. It is a unity-gain preamplifier that can either be operated from the anode of the PM tube or from one of its dynodes. There are switch-selectable input capacities which can provide signal attenuators and serve as an impedance matchers between the PM tube and linear amplifier. This switch is set to 200 pf. The cable linking the PM tube to preamplifier is about 60 cm which is short enough to prevent external noise pick up.

TC 202BLR is a general purpose linear amplifier used in the system. It provides pulse shaping and amplitude gain and is connected to the preamplifier. The amplification factor or gain can be adjusted over a wide range through the combination of coarse and fine controls. The gain for the experiment was set to 108. The gain must be set high enough to assure suitable dynamic range for the isotope to be measured. It must be set low enough to assure that the amplifier does not saturate by high energy positrons.

4.2.3 Single-Channel Analyzer

The SCA produces an output pulse only if the input pulse amplitude lies within a certain range. This range can be defined by setting the lower-level discriminator labeled E and the window width labeled ΔE . A TC 441 model is used in the system. The lower level discriminator is set to eliminate instrumentation noise.

4.2.4 Timer and Counter

A TC 533 model counter is used to record the pulse from the SCA over a fixed period of time. It is a seven-decade counter and it is connected to SCA through the positive input.

A TC 541 model timer is connected to the gate in the counter. The function of this timer is to start and stop the accumulation period of pulse for the counter.

4.3 Detector Calibration

After the detector system has been set up, it needs to be calibrated to determine the detector efficiency. The true activity in the blood can then be calculated according to the detector efficiency. There are normally four isotopes (N-13, O-15, F-18, C-11) used in PET. In order to properly define the detector system, calibrations should be performed with isotopes within blood and water. Therefore, 8 calibrations were made. The calibration procedure used for C-11 in water is described as follows.

- 1) Set up the detector system as described in the previous section.
- 2) Connect an oscilloscope into the output of the linear amplifier (The function of the oscilloscope is to monitor the linear amplifier output to set the lower and upper levels of the SCA and to set the linear amplifier gain).
- 3) Obtain 440 μCi C-11 (half life = 20.3 min) and mix it with 500 ml water in a container.
- 4) Set the timer to 10 second.
- 5) Turn the power supply on.

- 6) Take a background count and record it.
- 7) Use a syringe to take 20 ml water from the container and then connect the syringe to the tubing leading to the scintillation probe. (Carefully push the water into the probe until water is observed coming out of the other end of the tubing).
- 8) Adjust the linear amplifier gain based on the pulse amplitude.
- 9) Set the discriminator to eliminate dynamic noise and to output pulses from the positrons.
- 10) Record the time and start the counter. Record the counts and convert to counts per second (cps) corrected for background activity.
- 11) Wait 10 minutes (half time period of isotope half life) and count again.
- 12) Repeat the procedure 10) and 11) until at least 5 half lives of the isotope have elapsed.
- 13) Calculate the true activity concentration at each time point. The true activity concentration can be calculated as

$$A = A_0 * e^{-bt} \quad 4.1$$

where A = activity concentration at time t.

A_0 = initial activity concentration measured by a well counter.

b = decay constant ($b = 0.693/\text{half-life}$).

t = time elapsed when each counting starts.

- 14) Enter the observed count rate in cps of each point and the true activity concentration in $\mu\text{Ci/ml}$ to a spreadsheet. Figure 4.3 shows the observed activity vs. the true activity concentration.
- 15) Apply a linear regression to the data and obtain the efficiency of the detector (0.46 for C-11).

Repeat the procedure for other isotopes. Table 4 shows the detector efficiency in both water and blood.

The relationship between β^+ energy and efficiency is shown in Figure 4.4 and 4.5. It indicates that as the β^+ energy increases the detector efficiency also increases. According to these calibration results, it can be concluded that the detector has acceptable efficiency for clinical use. Concentration as low as $0.25 \mu\text{Ci/ml}$ are needed for clinical use. This will result in 750 counts in 10 seconds which will provide a suitable statistical accuracy.

4.4 Sensitivity Analysis and Dead Time Evaluation

4.4.1 Introduction

Dead time is defined as the minimum time separation between two events for which a detector system can respond.

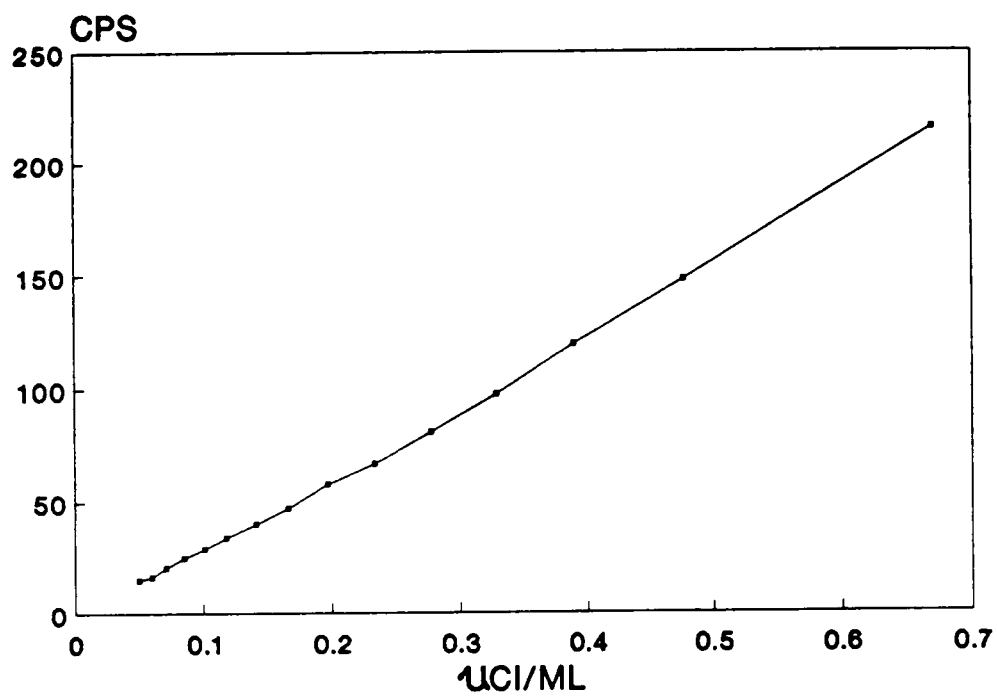


Figure 4.3. Calibration Curve of C-11 in Water

Table 4. Detector Calibration Result

Isotope	Efficiency	β^+ Energy (Mev)
F-18 blood	0.46	0.635
F-18 water	0.34	0.635
C-11 blood	0.56	0.96
C-11 water	0.45	0.96
N-13 blood	0.66	1.198
N-13 water	0.63	1.193
O-15 blood	0.80	1.73
O-15 water	0.77	1.73

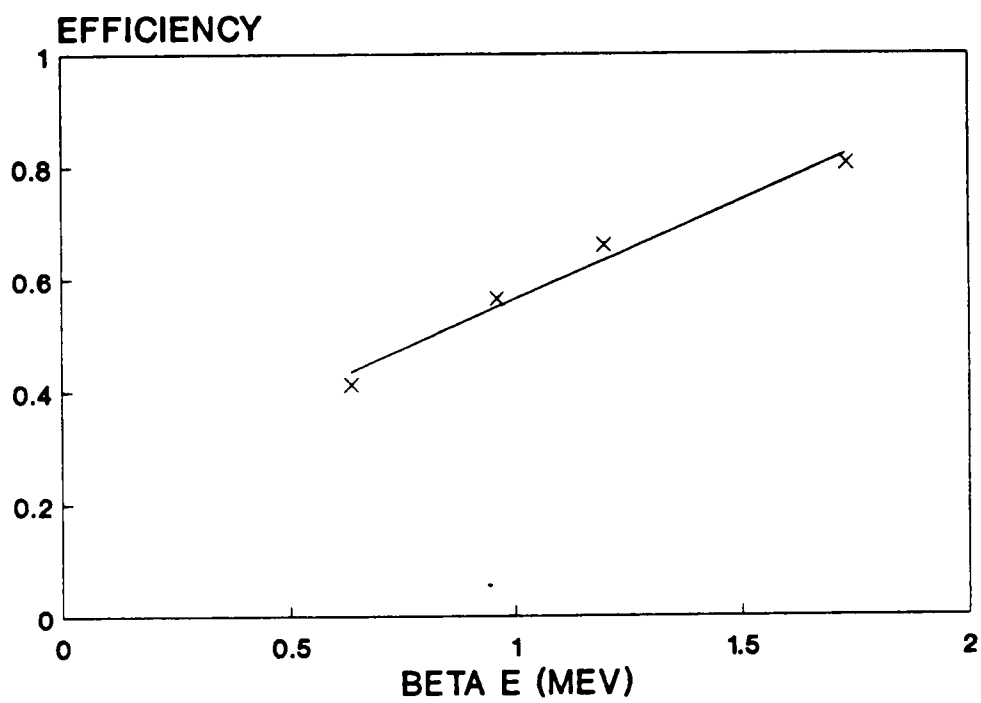


Figure 4.4. Curve of Detector Efficiency vs.
Positron Energy in Blood

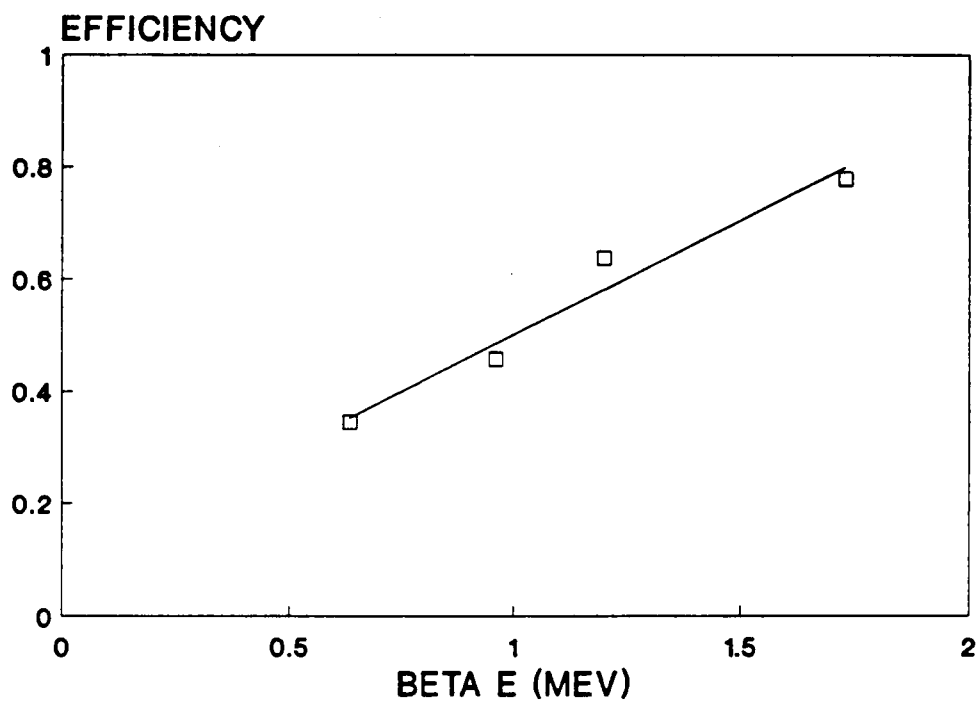


Figure 4.5. Curve of Detector Efficiency vs.
Positron Energy in Water

There are two models of the dead time behavior of the counting system. They are the paralyzable and the nonparalyzable response models. The nonparalyzable model assumes that a fixed time τ follows each event during which pulses are lost and do not affect the detector. The paralyzable model assumes that although they are not recorded as counts, the events that occur during the dead period affect the detector and extend the dead period. So, in the paralyzable model, the dead period is not always of fixed length.

The relationship between the true event and the measured counts incorporating the dead time τ has been derived as [18]:

$$n=m/(1-m\tau), \quad 4.2$$

for the nonparalyzable model, and

$$m=n*e^{-m\tau}, \quad 4.3$$

for the paralyzable model, where n =true count rate(cps), m =measured count rate(cps), τ =dead time(sec).

4.4.2 Method of Dead Time Measurement

Methods of dead time measurement are based on the fact that the observed count rate varies nonlinearly with the true count rate. By assuming that one of the specific models is applicable and measuring the observed count rate for several different true count rates, the dead time can be calculated [19].

There are two methods which are commonly used for measuring dead time. They are the two-source methods and the decaying source method. The two-source method is more applicable to the measurement of dead time for relatively long half-life sources. Whereas, the decaying source method is used for short-lived radioisotope sources. Since PET uses short-lived isotopes, the decaying source method is used in evaluating the dead time of this detector system. This technique is based on the empirically determined behavior of the true count rate:

$$n=n_0*e^{-bt}+n_{bk} \quad 4.4$$

where n_0 is the true count rate at the beginning of measurement, n_{bk} is the background count rate and b is the decay constant of the specific isotope used in the measurement. Assuming negligible background, equation 4.4 can be written as:

$$n=n_0*e^{-bt}. \quad 4.5$$

By inserting equation 4.5 into equation 4.2 and carrying out appropriate algebra, the following relationship for the nonparalyzable model can be obtained:

$$me^{bt}=-n_0\tau m+n_0. \quad 4.6$$

If we define $y=me^{bt}$ and $x=m$, a straight line may be obtained with a slope equal to $-n_0\tau$ and y intercept n_0 . Therefore, τ can be calculated as:

$$\tau=\text{slope}/n_0. \quad 4.7$$

The result may not be a straight line for a real counting

system. However, by fitting the best straight line to the measurement data, the slope and intercept can be obtained.

The method described above can be applied to the paralyzable model. Equation 4.8 can be obtained by inserting equation 4.5 into equation 4.3 as:

$$bt + \ln(m) = -n_0 \tau e^{-bt} + \ln(n_0). \quad 4.8$$

If we identify $y = bt + \ln(m)$ and $x = e^{-bt}$, a line with slope of $-n_0 \tau$ and y intercept of $\ln(n_0)$ can be obtained. Next, τ can be calculated as:

$$\tau = \text{slope} / n_0 \quad 4.9$$

where $n_0 = e^{\ln(n_0)}$.

4.4.3 Measurement of Dead Time

The dead time evaluation of a detector system can be performed only if a high count rate is achieved. The dead time for this detector system is evaluated using a 2.5 mCi/ml concentration of N-13 in water and repeating the calibration procedure outlined in section 3. These result are shown in Table 5.

The corresponding values of y and x, defined previously, can be generated for each dead time model. Figures 4.6 and 4.7 show the scatter plots of the measured data for each model. The calculated dead time of 2.53 microsecond and 1.3

Table 5. Test Data for N-13 in Water in Dead Time Evaluation

Time (min)	Actual Count Rate (cps)	Measured Count Rate (cps)
1	1504877	286368
10	805038	245999
18	461556	186015
33	162746	86710
45	70674	41339
57	30691	18336
71	11598	7310
81	5787	3675
88	3558	2232
95	2187	1408
102	1344	854
110	771	504
123	312	210

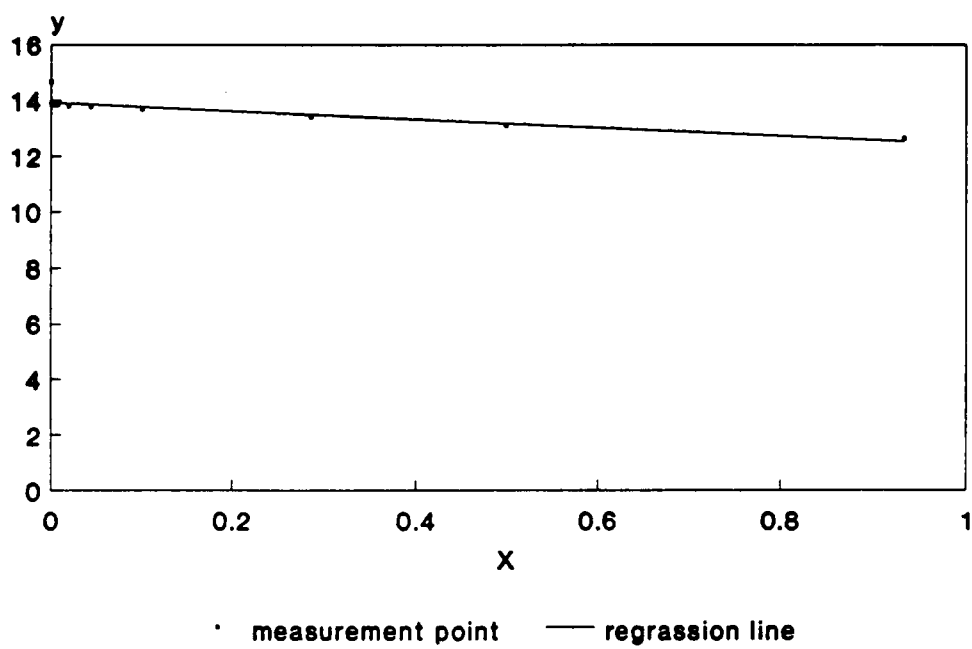


Figure 4.6. Evaluation of Dead Time with
Paralyzable Model

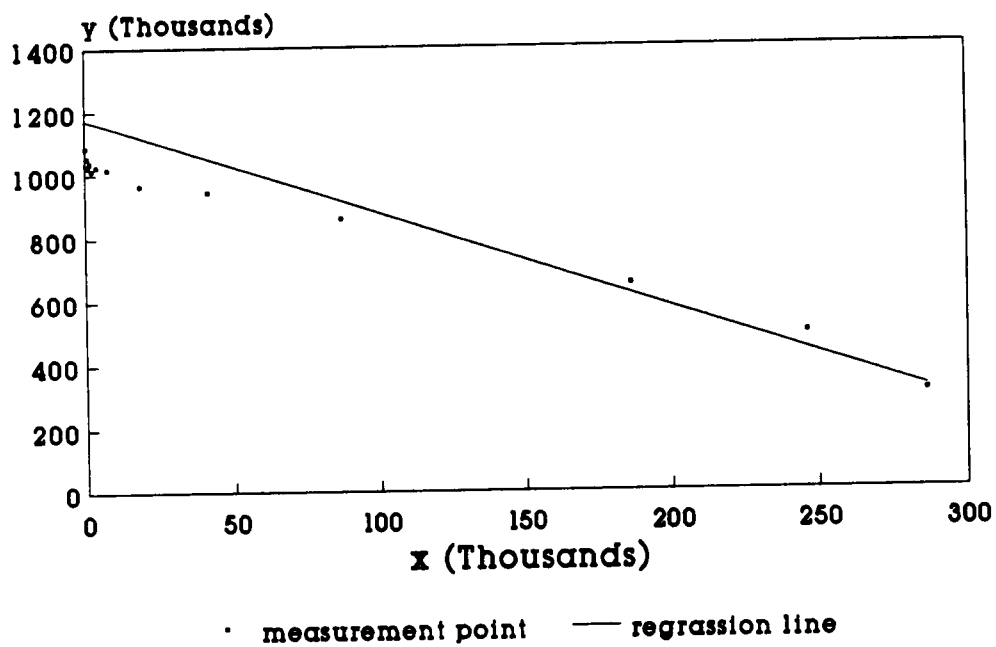


Figure 4.7. Evaluation of Dead Time with
Nonparalyzable Model

microsecond for the nonparalyzable and paralyzable models are obtained, respectively. This result is obtained by applying a linear regression to the measured data and calculating the dead time as previously described. To verify these results, two synthetic true count rates are generated by replacing r by these values in equations 4.2 and 4.3, respectively. Figure 4.8 shows a plot of these synthetic data fit to the true model. Since both fits are not ideal, modification of dead time for each model is needed. Both values of r are adjusted and new synthetic curves are generated for each model. These curves are compared to their respective true models. This procedure is repeated until a "best fit" is obtained for each model. The "best fit" values of dead time for the nonparalyzable and paralyzable models are 2.83 microsecond and 1.3 microsecond, respectively. Figure 4.9 shows that this synthetic data is fit almost perfectly by the nonparalyzable model. Therefore, this detector system should be evaluated using a nonparalyzable model.

4.5 Data Acquisition

4.5.1 Review of Principle

The multichannel analyzer can be used in a multiscaling mode to record a time trace of the activity. Each memory location of the analyzer is then treated as an independent

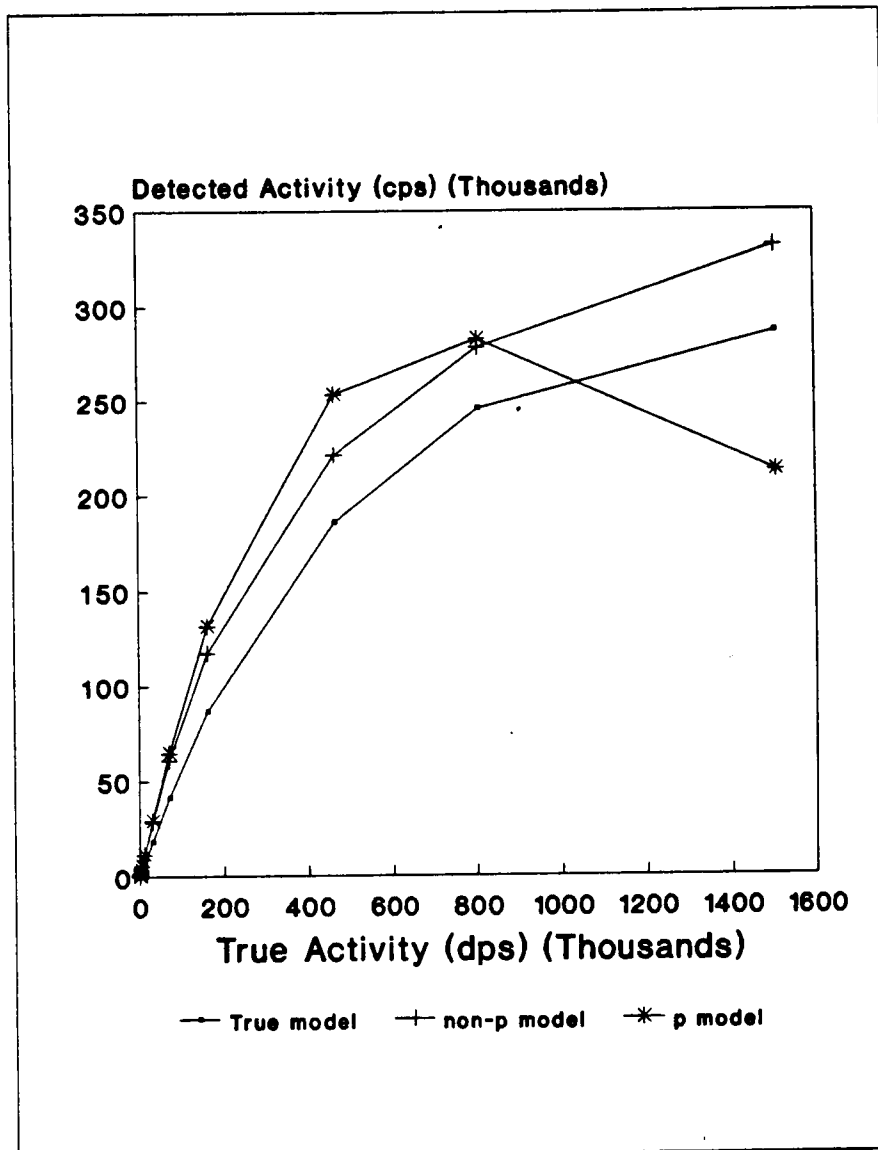


Figure 4.8. Synthetic Data Fitting to the Test Data

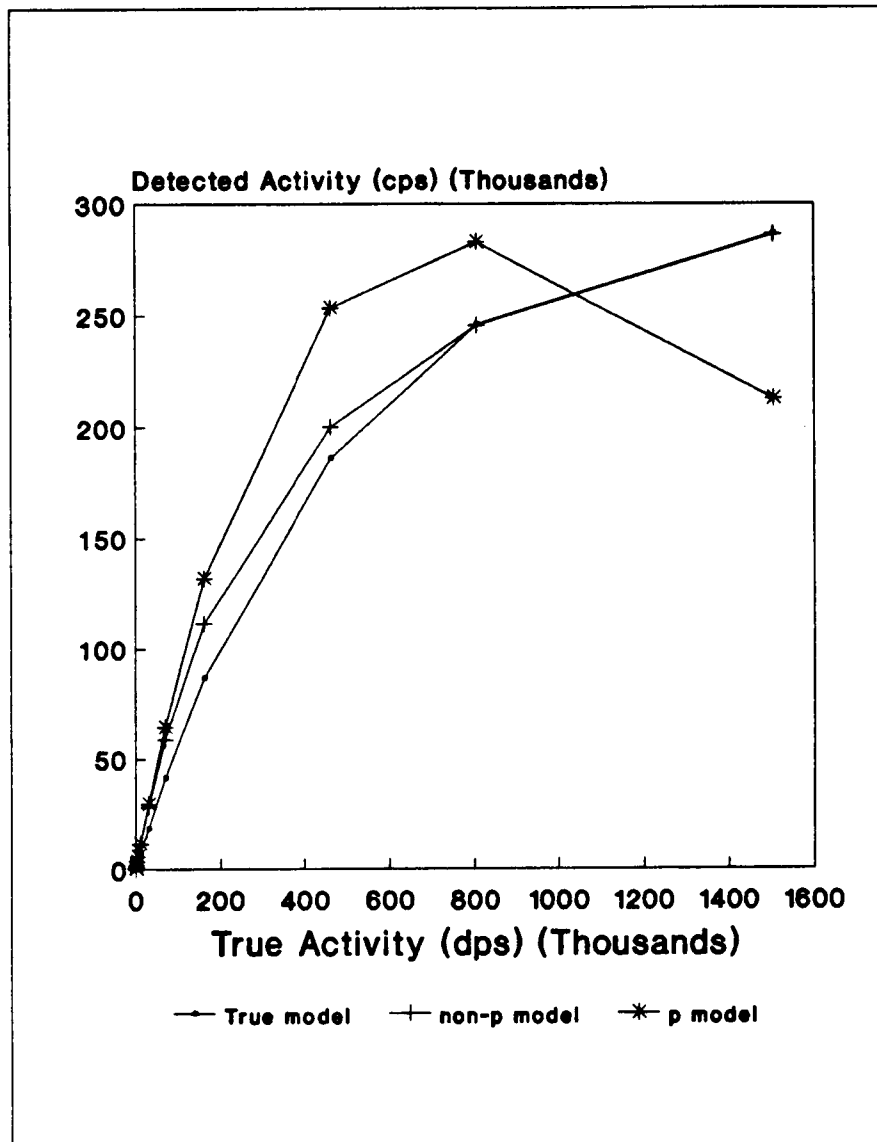


Figure 4.9. Best Fit of Synthetic Data to the Test Data

counter. All pulses that enter the MCA are counted. Pulses that arrive earlier are stored in the memory location for the first channel. When a period of time, the dwell time, has elapsed, the analyzer skips to the second channel and records the pulses at that memory location. Each channel is sequentially allocated one dwell time for accumulating counts. The data collected represents a relationship expressed as the number of counts per unit time.

4.5.2 Data Acquisition

As shown in Figure 4.2, the multichannel analyzer is connected with the SCA output of the detector system. The Nucleus Personal Computer Analyzer (PCA) functions as an MCA in this system. It includes a PCA card which is physically installed in an IBM-PC (or compatible), along with an operational software. This PCA allows the personal computer to function as a multichannel analyzer. During data acquisition, the PCA is used in the multiscaling mode. The dwell time is set to 1 second and the pump rate is set to 1 (ml/min). PET data acquisition, withdrawal of arterial blood through a pump, and initial intravenous injection of the tracer, are initiated simultaneously. Figure 4.10 shows the instantaneous count rate with respect to time (input function) from an experiment on a dog. The data acquisition time in this experiment is 30 minutes. However, as is described in

Automated Blood Probe Activity

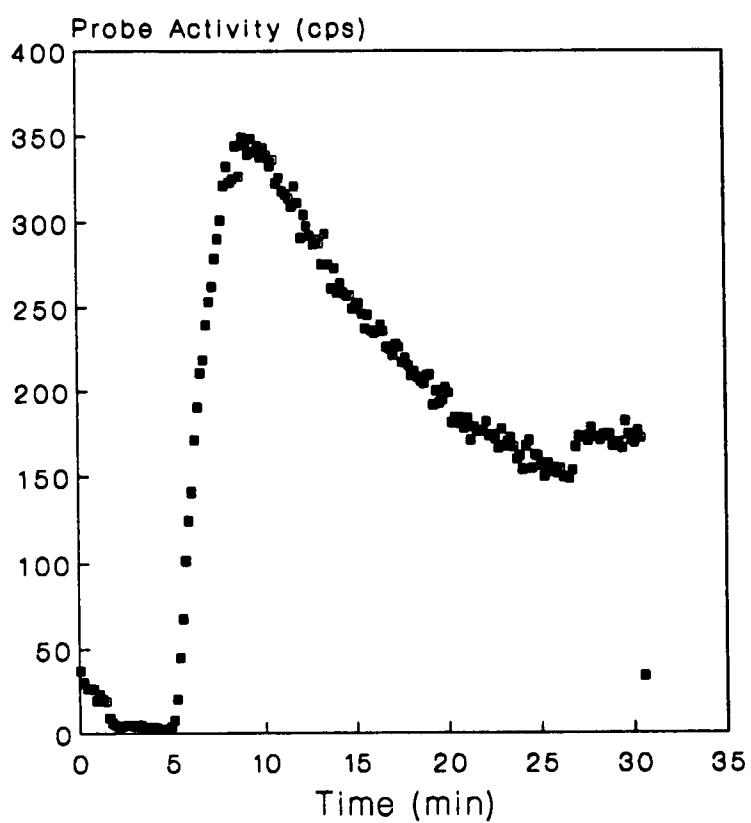


Figure 4.10. Blood Probe Activity vs. Time

the following chapter, the data collected directly from the MCA should be corrected for dispersion and delay due to the arterial tubing.

CHAPTER 5

APPLICATION OF METHODOLOGY

5.1 Clinical Application

5.1.1 Introduction

Coronary artery disease is a common illness affecting people of all ages. Generally, this is caused by blood occlusion of the coronary artery as shown in Figure 5.1. This occlusion causes a blood supply shortage in the myocardium tissue in the descending coronary artery area. Figure 5.2 shows its effects on this tissue. These effects are: myocardial ischemia (minor tissue injury), myocardial injury, and myocardial infarction (tissue death). Myocardial ischemia and injury can be treated by either bypass surgery of the coronary artery or proper medicine. As of now, there is no treatment for myocardial infarction.

Although PET provides a tool to show a cross-sectional image of the heart, it can not identify these effects directly from the image. This is due to the fact that patients who are at risk of infarction may have either resting myocardial ischemia or exercise-induced myocardial ischemia and the precision of the PET image is limited when reconstructing this

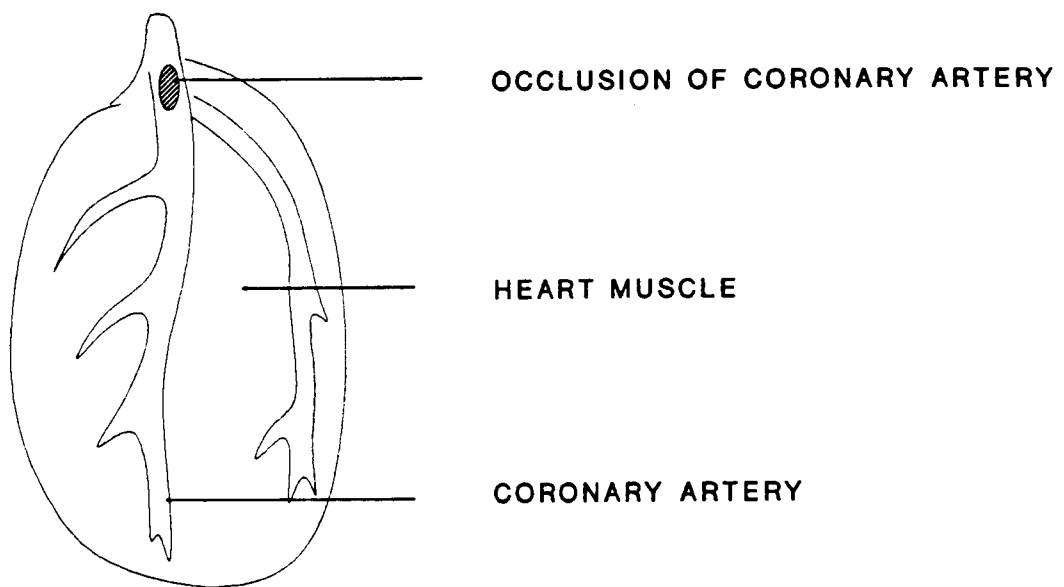


Figure 5.1. Heart Structure

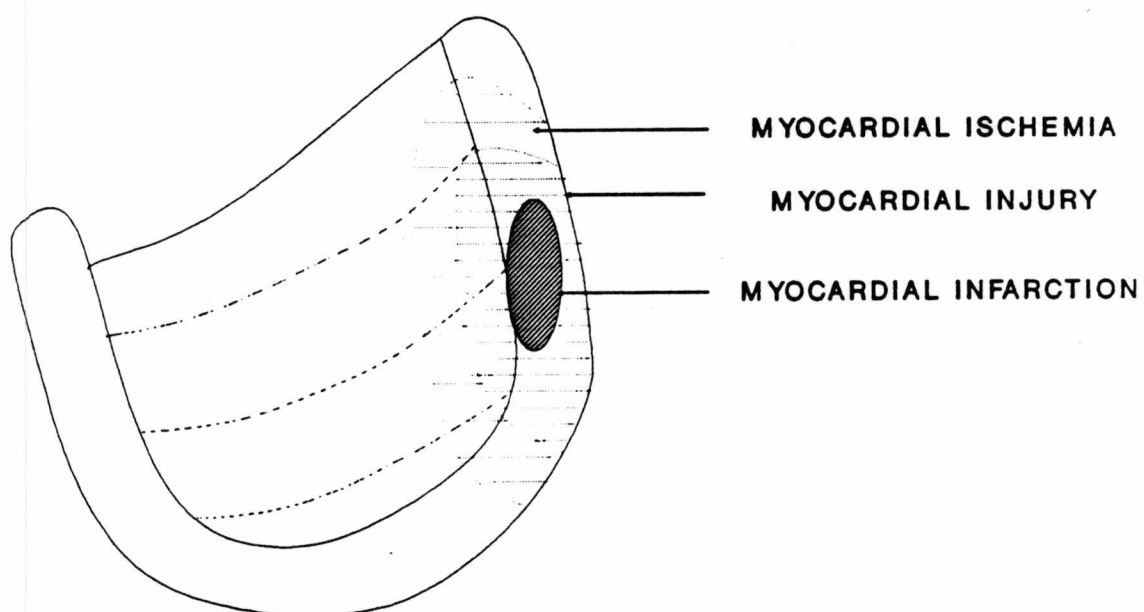


Figure 5.2. Effects of Coronary Artery Disease

phenomenon. The quantitative PET method, myocardial blood flow quantification by two-compartment model, is therefore used as a tool to ascertain these effects.

5.1.2 Model Application

The general approach of this quantitative method is to calculate the regional myocardial blood flow in different regions of interest in the myocardium. Normally a dynamic PET image of the myocardium can be divided into 8 sectors or regions of interest as shown in Figure 5.3. The RMBF in each region of interest is then calculated using the method described in the previous chapters. There are two possible methods for evaluating the myocardial ischemia effect: cardiac reserve and simple threshold method [4].

Cardiac reserve is defined as the ratio of the stress RMBF to the rest RMBF. Dipyridamole is administered to patients to obtain the stress RMBF. Analysis of this ratio provides the information needed to evaluate the myocardial ischemia. If the value of cardiac reserve for a specific region of interest is lower than for others, there is a possibility that this myocardial region has stress-induced myocardial ischemia.

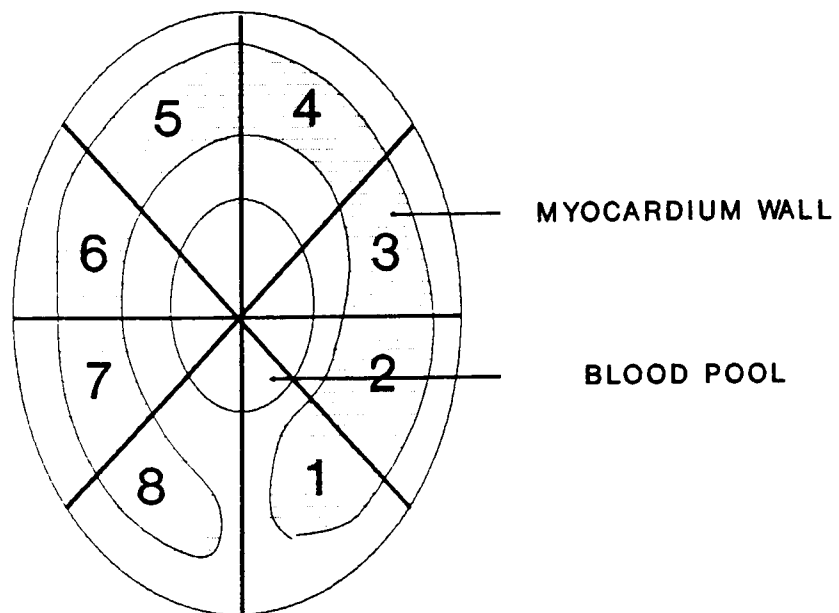


Figure 5.3. Myocardium Structure

The simple threshold method uses the RMBF value to define a threshold. Below this threshold, myocardial ischemia is assumed. It is not easy to determine this threshold value because of physiological differences in people.

More research work is needed in validating these methods. However, the regional myocardial blood flow calculation developed in this thesis provides the basic tools for this future research.

5.2 Result Comparison with "First-Pass" Technique

5.2.1 "First-pass" Flow Model

It was hypothesized by Saperstein [20] that during the first or initial pass of the radioactive tracer through an organ there exists a time when all the tracer is within the region of interest and no tracer reaches the venous drainage during this time. The "first-pass" flow model is developed based on the basic law of conservation of mass, that the amount of radioactivity detected in a system is equal to the amount that is delivered to that system minus the amount that is left. The physical model that describes the dynamics of the tracer in an organ is shown in Figure 5.4, in which the detected activity $Q(t)$ can be describe by the following equation :

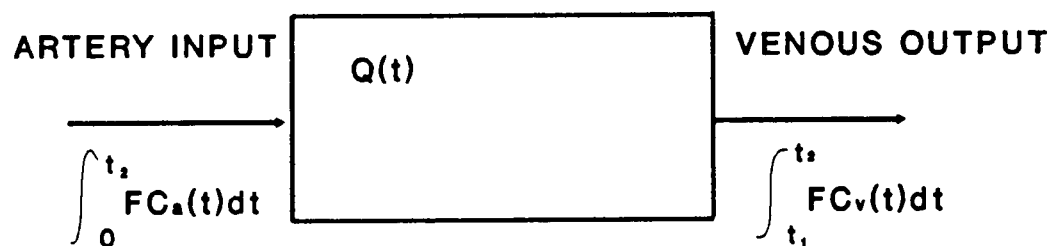


Figure 5.4. Physical Model of Tracer Dynamics in Tissue

$$Q(t) = \int_0^{t_2} FC_a(t) dt - \int_{t_1}^{t_2} FC_v(t) dt \quad 5.1$$

where $C_a(t)$ is the arterial concentration, $C_v(t)$ is the venous concentration, F is the flow rate to that region, and t_1 is the time delay of radiotracer through that organ. If the time of data acquisition, t_2 , is smaller than the organ delayed time t_1 , the venous concentration $C_v(t)$ is zero. Therefore, the detected activity is equal to the total amount delivered to the organ up to that time (assuming the observed data has been corrected for the detector efficiency). It can be described as:

$$Q(t) = \int_0^{t_2} FC_a(t) dt. \quad 5.2$$

F can be obtained from:

$$F = \frac{Q(t)}{\int_0^t C_a(t) dt} \quad 5.3$$

The derivation of this equation also assumes that all the tracer delivered to the system is extracted from the blood; in other words the extraction fraction is unity. Thus, no tracer outflow occurs from that organ and the condition $C_v(t)=0$ is also satisfied. This equation has been widely used in calculating the RMBF [4].

5.2.2 Results Comparison and Analysis

Figure 5.5 shows RMBF results calculated by the two compartment model method and the "first-pass" method, respectively compared with the microsphere method. The RMBF is calculated using 8 sectors of the myocardium in 12 different dogs studied at the UCLA medical center. This gives a total of 96 test points. Comparison of these results with the ones obtained from the microsphere technique (the most accurate method) indicates that the two compartment model method gives more accurate results than the "first-pass" method as its scatter plot is closer to the identity line. It also indicates that the "first-pass" model underestimates the RMBF at high flow rates. Schelbert et al. have shown the tracer extraction to be inversely related to the myocardial blood flow. Therefore, incorrectly assuming unity extraction fraction ("first-pass" model) at high flow rates results in this underestimation.

Attempts have been made to compensate for this underestimation [21] by correcting the flow value by incorporating the extraction fraction into the "first-pass" equation as

$$F = \frac{Q(t)}{E \int_0^t C_a(t) dt} \quad 5.4$$

Kinetic Model rMBF Estimates

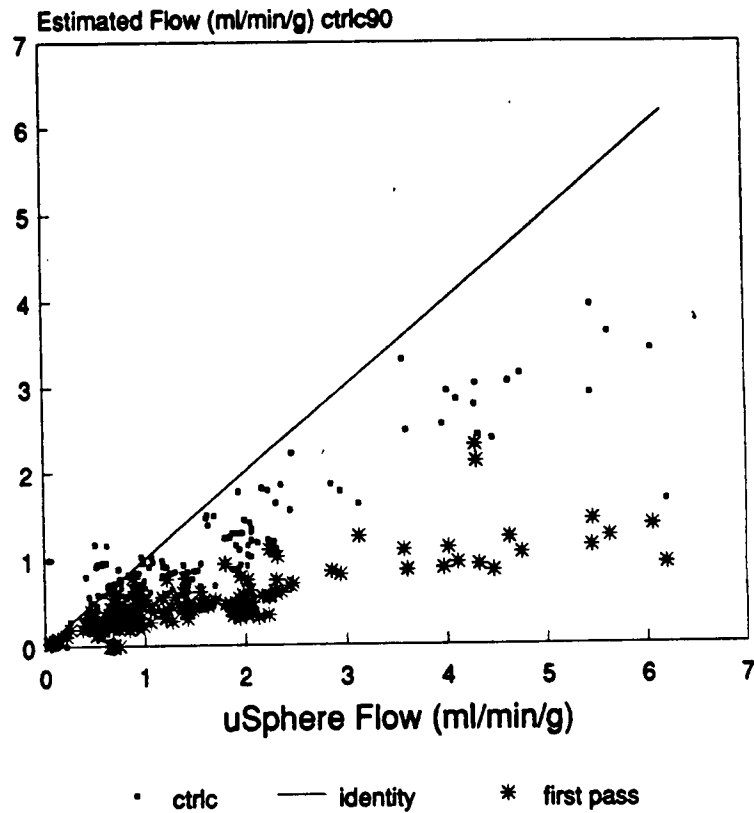


Figure 5.5. Comparison of Results from the Two Compartment Model and the "First-Pass" Method

where E is the extraction fraction of tracer, and $Q(t)$ and $C_a(t)$ have been previously defined. However, this model still cannot give an accurate result because the spillover factor for PET image data cannot be defined by this model. As discussed in the previous chapter, this is required in order to get the true tissue activity $Q(t) = Q_1(t) + Q_2(t) + SPF * C_a(t)$.

Mullani and Gould [3] developed a peak-counts flow model based on the "first-pass" technique. This model does not require the estimation of extraction fraction but requires that the time for making the blood flow measurement be short enough such that none of the radiotracer has left the ROI during the period of data acquisition. However, a potential problem using this model is that for many tracers the minimum organ delay time is too short to accurately measure the myocardial time activity curve due to PET count rate limitations.

CHAPTER 6

SUMMARY

6.1 Conclusions

It has been stated that the purpose of this research is to use the two compartment model method to calculate the regional myocardial blood flow. This includes the analysis of the model representing the tracer dynamics in tissue, the development of the software package that is used to perform the model identification, and the development of the detector system used to determine the artery input function. Several issues related to both the model and the detector system have been identified and examined: methodology, model characterization, detector system, and applications.

The methodology indicates that a two compartment mathematical model is appropriate for representing tracer dynamics in the tissue. Overcorrection of the myocardial tissue activity due to the cross-contamination from the blood pool to the myocardium is compensated by mathematically incorporating the spillover factor into the two compartment model. It also defines a procedure to reduce the number of parameters in the model by combining the extraction fraction model to the definition of extraction fraction.

It is also shown that the maximum likelihood algorithm can be used for parameter identification of the model. A computer software code utilizing this algorithm for parameter identification has been implemented in a Sun 3/280 system.

Model characterization indicates that the model provides accurate linear response to the blood flow over a wide range. It also shows that the model is insensitive to the variations of tracer distribution volume and the reverse rate constant. Finally, model characterization of noise sensitivity and integration integral shows that these conflicting effects need to be optimized in practical applications of this model.

The evaluation of the detector system indicates that this plastic scintillation detector system has an acceptable efficiency for data acquisition. A nonparalyzable model is used to identify the detector dead time. At high count rates, the dead time loss is corrected by using the defined dead time.

Finally, the comparison of dog study results obtained by the two-compartment model method and the "first-pass" technique indicates that the two compartment model method provides more accurate results. Therefore, it is more suitable for future clinical use.

6.2 Future Work

There are several areas where additional work should be performed. Some recommendations for future work are presented below.

1. A backpropagation neural network method can be applied in calculating the RMBF. A recent application of this method has been implemented in a VAX workstation [22] and IBM-PC computer [23]. The RMBF was calculated by the two compartment model for eight sectors using the "Ctrl-C" program and then used to train the neural network for an additional 24 sectors. The comparison of results from "Ctrl-C" and the neural network has demonstrated the feasibility of using a neural network coupled with the two compartment model to estimate the RMBF. Therefore, software performing this neural network method may be written in fortran implemented in Sun 3/280 and incorporated with "Ctrl-C" during future model identification procedures. Due to the fast response of the neural network prediction, the identification time may be greatly shortened. This provides a method for generation of parametric blood flow images [24].

2. The dispersion of the detector system due to the tubing connection between the patient artery and the beta probe should be defined in order to use this detector system

in obtaining the artery input function. The dispersion measurement may be performed using a radioactive whole blood source in place of the artery source to provide a step function of radioactivity in the blood. Therefore, the time activity curve measured by the beta probe is a convolution of the true input function and the dispersion due to the withdrawal apparatus. By providing a step input function, deconvolution can be facilitated. A least-square nonlinear regression may be used to adjust the parameters of the assumed input function to minimize the difference between the function and the measured curve.

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APPENDICES

APPENDIX A
CTRL-C USER MANUAL

1. Introduction to Ctrl-C

Ctrl-C is a conversational computer-aided engineering system that provides an integrated software environment with commands for matrix analysis, digital signal processing, graphics and control system analysis. This manual augments the Ctrl-C documentation and it specifically addresses blood flow problems associated with Positron Emission Tomography (PET) diagnostic measurements. Tools of matrix analysis and maximum likelihood system identification (a mathematical method for identifying parameters of differential equations) are used by the Ctrl-C software package. They may be effectively utilized for analyzing PET data. This manual is designed to be an introductory guide to modeling with Ctrl-C. More information can be found in the Ctrl-C User's Manual and the Sun OS Manuals.

1.1 Getting Started

Ctrl-C is capable of operating on a variety of host computers. In the University of Tennessee Medical Center at Knoxville (UTMCK) it is operated on a Sun 3/280 Computer System with a floating point accelerator. Prompts for the Ctrl-C software and the SUN operating system are as shown below:

[> indicates Ctrl-C prompt.

scanner% indicates SUN host operating system prompt.

1.1.1 Entering Ctrl-C

With the SUN System prompt displayed, the command to enter the Ctrl-C command interpreter is entered as follows:

```
scanner% ctrlc
```

The system will respond with the following:

```
[ > CTRL-C <]
```

```
system control technology
```

```
version 2.2
```

```
Intro, browse, help, and NEWS are available
```

```
[ >
```

1.1.2 Entering Commands

When the Ctrl-C command interpreter is ready (prompt [> displayed), the user may begin to enter commands. It is possible to enter more than one command on a line by separating each command with a comma (,). A semicolon (;) may also be used to separate commands on a line; however, the semicolon will suppress the display of results on the terminal screen. The command line may be extended by entering the notation '...' at the end of the line. The use of comma to separate commands results in the display of the input as well as the output, as shown below.

Example: [> a = 16, b = 2.5, c = a/b

```
A = 16 B = 2.5 C = 6.4
```

```
[ >
```

If a semicolon is used to separate commands, the input data is

suppressed from the display as illustrated by the following example.

Example: [> a =16; b = 2.5; c = a/b

C = 6.4

1.1.3 Comment Lines

Comments may be entered on a command or data line to identify certain inputs. They will not be treated as part of the command if they are preceded with double slashes (//). The syntax is as follows.

Example: [> a = 16; b = 2.5 //Assigned values for A and B

The same effect can be achieved by the use of the '..', command line continuator, which causes the rest of the line to be ignored as shown below:

[> a = 16; b = 2.5 .. Assigned values for A and B.

1.1.4 Getting Help

The help files display approximately one full screen of summary information, including the syntax, for each of the Ctrl-C commands and functions. The syntax for help command is as follows:

[> help {topic}

1.1.5 Creating a Session Diary (hard copy)

There are times when it is extremely helpful to keep a record of inputs and results when working with a long session.

Ctrl-C provides a command diary that will record all terminal activities. The command is as follows:

```
[ > diary
```

A file called Diary.lis will automatically be generated after issuing this command and the diary file will be closed when one enters,

```
[ > diary -off
```

1.1.6 The Exit Command

The exit command causes a normal termination of the current Ctrl-C session, as shown below

```
[ > exit
```

1.1.7 Entering a variable

The name and content of a variable can be defined by the user. It can be a single number, or a matrix (one or several lists of data) and a character string.

Example: [> a = [1 2 3; 4 5 6; 7 8 10]

```
A = 1. 2. 3.
```

```
4. 5. 6.
```

```
7. 8. 10.
```

1.1.8 System-Defined Variables

System-defined variables are reserved by Ctrl-C for special data and are used to tailor the Ctrl-C operating environment. Several of particular interest are:

line	sets line count limit for output since last input
term	defines terminal type
hard	defines graphic hardcopy device

1.1.9 Viewing the Names of the Variables

Typing WHO while in Ctrl-C prompt causes the current variable names assigned by user to be listed.

1.2 Matrix Analysis

Matrices are defined as two-dimensional tables of numbers, where each number is associated with a row and a column position. Matrices with one row and column (1 and 1) are scalors, and 1 by n and m by 1 matrices are row and column vectors.

Example: A = [1 2 3 4 5] row vector

A = [	1	
	2	
	3	column vector
	4	
	5]	

1.2.1 Entering Matrices

When entering data into a matrix variable, the list is enclosed in a pair of left and right brackets '[...]' with blanks or commas ',' separating the elements in the row, and semicolons ';' or a 'return' separating the rows. When assigning a variable name to a matrix, remember that entering

a new value under an existing variable name causes the new value to overwrite the existing values under the variable name. An example matrix input (and system output) is given below. Note: Ctrl-C is not case sensitive.

Example: [> a = [1 2 3; 4 5 6; 7 8 9]

```
A =  1.  2.  3.
      4.  5.  6.
      7.  8.  9.
```

1.2.2 Special Matrix Functions

It is sometimes necessary to create matrices of special types. The following set of functions is available for building specific types of matrices.

ones generate a matrix of ones

rand generate random numbers and matrices

A 3 x 3 matrix of ones can be generated by the following command.

Example: [> ones (3)

```
ANS =  1.  1.  1.
        1.  1.  1.
        1.  1.  1.
```

The creation of a 3 x 2 matrix of ones is shown below.

Example: [> ones (3,2)

```
ANS =  1.  1.
        1.  1.
        1.  1.
```

The command `ones (a)`, where `a` is an `m-by-n` matrix, produces an `m-by-n` matrix with each element being equal to 1.

Example: `[ > a = [ 1 2 3; 4 5 6 ]`

`[ > c = ones (a)`

`C =    1.   1.   1.`

`1.   1.   1.`

Matrices with components of random numbers can be generated by the `RAND` command. The argument used with the `RAND` command represents the dimension of the matrix. Use of the `RAND` command with no argument will result in a scalar.

Example: `[ > c = rand(3)`

 Builds a 3-by-3 random matrix.

By default, random numbers are uniformly distributed in the interval (0.0 through 1.0). The `RAND ('Normal')` command switches to a normal distribution with a range -1 through 1 with a mean of 0.0 and a variance of 1.0. The following commands generate a 3 x 3 matrix with a normal distribution.

Example: `[ > rand('Normal')`

`[ > c = rand(3)`

1.2.3 The Display Command

Matrices may be displayed by typing the name of matrix and `'return'`. This is illustrated below.

Example: `[ > a`

`A =   1.   1.   1.`

`1.   1.   1.`

1.2.4 Listing Matrix Dimensions

The numbers of rows and columns of a matrix may be displayed by using SIZE command. The following command and associated output show that matrix a has 2 rows and 3 columns.

Example: [> SIZE(a)

ANS = 2. 3.

1.2.5 Matrix Transposition

Matrix transposition is accomplished by interchanging row and column positions of a matrix without changing the value of its components. The transpose operation is accomplished by typing a single quotation mark (') to the immediate right of the variable name or expression. This is illustrated below.

Example: [> Ca = [1 2 3; 4 5 6]

Ca = 1 2 3

4 5 6

[> Ca' // Transpose

ANS = 1 4

2 5

3 6

1.2.6 Addition of Matrices

Two matrices may be added to each other only if their dimensions are the same (the numbers of rows and columns are the same). If A and B are matrices, then A + B will result in a matrix whose individual elements are the sum of the

corresponding individual elements of matrices A and B

Example: [> A = [1 2 3; 4 5 6]

[> B = [7 8 9; 0 1 2]

[> C = A + B

C = 8 10 12

4 6 8

1.2.7 Subtraction of Matrices

Two matrices may be subtracted from one another if their dimensions are the same. If A and B are matrices, then $A - B$ will result in a matrix whose individual elements are the difference between the corresponding individual elements of matrices A and B.

Example: [> A = [1 2 3; 4 5 6]

[> B = [7 8 9; 0 1 2]

[> C = A - B // C is equal to difference of A and
B.

C = -6 -6 -6

4 4 4

1.2.8 Multiplication of Matrices

Two matrices can be multiplied using the operator (*), as long as the number of columns in the first matrix is equal to the number of rows in the second matrix. For example, the matrices of $A(m,n)$ and $B(n,p)$ can be multiplied as $A * B$.

```

Example: [ > A = [ 1 2 3; 4 5 6 ]
          [ > B = [ 1 0; 2 4; 0 7 ]
          [ > C = A * B
          C = 5  29
              14  62

```

```

Example: [ > 2 * A    // scalar multiplication
          ANS =  2   4   6
                8  10  12

```

1.2.9 Sub-Matrix Assignment

Individual rows and columns can be referenced using a colon ':' for free subscript. The first row of Matrix a can be accessed by a(1,:), and the jth column by a(:,j).

```

Example: [ > a = [ 1 2 3; 3 4 5 ]
          [ > c = a (1,:)
          c = 1.  2.  3.
          [ > c = a(:,2)
          c =  2
              4

```

1.3 Operating with Disk Files

Ctrl-C provides the user with the ability to communicate with other application programs and operating systems by means of input and output files stored on the disk.

1.3.1 The Save Command

The save command is used to store any or all of the user defined variables onto the system. The format is as follows:

```
[ > save {var1} {var2} ... {varn} > filename
```

Example:

```
[ > save a b > spring.dat // save a and b in spring.dat
```

1.3.2 The Load Command

In Ctrl-C, the load command is used to load variable(s) from the disk. The basic syntax of load command is:

```
[ > load {var1} {var2} ... {var1} < filename {options}
```

There are several load command options available; such as -f, -b, -bd, etc. Option -f specifies an unstructured formatted file. There is another option which allows portions of files to be read in. The -cnn attribute designates the number of columns to be loaded.

Example:

```
[ > load m < spring.dat -f -c3 // load the first 3  
columns from an unstructured file spring.dat into a variable  
m
```

1.4 Graphics and Plots

One of the most important features of the Ctrl-C software is its support for graphics. This feature allows the user to create complex graphics using the same natural syntax with which Ctrl-C manipulates matrices. Ctrl-C provides two-

dimensional X-Y engineering plots using the PLOT command in conjunction with TITLE, XLABLE, and ERASE commands to create line plots and bar charts.

1.4.1 The Plot Command

The plot command performs the actual plotting. The general syntax of the plot command is:

```
[ > plot ( v1 {,v2} . {,vn} )
```

Example:

```
[ > X = { 1 2 3 4 5 }
```

```
[ > y = [ 2 4 6 8 10 ]
```

```
[ > plot (x,y)
```

1.4.2 Plot Labeling

The TITLE, XLABLE and YLABEL commands are used to put title and coordinate labels on a plot. The general syntax for these commands are:

```
[ > title ( ' text string' )
```

```
[ > xlabel ( 'text string' )
```

```
[ > ylabel ( 'text string' )
```

The title command is used to put a title at the top of a plot created using the plot command.

Example:

```
[ > plot (X,y), title ('velocity wave' ), xlabel ( 'time'), ylabel ( 'distance' )
```

1.4.3 Erasing Plots or Text

The erase command is used to erase the graphics screen.

Example:

```
[ > plot (x,y)
[ > erase
```

1.4.4 The DISPLAY Command

The DISPLAY command can display the values of variables on the screen. The format is

```
[ > disp ( 'prompt character string' ), variable name
```

Example:

```
[ > disp ( 'value of m' ), m
value of m
      0.0
```

1.5 Hardcopy Output

There are two methods for assigning a hardcopy output for plots. The first method is to set TERM variables to the defined name of the Ctrl-C supported hardcopy device. The second is to use the replot command and the variable HARD to obtain the hardcopy image of the graph that is already on the interactive terminal screen.

1.5.1 Hardcopy Using the Term Variable

In this case, the user sets the variable TERM to a desired terminal name (one that supports graphics) that is defined and supported by Ctrl-C. With this method, all the plotting commands are used as they work with the interactive terminal. However, the output resulting from the Graphics command, will be redirected to a default diskfile containing the hardcopy of image of the plot instead of appearing on the screen. This file can then be spooled to a local graphics hardcopy device for an actual hardcopy graph. The following table lists the terminal types that support hardcopy and the default file name associated with each device.

Terminal Type	Default Filename
DEN	CTRL-C.PEN
PTX	CTRL-C.PTX
IMAG	CTRL-C.IMG

Once the output file is generated, it must be closed prior to spooling it for printing.

Example:

```
[ > term = 'ptx'          // Assign term type ptx
[ > plot (x,y)            // plotting commands
[ > redterm -close        // close file
[ > $lpr -v ctrlc.ptx //operating system command to print
                        file
```

1.5.2 Hardcopy Using the Replot Command

In this case, the user must first define a hardcopy device name to the reserved variable HARD, and then use the replot command to generate a hardcopy image of the plot in the default file (same as in the first method) from the interactive terminal. The procedure is the same as the first method.

Example:

```
[ > hard = 'sun'    // Assign hardcopy device SUN
[ > plot (x,y)      // plotting command
[ > replot          // generate a hardcopy image
[ > redhard - close // close file
[ > $lpr -v ctrlc.sun
```

1.5.3 The RAST Command

In Ctrl-C, the RAST command store the most recent picture on the screen to a file named ctrlc.rast. The user can also use this command to get a hardcopy.

Example:

```
[ > plot (x,y)    // plotting command
[ > rast          // generate an image file of current
                  screen
[ > $lpr -v crtlc.rast // operating system command to
                      print the file
```

1.6 Programming in Ctrl-C

There are times when [due to the frequency of usage of the same set of sequential functions, complicated applications (with many steps), or running in batch mode] it is more efficient for the Ctrl-C commands to be first assembled in a file and then executed.

1.6.1 Do-procedures

The do-procedure is a sequence of Ctrl-C statement contained in a file. The filename should have a .ctr extension. Statements of a do-procedure are executed just as if they were entered interactively line by line. To create a do-procedure, use your favorite text editor to create a file containing a sequence of Ctrl-C statements.

Example:

```
[ > $vi bf.ctr      // edit a file containing command
                        procedure under sun operating
                        system

plot (x,y);           //command procedure content
title ( 'velocity' );
xlabel ( 'distance' )
```

To execute this procedure, issue the command

```
[ > do bf
```

which will execute the above sequence of commands to produce a plot.

1.6.2 User-defined Functions

A user-defined function is created in the same way as a do-procedure (i.e., a file containing the function is created using a text editor). A user-defined function consists of three parts.

1. A function header
2. A body containing Ctrl-C statement
3. A RETURN statement

The first line of a user-defined function file must be the function declaration line. The format of this line is

```
// [ out1, out2, ... ] = function-name ( in1, in2... )
```

where:

out1, out2 are the output variables to be returned by the function, in1 and in2 are input variables passed to the function, and function-name is the function name.

A function must have an input argument if it is to have output arguments.

Example:

```
// [ m,s ] = test (x,y)
.. inputs x,y
.. outputs m: sum of x and y
.. s: division of x and y
    m = x + y;
    s = x/y;
    return
```

To call the function, use the DEFF command. The DEFF (define function) command reads the latest version of the function from your directory into Ctrl-C function library. The format of DEFF is

```
[ > deff function-name
```

Example:

```
[ > deff test          .. read the test function into Ctrl-C
[ > x = 3; y = 4        .. get the inputs value
[ > [m,s] = test (x,y) .. call function to find out m and s
      m = 7
      s = 0.75
```

You do not have to use the same variable (argument) names you defined for the function when you call the function. You may also use other names instead. But the format (argument position in the function) should be the same.

1.6.3 The Pause Command

The pause command may be used within the body of a procedure to temporarily suspend execution of the program. Program execution will resume when the carriage return is pressed.

1.6.4 Vector Variables

A vector is a special form of matrix. The content of a vector variable can be a single row or column.

Example:

```
[ > X = [ 1 2 3 4 5 ] // a row vector
```

```
[ > y = [ 1
```

```
2
```

```
3
```

```
4
```

```
5 ] // a column vector
```

To refer to any specific value of the row or column, use a number within () to indicate the position of the value.

Example:

```
[ > c = x(3)
```

```
c = 3
```

2. Maximum Likelihood System Identification

Ctrl-C provides an implementation of the maximum likelihood method of system (model) identification. It estimates the parameters of the state-space model (i.e., F , K_1 , etc. in the blood flow problem) from a block of input/output data. This section describes the use of the Ctrl-C maximum likelihood method.

2.1 The Basic Principle

To illustrate the maximum likelihood method, a population is assumed to have a density function which contains parameters p , which are to be estimated by a certain statistic. Thus, the density function can be denoted by $f(x,p)$. Assuming that there are n independent observations, the joint density function for these observations is

$$L=f(x_1,p)*f(x_2,p)*f(x_3,p)*.....*f(x_n,p).$$

This is also defined as the likelihood function. With the observation fixed, the maximum likelihood process chooses the parameters p to maximize the likelihood function.

When the observed values are given, the likelihood function becomes a function of variable p . Since L is always non-negative, the $\ln L$ can be used to obtain the summation form of the previous equation as follow:

$$\ln L=\ln f(x_1,p)+\ln f(x_2,p)+.....+\ln f(x_n,p).$$

Maximization of the likelihood function L is equivalent to the minimization of its negative logarithm. This can be obtained

by solving

$$\frac{d(\ln L)}{dp} = 0 \quad (1)$$

It is more convenient numerically to work with this negative log likelihood function, which will be called llf in the Ctrl-C program.

2.2 Overview of the Problem

The goal of maximum likelihood system identification is to estimate the model (or system) parameters so that the model reproduces the measured data as closely as possible.

Consider the general form of the matrix differential equations

$$\dot{x} = A \cdot x(t) + B_u \cdot U(t) + B_w \cdot W$$

$$y = C \cdot x(t) + D_u \cdot U(t) + V$$

where A , B_u , C , D_u , $x(t)$, $U(t)$ have been defined previously. B_w is process noise coefficient. W and V are process noise and measured noise. Their covariances are Q_d and R , respectively. The blood flow model is therefore constructed as shown by Equations (2) and (3) with the generalization that the A , B_u and D_u matrices are composed of parameters to be identified:

$$\begin{pmatrix} \dot{Q}_1(t) \\ \dot{Q}_2(t) \end{pmatrix} = \begin{pmatrix} -\frac{(F+K_1)}{V_1} & \frac{K_2}{V_2} \\ \frac{K_1}{V_1} & -\frac{K_2}{V_2} \end{pmatrix} \begin{pmatrix} Q_1(t) \\ Q_2(t) \end{pmatrix} + \begin{pmatrix} F \\ 0 \end{pmatrix} C_a(t) + \begin{pmatrix} 0 \\ 0 \end{pmatrix} W \quad (2)$$

$$Y = [1 \ 1] \begin{pmatrix} Q_1(t) \\ Q_2(t) \end{pmatrix} + [spf] * C_a(t) + V \quad (3)$$

2.3 Ctrl-C Implementation

There is no explicit function which can obtain the identification directly. Rather, there are three functions, P2SS, LIKE, and MLSTEP that are used together to perform the maximum likelihood identification.

2.3.1 The P2SS function

The first function, P2SS, is written by the user for his system ("P2SS" is an acronym for "parameters to state space"). P2SS defines the system to be identified. It must describe a state-space equation (eg. equations (2) and (3)). P2SS must contain Ctrl-C statements that are used to describe the state-space function. All the parameters (both to be identified and not to be identified) are represented by a parameter vector, P. All parameters to be identified must be elements of P (although not all P elements need to be identified). P2SS is used within LIKE and MLSTEP and must have a calling sequence of the form

$$[A, B_u, B_w, C, D_u, Q_d, R, x_0] = \text{P2SS}(p),$$

where the definitions of A, B_u, B_w, C, D_u, Q_d, R have been stated previously and x₀ is the initial condition. The Ctrl-

C statements in the body of P2SS map the parameter vector into the state-space description.

Given the state-space equations (2) and (3)
and the known constants in the model,

$$V_1 = 0.8$$

$$K_1 = EF/(1 - E)$$

$$E = 1 - 0.607 \exp(-1.25/F)$$

$$K_2/V_2 = 0.0$$

The measured data ($Q_1 + Q_2$ and Ca) are obtained as a function of time.

One can write the following P2SS function (a command file named P2SS.ctr) to express the blood flow state space model.

```
// [ A, Bu, Bw, C, Du, Qd, R, x0 ] = P2SS(p)
// Blood flow state-space definition
//
dt = p(10);      .. distributed time period (the time
                  interval of PET data acquisition)
f = p(11);      .. blood flow
spf= p(1);      .. spill over factor
v1 = p(12);    .. volume of distribution
deff rates.ctr  .. call the function to calculate e
                  and K1
[ e, k1 ] = rates (f);      .. calculation of e and K1
a = [ -(f + k1)/V1   z;
      k1/V1         -z];    .. state-space matrix
bu = [ f; 0 ];      .. input matrix
bw = [ 0; 0 ];      .. process noise coefficient matrix
C = [ 1 1 ];        .. output matrix
d = [spf]           .. feedthrough matrix
q = p(15)           .. process activity noise covariance
                  matrix
r = [ p(6)];        .. measurement activity noise
                  covariance matrix
x0 = [ p(8); p(9)]; .. state initial condition
[ ad, bd ] = c2d(a, [bu, bw], dt); .. convert the
                                  coefficient matrix
                                  to discrete system
                                  coefficient matrix

bud = bd[:, 1];     .. find bud from bd
bwd = bd[:, 2];     .. find bwd from bd
```

```

qd = q/dt;          .. convert to discrete system noise
                     covariance (the  $Q_d$  defined
                     previously)

```

In this program we refer the function `c2d ( )` which is used to convert the continuous system to a discrete system. This is because only discrete systems can be identified by this maximum likelihood method implemented in Ctrl-C. Also, elements of the state-space model matrix are set equal to elements of the parameter vector, p .

2.3.2 Access of the Input Data and Comparisons of the Model Results with Measured Data

Before the identification of the model, the necessary information such as the value of the known parameters should be given. It is essential to obtain the model output for comparison with data after the identification. Suppose we have a data file `dog.dat` which contain the data of $Q_1 + Q_2$ (PET measured activity from a ROI) and $C_a(t)$ (the measured input activity concentration) with respect to time, t . That is, the first column of data corresponds to time, the second column to $Q_1 + Q_2$, and the third to $C_a(t)$. The following command file can assign the data to the variables respectively.

Edit a file named `input.ctr`

```

load m < dog.dat -f -c10
t = m(:, 1)      .. Assign the first column to variable t
qtot = m(:, 2)   .. Assign the third column to qtot
Ca = m(:, 10)    .. Assign the 10th column to Ca

```

Now edit a file named bf.ctr to get all the input data and depict the truth model.

```
// input data file for model
//
do input.ctr;    .. get the data from dog.dat and assign
                  them to t, qtot, Ca respectively

line = 500;      ..
dt = 1/10;       .. define the sampling period. PET use
                  6 second which is equal to 1/10 min.
p = 0*one (15, 1); .. define a p vector and initialize
                  all the value of P to zero
p(10) = dt;      .. assign dt to the parameter vector
p(11) = 1.0;     .. give an initial estimated value of
                  f.
p(1)=0.1         .. give an initial value of spf
p(12) = 0.8;     .. value of  $V_1$ 
p(15) = 0.0004;  .. process activity noise covariance
p(6) = 0.000025; .. measurement activity noise
                  covariance
deff P2SS.ctr    .. call function P2SS
[ ad, bud, bwd, c, d, qd, r, x0 ] = P2SS(p);
p(2) = K1;
U = Ca';         .. transpose the column vector to row
                  vector and assign it to U
y = qtot;        .. assign  $Q_1 + Q_2$  to y
ty = ['Q (prior to the identification)']; .. Assign a
                  character string to a variable
ty1 = ['Q (after the identification)'];
plot (t, y), ylabel (ty),...
ptrue = p;       .. Assign all the value of p to ptrue
save dt t u y ty ty1 ptrue > p.dat .. save all the
                                  variables to a data
                                  file

// end of input.dat
```

In this command file, several functions (command files) which have been defined previously are called. The main purpose of setting up different user-defined functions to get input data is to make programming more flexible and easier to be modified if necessary.

2.3.3 Model Identification Program

The P2SS function describing the model to be identified and the input data file have been set up in order to get the input data. Based on these functions and data, by using Ctrl-C functions (LIKE and MLSTEP), the model can be identified. The identification commands may also be contained in a command file which can be named as Id.ctr. The LIKE function has the following general form:

```
[ llf, yest, b, K ] = like (po, 'p2ss', u, y)
```

LIKE returns:

llf the negative log-likelihood function. This value
 of llf reflects the quality of the identification
yest the estimated measurement output
b the innovation covariance matrix (used to
 calculate the llf)
K the state estimator feedback gain matrix

The arguments of the LIKE function are:

po initial parameter vector including the ones to be
 identified and not to be identified
'p2ss' the function defined for the mapping of state-
 space equations of the model
u the input to excite the model
y the truth output of the model

The LIKE function is the primary routine associated with identification process. It obtains the new output value of

the cost function (measure of the goodness-of-fit of the data to the model response) after the estimation. The MLSTEP function performs a simple iteration of the algorithm to maximize the likelihood function. The general form of MLSTEP function is:

```
[ pnew, marq, llf, gr, h ] = mlstep (po, pid, 'p2ss', u,  
y, pert, marq)
```

where

pnew	the new value of p after the iteration of the identification
marq	initial and updated value of the Marquardt parameter
gr	gradient of llf with respect to parameters evaluated at po (used to calculate the change of parameter p)
h	Hessian of llf with respect to parameters evaluated at po (used to calculate the change of parameter p)
pid	parameters to be identified
pert	perturbation size used to compute the gradient and Hessian

The content of identification command file Id.ctr is

```
// MAXLIKE Identification  
//  
deff p2ss      .. model structure definition  
load < p.dat   .. get input data
```

```

p = ptrue;      .. true parameter array
..
disp ('true values')
[ p(11) p(12)] .. display the initial value of f and spf
                  prior to the identification
..
[ llf, yest, b, K ] = like (p, 'p2ss', u, y);    ..use
                                                the input data to get
                                                the llf and estimated
                                                output yest
disp ('interval value'), llf .. display the value of llf
plot (t, yest, t, y), title (ty), .. depict the output
                                      according to estimated
                                      value and the true
                                      value of output
                                      respectively

end;
..
pid = [ 11,1 ];    ..indicate the parameters to be
                    identified, i.e. p(11), p(1).
marq = 0;          ..give an initial value for marq
pert = 0.001;      ..assign a value to determine the
                    perturbation size
..
[ pnew, marq, llf, grad, hes ] = mlstep (p, pid, 'p2ss',
u, y, pert, marq); ..take carry out iterations and
                    provide a new value of
                    variable llf.
[ llf, yest, b, K ] = like (pnew, 'p2ss', u, y); .. use
                    new p vector value pnew to
                    obtain the estimated output yest.
plot (t, yest,t, y), title (ty1), .. depict the
                    estimated output and the truth
                    output according to the newly
                    estimated value of yest.

end;
pause
// end

```

The values of parameters are continuously adjusted during the minimization of the "cost" functions (the llf value). The final value of the identified parameter will be printed on the screen. Also, one may use Ctrl-C commands such as DIARY and RAST to obtain a hard copy output of the records and figures. For more detailed information about how to use the Ctrl-C to

perform the maximum likelihood identification, see the Ctrl-C manual.

APPENDIX B
MODEL IDENTIFICATION PROGRAM

```

// comand procedure for running the blood flow data
emod=1;                ..stop on errors
rand('normal');
file = input('Enter Patient/Dog Filename: ','TEXT')
l1= 'load m <';
l2 = file;
l3 = ' -f -c10';
loadfile = [ l1 l2 l3 ];
loadfile[];
limit=input('Enter upper limit time interval number: ');
n=2;
//----- run maximum likelihood functions for 8 sector data-----
do th2
do th2
do th2
do th2
do th2
do th2
do th2
do th2
do th2
//
//----- save results-----
save r >result.dat -f -(lx,8f9.3);
//
//-----option to get result hard copy-----
$!pr -h result.dat;
//
//-----get good plot -----
hard='hpgl';
replot
redhard -close
$hpgl2ps -a -l 0.6,0.1,1 ctrlc.hpgl >ctrlc.post
//
//-----option to get plot hard copy-----
$!pr -h ctrlc.post
//
//end of th.ctr

```

```

// [ad,bud,bwd,c,d,qd,r,x0] = th1(p)
//
// blood flow analysis
//
dt = p(10);           ..discrete time period
z=p(5);               ..value of z
spf=p(1);             ..spillover factor
f= p(11);             ..blood flow
vl=p(12);             ..distribution volume
z=p(5);
[e,kl]=rates(f);
a = [-(f+kl)/vl      z;
      kl/vl         -z];
bu = [f; 0];
bw = [0; 0];
c = [1  1];
d = [spf];
q = p(15);
r = [p(6)];
x0= [p(8); p(9)];     ..initial condition
[ad,bd]=c2d(a, [bu bw],dt);
bud = bd(:,1);
bwd = bd(:,2);
qd = q/dt;
//
// end of th1.ctr

```

```

// th2.ctr
//-----Input-----
t=m(1:limit,1);
qtot=m(1:limit,n);
ca=m(1:limit,10);
//-----Variable definition-----
f=1;          ..initial value of blood flow
p = 0*ones(15,1); ..assign zero to all elements of vector p
p(10)=6/60;   ..discreted time period
p(1)=0.1;     ..initial value of spf
p(11) = f;    ..initial value of f
p(12) = 0.8;  ..value of volume of distribution
p(5)=0;       ..value of z
p(15)=0.;     ..process activity noise covariance
p(6)=0.00001; ..measurement activity noise covariance
deff rates.ctr
[e,k1]=rates(f); ..calculate extraction fraction and rate constant
glob(e);        ..define e as a global variable
glob(k1);
p(2)=k1;        ..assign k1 to an element of the p vector
p(3)=e;
//-----
u = ca';        ..transpose vector ca to a row vector
y=qtot';
ty1=[' Prior to Identification']; .. assign a title to a variable
ty2=[' After Identification'];
disp(' initial values:')
[p(11), p(1),p(12)]
//-----Like call-----
deff th1.ctr
[llf,yest,b,k]=like(p,'th1',u,y);
disp(' Cost Function, llf = '),llf
erase;
plot(t,yest,t,y),title(ty1),
//-----
// Maximum-Likelihood identification run
//
marq=0;          ..assign initial value to Marquardt parameter
pert=0.001;      ..assign the perturbation size
lold=1.e4;       ..assign initial value to llf variable
mfc=0.01;        ..assign a precision to contral the iteration of mlsetp
pid={1,11};      ..define the parameter to be identified
pret=p;
disp(' Initial parameter values'),[pid', p(pid)]
pold=pret(pid);
//-----for loop -----
for j=1:10,..
    disp(' '),disp([' iteration no.',str(j)]),..
    [pret,marq,llf,grad,hes]=mlstep(pret,pid,'th1',u,y,pert,marq);..
    rc=abs(llf-lold),..assign the differenc value of llf to contral iteration
    lold=llf,..
    if rc<mfc,exit;end;
f=pret(11),spf=pret(1),..
//-----
p=pret;
[llf,yest,h,k]=like(p,'th1',u,y);
//-----plot the final estimated model-----
y=y*37;          ..convert y to a new value in unit of bkq/gm
yest=yest*37;
erase;
plot(t,yest,t,y),title (ty2),ylabel ('Total Activity (kbq/g)'),..
    xlabel ('Time (sec)'),..
//-----output-----
h=[n-1 pret(11) pret(1) e pret(12) pret(5) k1 ];
r(n-1,:)=h;      ..command procedure switch

```

```

zz=[n-1 0 0 0 0 0 ];
g(2)=0;
hh=sum(h);
if hh=g(n)+1,r(n-1,:)=zz;g(n+1)=sum(h);n=n+1;else g(n+1)=sum(h);n=n+1;end;
end;
// end of th2.ctr

```

```

//[e,kl]=rates(f)
//
//rate constant function
..f=0.1;
e=1-0.607*exp(-1.25/f);
if e >0.9988, e=0.9906;
kl=e*f/(1-e);

```

APPENDIX C
SYNTHETIC DATA GENERATION PROGRAM

```

a=0.65,
b=0.1,
f=0.01667
v1=0.8,
e=1-0.607*exp(-1.25/(60*f));
k1=e*f/(1-e),
k=(k1+f)/v1,
c=k1/v1,
t=[3
9
15
21
27
33
39
45
51
57
63
69
75
81
87]
ts=t-3*ones(1:15)';
te=t+3*ones(1:15)';
cc=a*t.*exp(-b*t);
q11i=(a*f)/(k-b)*(-1/b*(ts.*exp(-b*ts)+1/b*exp(-b*ts)));
q12i=(a*f)/(k-b)*(1/(k-b)*1/b*exp(-b*ts)-1/(k-b)*1/k*exp(-k*ts));
qi=q11i+q12i;
q21i=a*c*f/(k-b)**2*(1/b*(-1/b*exp(-b*ts)-ts)-1/k*(-1/k*exp(-k*ts)-ts));
q22i=-a*c*f/(k-b)*(1/b*(-1/b*(ts.*exp(-b*ts)+1/b*exp(-b*ts))));
q23i=-a*c*f/(k-b)*(-1/b**3*exp(-b*ts)-1/b**2*ts);
qqi=q21i+q22i+q23i;
qtoti=qi+qqi;
//-----
..
qq11i=(a*f)/(k-b)*(-1/b*(te.*exp(-b*te)+1/b*exp(-b*te)));
qq12i=(a*f)/(k-b)*(1/(k-b)*1/b*exp(-b*te)-1/(k-b)*1/k*exp(-k*te));
qqi=qq11i+qq12i;
qq21i=a*c*f/(k-b)**2*(1/b*(-1/b*exp(-b*te)-te)-1/k*(-1/k*exp(-k*te)-te));
qq22i=-a*c*f/(k-b)*(1/b*(-1/b*(te.*exp(-b*te)+1/b*exp(-b*te))));
qq23i=-a*c*f/(k-b)*(-1/b**3*exp(-b*te)-1/b**2*te);
qqqi=qq21i+qq22i+qq23i;
qqtoti=qqi+qqqi;
..-----
qtot=(qqtoti-qtoti)/6;
m(1:15,3)=cc;
m(1:15,2)=qtot;
m(1:15,1)=t;
save m >ywit.dat -f -(lx,3f12.3);
erase;
qtot=qtot*37;
plot(t,qtot),title('synthetic data curve for blood flow'),...
    xlabel('time (sec)'),ylabel('total activity (kbq/g)');
end;

```

VITA

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He received a scholarship from the University of Cincinnati in September 1988 and began the study of Nuclear Engineering. In the January of 1989, he accepted a graduate assistantship at The University of Tennessee, Knoxville and started study in Radiation Protection Engineering (Health Physics) toward a Master of Science degree.