A NONINVASIVE THERMAL METHOD
FOR THE
QUANTIFICATION OF TISSUE PERFUSION
by
Joseph Tony Walsh, Jr.
S.B. Massachusetts Institute of Technology
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Submitted to the Department of Electrical Engineering and Computer Science in partial fulfillment of the requirements of the Degree of
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Signature of Author
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Certified by
Thesis Supervisor

Accepted by
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ABSTRACT

A noninvasive thermal diffusion probe has been constructed from two
flake thermistors. An analytical one-dimensional Cartesian heat
transfer model of the heated flake thermistors has been evaluated.
Results indicate that the one-dimensional Cartesian model is inadequate
for the rather small spatial dimensions of the probe, and that a
spherical model is more appropriate. Numerical analysis verifies this
hypothesis. Probe calibration is discussed and preliminary results
presented.

The ability to accurately quantify thermal conductivity with the
noninvasive probe was demonstrated by testing with materials of known
thermal properties. The ability to accurately quantify perfusion with
the noninvasive probe was evaluated using an isolated rat liver
perfusion technique. The isolated perfused liver technique allows for
independent quantification of the true perfusion by total venous
collection and the use of radiolabeled microspheres for determination of
proportional distribution of total flow. Experimental results
demonstrate that the noninvasive probe is quite sensitive to changes in
the level of perfusion within the surface region of tissues.

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a = characteristic probe dimension (cm)
c = specific heat (W-s/gm°C)
f(t) = transient power function (s⁻¹⁄₂)
F = total liver flow (ml/min)
F( ) = Laplace transform of f(t)
g = heat generation term (W/ml)
G = heat generation term (W/ml)
K = thermal conductivity (W/cm°C)
m = mass (gm)
n = √w c bl/K m

Subscripts

q = heat flux (W/cm²) a - arterial
r = radial distance (cm) bl - blood
s = Laplace variable (1/s) eff - effective
t = time (s) ext - external
T = Temperature (°C) f - flake thermistor
V = temperature difference (°C) i - index number
w = tissue perfusion (gm/ml-s) m - tissue medium
x = integration variable (cm) met - metabolic
α = thermal diffusivity (cm²/s) ss - steady state
ρ = density (gm/ml) T - total
Γ = steady state power (W/ml) 0 - initial
β = slope of transient power (W-s¹⁄₂/ml)
δ = spacial decay constant (cm)
Ψ = series expansion of V
ΔT = volume average temperature step (°C)
Chapter 1.1 Objective of Research

The objective of this research is to develop a noninvasive technique for the measurement of tissue perfusion. Because a thermal method is used one can also measure the following properties: temperature, thermal conductivity, and thermal diffusivity. Temperature is a familiar parameter describing the energy of a system. Thermal conductivity is a measure the ability of a system to transport heat under steady state conditions from a region of high temperature to that of a lower temperature. Perfusion, strictly a biological phenomenon, is a measure of blood flow through a capillary bed. While flow in a single capillary is a vector quantity, because of the nature of capillary distribution, blood flow in a macroscopic capillary bed is normally treated as a nondirectional scalar quantity. Figure 1.1 illustrates this property. Consequently, perfusion is described in terms of a volume of blood passing through a mass of tissue per unit time (e.g. \( \text{ml\, blood/100gm\, tissue - min} \)).

On a conceptual level the operation of the noninvasive probe is straightforward. The essence of the probe is a thermistor, a resistor whose resistance is a strong function of temperature. The thermistor probe is used as both a sensor and a heater. When used as a sensor, temperature is calculated from the measured thermistor resistance. Used as a heater, power is supplied to the thermistor in a manner such that the thermistor is heated to a specific temperature above the baseline temperature. The power requirement of the thermistor is indicative of the thermal properties of the medium abutting the thermistor. The more thermally conductive the medium the greater the power that will be required to maintain the thermistor at the elevated temperature.
Similarly, the more perfused the medium the greater the power that will be required. Thus, by monitoring the power requirements of the heated thermistor, a measure of both thermal conductivity and perfusion can be obtained.
Figure 1.1 A schematic of a capillary bed indicating both the vectorial nature of blood flow in each capillary and the net nondirectional scalar nature of perfusion throughout the entire tissue region. (Adapted from Guyton [1].)
Chapter 1.2 The Significance of a Noninvasive Perfusion Measurement

It is recognized that the transport of nutrients and waste products is primarily the function of blood. Thus, a noninvasive measurement of perfusion has long been sought. This measurement would greatly aid clinicians and researchers in many areas of medical practice and physiologic investigation. A most compelling reason to develop a device for the noninvasive measurement of tissue perfusion was expressed in a series of discussions and lectures given by Dr. J. Bruner of the Massachusetts General Hospital. These talks focussed on the procedures that anesthesiologists perform during surgery. In particular, there were discussions on the measurement of patient blood pressure—a measurement that is routinely obtained at five minutes intervals. There was certainly no consensus as to why this measurement was taken; apparently, however, it is felt that because blood pressure is the driving force for perfusion, one can extrapolate a measure of organ perfusion by measuring blood pressure.

In fact, what is known is that over quite a wide range of blood pressures, perfusion is quite constant. Figure 1.2 clearly illustrates this. One notes that in the "flat" region of the curve there is considerable autoregulation; that is, the arterioles close down in response to an increase in blood pressure in order to maintain a constant perfusion. However, even if blood pressure is constant the arterioles can open or close thereby regulating perfusion. One therefore sees that the extrapolation of perfusion from the measurement of blood pressure is not necessarily straightforward. Consequently, a device that could measure perfusion as noninvasively as blood pressure
is measured would be a very important diagnostic and physiological monitoring tool.

Following are examples of applications for the noninvasive perfusion instrument; by no means does this purport to be a complete listing.

Burn Patients

The treatment of patients with severe burns is said to be one of the most difficult tasks in medicine. Essential to the successful management of these patients is the replacement of the damaged skin tissue. When a section of skin incurs third degree burns, it loses its ability to regenerate. Thus, a piece of histocompatible tissue must be grafted onto the burn region. It is realized that the nutritional status of the graft is a function of the level of graft perfusion. Thus, if the perfusion to a new graft could be quantitated, then an assessment of the probability of graft success could be made. This quantitative measurement must not damage the already compromised tissue, thus a noninvasive measurement of perfusion is required.
Prenatal Care

The growth and development of a fetus is critically dependent upon the oxygen and nutrients supplied by the mother. Thus, it would appear that maternal uterine perfusion is indicative of the nutritional status of the fetus. Further, it has been proposed that cervical perfusion is proportional to uterine perfusion [3]. Therefore, if one could assess cervical perfusion, then one could determine the nutritional status of the fetus. Clearly, a minimally traumatic cervical perfusion measurement could be made with a "noninvasive" probe placed on the tip of the cervix.

Plastic Surgery

Some of the problems associated with plastic surgery can also be addressed by a measurement of perfusion. In brief, the post-operative success of reconstructive surgery is critically dependent upon the nutritional status of the affected area. Consequently, a noninvasive determination of the local tissue perfusion would be ideal in the assessment of this nutritional status.
Pharmacology

The response of tissue to pharmacologic agents is critical in patient care. In particular, the vasoactive nature of a drug is an important determinant of the clinical effects of the drug. A perfusion measurement that itself would not alter perfusion would be beneficial in determining a drug's vasoactive effects.

Coronary Artery Bypass Surgery

The coronary bypass is the most often performed surgical procedure in this country. The success of this operation could be more easily assessed given a method to quantify perfusion on the endocardial surface. Currently, several methods are utilized to determine ventricular function; for example, radioactively labeled metabolites are used to map myocardial perfusion. These methods, though, are qualitative in nature. However, by threading the "noninvasive" probe via a catheter into the heart, one could continually measure perfusion on the endocardial surface without incurring further injury to the already compromised cardiac tissue. One could also measure epicardial perfusion pre- and post-operatively by simply placing the noninvasive probe on the surface of the heart at the time of surgery. Such a method could improve the care of coronary bypass patients both during the surgical procedure and post-operatively by allowing for the real-time assessment of cardiac perfusion and thus graft effectiveness.
Blood Gas Analysis

One of the most routine tests performed in clinical medicine is blood gas analysis. The results are vital in the diagnosis of a myriad of respiratory, cardiovascular, and metabolic disorders. The test involves drawing and analyzing a sample of blood. The limitations of the procedure are obvious: the method is invasive and relatively slow. Work is currently in progress for the real time noninvasive transcutaneous measurement of blood gases and blood pH. Critical to this measurement is the simultaneous quantification of perfusion and capillary blood temperature – perfusion so that the gas transport rates can be calculated, and temperature so that gas solubilities can be determined.

Research

Basic and clinical research have been dependent upon measurements such as blood pressure, cardiac output, pH, partial pressure of oxygen, and partial pressure of carbon dioxide to determine the effects of various physiological insults. In many cases the measurement of perfusion would be more appropriate. The availability of a noninvasive perfusion measurement instrument could greatly aid researchers in their work.
Figure 1.2 The relationship between perfusion pressure and canine muscle blood flow. The quiescent operating point is indicated by the "x". The squares indicate the conditions immediately after an abrupt change in pressure. The circles indicate the conditions in the steady-state. Note the relatively constant blood flow over this wide range of perfusion pressures. (Adapted from Berne and Leve [2].)
Chapter 1.3 The History of Tissue Perfusion Measurements

An understanding of previous work done in the field of perfusion measurements will give a perspective of the extent of the previous effort and the direction that such efforts took. Further, a better appreciation of the direction and scope of the work herein documented can be gained by reviewing these past efforts. The review is divided into two sections: first, indirect, "qualitative", measurements of tissue perfusion will be reviewed, then direct, "quantitative", methods of measurement will be discussed. As a matter of definition, an indirect measurement of perfusion involves a qualitative, often subjective, assessment of an organ's perfusion based upon the "measurement" of parameters that are presumed to correlate with perfusion. For example, if the back of a patient's hand is reddish in color and warm to touch, one usually concludes that the hand is well perfused; color and temperature are indirect measures of perfusion. On the other hand, direct measures of perfusion are objective, and yield results that are highly correlated with the perfusion rate. It would be quite safe to say that in the clinical environment there are at present no methods available for the direct quantification of tissue perfusion; yet a need for such a method clearly exists.

1.3.1 Indirect Measurements of Perfusion

Several methods exist for the quantification of arterial (or venous) blood flow. Electromagnetic flowmeters and Doppler flowmeters are well-established tools in both the clinical and research worlds [4]. Indicator dilution methods also give quite accurate and reproducible
measurements [1]. However, although accurate quantitative measures of
blood flow are available, the extrapolation of arterial blood flow to
tissue perfusion can often be difficult. For example, even when
pulmonary artery blood flow is normal, local lung parenchymal perfusion
may be greatly reduced due to distal fistulas or obstructions, e.g.
emboli. Thus, quantitative blood flow measurements must be considered
indirect qualitative measurements of tissue perfusion.

A myriad of other measurements of tissue perfusion exist.
Temperature and color have already been mentioned. Blood pressure is
commonly used in surgical settings; however, as was discussed doubts
about its efficacy exist. The measurement of arterial flow rate to an
organ or limb segment can be done by measuring the initial change in
volume immediately after venous outflow occlusion. This technique,
called plethysmography, is used; however, the utility of finger or whole
arm perfusion is limited [4]. In cardiology, the electrocardiogram
(ECG) is used to assess myocardial perfusion. It is well known that
depressed ST segments are indicative of myocardial ischemia [5].
Presently in clinical practice it is felt that the arteriogram offers
the best assessment of peripheral vasculature patency. Arteriograms are
performed by injecting a radio-opaque dye into the artery of interest
and obtaining serial X-ray images of the distal vasculature as the dye
passes through them. These and other indirect measurement methods are
extensively discussed in reference [4].

1.3.2 Direct Measurements of Perfusion

There are relatively few methods available for the direct
measurement of tissue perfusion. The majority of these methods use
radioactive tracers. Two radioactive tracer methods are discussed below. A brief review of the history of thermal methods follows.

### 1.3.2.1 Radioactive Microspheres

Radioactive microspheres are small (typically 15 microns in diameter) plastic spheres which have radioactive nuclides bonded to their surface. When injected into the circulation these spheres distribute according to the distribution of blood flow (or so it is generally assumed) and lodge in the capillaries of distal organs. Radioactive microspheres are not used clinically because it is not safe to inject materials that lodge in the capillary beds of major organs—the lodged microspheres may further corrupt perfusion in an already compromised tissue. Thus, radioactive microspheres are only used in animal research studies. There is considerable literature available which [6,7,8,9] discusses the techniques and concerns of extracting a measure of perfusion using the microsphere method (to which the interested reader is referred); however, conceptually there are two different methods of quantifying perfusion using microspheres. Figure 1.3 illustrates both of these methods. The more widely used method involves 1) injecting the microspheres into, for example, the left atrium of an animal; 2) withdrawing a reference sample of the distal arterial blood; and 3) counting the radioactivity in both the tissue region of interest and the reference sample. Quantification of perfusion follows directly, see Figure 1.3. The second method requires that the tissue of interest have a single arterial blood supply and that the total flow in this supply is known. As shown in Figure 1.3, quantification of perfusion follows directly from the quantification of radioactivity and the measured flow. Further discussion of the use of
microspheres can be found in Appendix G.

1.3.2.2 Thermal Methods

In the past fifty years over 100 investigators have published their attempts to measure tissue perfusion using thermal methods. The following review will only begin to do justice to their efforts; thus, the reader is referred to references [8,10,11] for a more thorough review and bibliography. Presented here is a synopsis that is intended to give an overview of the major works and the direction that such works have taken through the decades.

A natural first question when approaching the measurement of perfusion is why use a thermal method to determine perfusion? The answer lies in the requirements for a clinical instrument [8]. Such an instrument must

1) be safe for the patient,
2) be applicable to any vascular bed,
3) give accurate, reproducible results,
4) yield said results relatively quickly, and
5) be simple to operate.

Thermal methods for the quantification of tissue perfusion have the potential of meeting all of these requirements; few other modalities can make this assertion.

The first major contribution to this field was by von Herman Rein in 1928 [12,13]. In essence, Rein discovered that the thermal field surrounding a heated disk was altered by changes in perfusion.

Hensel, Betz, Bender, and associates extended the work of Rein by first developing a probe comprised of a small coil of wires and a
thermistor. The probe was heated and held at a constant temperature using the thermistor in a feedback control loop. These researchers found that in the presence of perfusion more power was required to heat the probe. They concluded that heat was dissipated via a) the thermal conductivity of tissue, and b) perfusion. An instrument was developed that measured relative changes in perfusion but was difficult to accurately calibrate. Apparently the separation of the perfusion contribution to the power requirement of the heated probe was not possible [14,15].

A second system used by these investigators employed similar heated probes; however, in this case the thermistors were used to monitor the temperature decay after the power was turned off. It was found that the time constant of this decay was indicative of perfusion [16].

At approximately the same time (circa 1950) Grayson was using self-heated thermocouples to quantify perfusion-induced increases in measured thermal conductivity [17,18,19]. Grayson used an equation credited to Carslaw [20] which relates the power supplied to a spherical heat source to the thermal conductivity of the surrounding medium:

\[ I^2R = 4Knwr^4 \]

where \( I \) = the heating current

\( R \) = the heating filament resistance

\( K \) = the thermal conductivity of the surrounding medium

\( r \) = the radius of the sphere

and \( \Phi \) = the temperature elevation of the sphere.

Grayson found that he could accurately measure the thermal conductivity of media of known conductivity. And further, in perfused tissue, he found a perfusion-induced increase in the measured thermal
conductivity that was linear with the perfusion rate [17]. Limitations of this method are that 1) the response is sensitive to local large blood vessels, and 2) the response lags behind instantaneous blood flow changes [21]. Further, Grayson acknowledged the need for the derivation of an analytic relationship between the power increment and perfusion.

In the 1960's, Perl and Hirsch presented work done using a transient heat clearance method [21]. Heat was injected into a small region of tissue (by self heating a thermocouple); the temperature between the heated and unheated regions was monitored. The efferent artery and the afferent vein of the organ were clamped for a few seconds. The monitored temperature difference was noted to be altered by the stoppage of perfusion. It was found that the time rate of change of the temperature difference was proportional to the rate of perfusion. At low rates this method compared well with cortical renal perfusion as calculated by para-aminohippurate (PAH) clearance; however, at high rates of perfusion the method underestimated cortical perfusion by as much as a factor of two. This work is mentioned for both its uniqueness and because it represents one of the first attempts to apply rigorous analytic modelling to the problem of perfusion quantification.

In the 1970's Bowman and Balasubramaniam contributed by making two conceptually important advances. First, using a suggestion made by Chato [22,23], these researchers utilized a single thermistor as both the heat source and the temperature sensor. Secondly, they developed a coupled analytic model which described the heated thermistor as a distributed mass within an infinite tissue medium [24]. Previously, the thermistor was treated as a lumped mass having a constant temperature throughout. These advances allowed the development of a system for the
measurement of thermal conductivity, thermal diffusivity, and perfusion [25,26,27,28].

Valvano and Bowman developed a microprocessor-based instrument implementing the system initially developed by Bowman and Balasubramaniam [29]. Using a canine gracilus muscle model, it was demonstrated that perfusion could be accurately quantified. Valvano and Bowman further refined the thermal model by obtaining an explicit expression for the time dependence of the power required to heat the thermistor. They also developed a rat liver model to be used in the evaluation of perfusion measuring devices [30,31]. Experimental data was presented demonstrating the ability to quantify perfusion. The contributions made by Balasubramaniam, Valvano and Bowman were vital to this present effort and will be expounded upon in Chapters 3 and 5 of this document.

Major contributions to the understanding of bio-heat transfer on the vascular level resulted from a theoretical study conducted by Chen and Holmes [32]. These investigators considered a control volume of tissue containing blood vessels. The effects on heat transfer of vessel size and blood velocity within the vessels were considered. One of the significant conclusions of this study was that equilibration of blood temperature with the surrounding tissue occurs between the terminal arteries and the pre-capillary arterioles. Previously, it was assumed that equilibration only occurred in the capillaries.

Recently, several investigators have focussed on methods to noninvasively quantify perfusion. Patera et. al. [33] found that if a flake thermistor was placed on the surface of a tissue medium and heated in a sinusoidal fashion, then the phase shift between heat flux and
temperature was a function of the perfusion. Unfortunately, at normal levels of perfusion the phase shift is quite small and therefore difficult to measure even given state-of-the-art instrumentation.

Valvano, Patel and Hayes are developing a noninvasive probe consisting of three spherical thermistors backed by an insulating barrier. The three thermistors, which all contact the tissue medium, are sequentially heated to a constant temperature and the power required to maintain that temperature step is monitored. These investigators have found, both experimentally and using finite element analysis, that the ratio of $\Delta T$/power is sensitive to thermal conductivity, thermal diffusivity and perfusion [34,35].

Castellana and associates are developing a noninvasive probe consisting of a single flake thermistor backed by a foam support. The single thermistor is placed on the surface of a tissue and heated to a constant temperature. A theoretical analysis, using a Fourier transform method of solving the Bio-heat equation, indicated that in the steady-state the heat flux from the thermistor is a function of the perfusion in the underlying tissue. Experimental results confirmed that heat flux was a sensitive measure of perfusion. Further, if the heat flux for one in a series of measurements was used as a calibration between heat flux and true perfusion, then the remaining measurements would be an accurate quantification of perfusion [36]. Actually, this latter finding is just further verification that the transducer is sensitive to changes in perfusion.
Figure 1.3 A schematic representation of the two microsphere methods used in the determination of regional perfusion.
Chapter 2 The Noninvasive Probe: Construction and Operation

The noninvasive probe was designed to take advantage of the considerable experience that had been gained in a decade of experimentation with the invasive probe. It was envisioned that the noninvasive probe (to be placed on the surface of a tissue) would operate in a manner similar to that of the invasive probe (which is inserted into a tissue).

The operation of the invasive probe is conceptually straightforward. On the tip of the invasive probe is a thermistor (thermal resistor) whose resistance is a strong function of temperature. The thermistor is used as both a temperature sensor and a heater. When used as a sensor, temperature is calculated from the measured thermistor resistance; used as a heater, power is supplied to the thermistor in a manner such that the thermistor is heated to a specific temperature above the baseline temperature. The power requirement of the thermistor is indicative of the thermal properties of the medium surrounding the thermistor; that is, the more thermally conductive the medium the greater the power that will be required to maintain the thermistor at the elevated temperature. A thermal model was developed for the invasive probe which allows for the quantification of thermal conductivity, thermal diffusivity, and perfusion from the measurement of the required power and the imposed temperature increment.
As originally conceived, the noninvasive probe could function in a similar manner except that it would not be inserted into the tissue medium. In the sensing mode the thermistor resistance would be indicative of the tissue's surface temperature; in the heating mode the power requirement of the thermistor would be indicative of the thermal properties of the abutting medium. In the case of the invasive probe all of the heat that left the thermistor entered the tissue medium—a similar situation was desired for the noninvasive probe. Thus the noninvasive probe was designed to consist of two thermistor flakes mounted back-to-back and separated by a thin dielectric film, see Figure 2.1. One flake serves as a thermal guard while the other "surface" flake is in thermal contact with the tissue medium. The probe (both flakes) is operated in two modes: sensing and heating. In the sensing mode, each flake resistance is monitored and the baseline temperature of the tissue is calculated from the resistance of the surface flake. In the heating mode, power is supplied separately to each flake so that the temperature of each flake is raised to a predetermined value. If the two flakes are heated to exactly the same temperature there is no net heat flux across the intervening dielectric and all of the heat that leaves the surface thermistor enters the abutting medium. Thus, when the probe is placed in contact with a medium, the power requirement of the surface thermistor is indicative of the thermal properties of that medium; that is, the more thermally conductive the medium the more power will be required to maintain the surface flake at its elevated temperature.
Figure 2.1 A cross-section through the middle of the noninvasive thermistor probe. The depth of the probe (dimension into the paper) is the same as the height, 0.1 cm.
Chapter 3 The Thermal Model

Conceptually the operation of the noninvasive thermal probe is straightforward: the power required to maintain a flake thermistor at a constant temperature above the baseline temperature of the abutting medium is indicative of the thermal conductivity and perfusion of that medium. Ideally, given the measurement of the power supplied, one would like a mathematical expression from which both perfusion and thermal conductivity could be calculated. This goal can theoretically be achieved by performing a detailed analysis of the heat flow for the flake-tissue system. The purpose of this chapter is to present this analysis and discuss some of the important results. First, however, the basics of heat transfer must be understood.
Chapter 3.1 The Basics of Heat Transfer

There are in general three basic mechanisms by which heat (thermal energy) can be transferred from one region to another: conduction, convection, and radiation [37, 38, 39]. Biological systems utilize all three mechanisms in order to maintain thermoregulatory balance: the sun provides warmth by radiating energy; a breeze cools or warms by moving air over the skin thereby convecting heat away or to; and a 65°F lake appears cooler than 65°F air because water has a higher thermal conductivity and thus conducts heat away from one's body more readily than does air. A self-heated thermistor does not radiate thermal energy however heat can be transferred from a heated thermistor by conduction and by convection (e.g. blood flow).

The basic law governing the conduction of heat was formulated by Fourier, who related heat flux, \( q(\overline{r},t) \), to a temperature gradient \( \nabla T(\overline{r},t) \):

\[
q(\overline{r},t) = - K \nabla T(\overline{r},t) \tag{3.1.1}
\]

Note that the magnitude of \( q \) is the quantity of heat (in watts) transferred per unit area normal to the direction of heat flow.

One can now consider an expression for the conservation of thermal energy in the control volume as shown in Figure 3.1. One sees that:

\[
\begin{bmatrix}
\text{rate of change of heat inside V}
\end{bmatrix} = \begin{bmatrix}
\text{net rate of heat entering V}
\end{bmatrix} + \begin{bmatrix}
\text{rate of heat generated in V}
\end{bmatrix}
\tag{3.1.2}
\]
The increase in internal heat is directly proportional to the density, \( \rho \), and the heat capacity, \( c \):

\[
\begin{bmatrix}
\text{rate of change of} \\
\text{heat inside } V
\end{bmatrix} = \int_V \rho c \frac{\partial T}{\partial t} \, dV \quad 3.1.3
\]

The net heat entering the volume \( V \) through the \( \Delta Y \Delta Z \) face as shown in Figure 5.1 is:

\[
\begin{bmatrix}
\text{net rate of} \\
\text{heat entering } V
\end{bmatrix} = -\frac{\partial q_x}{\partial x} \Delta x \Delta y \Delta z \quad 3.1.4
\]

Thus in general one can write:

\[
\begin{bmatrix}
\text{net rate of} \\
\text{heat entering } V
\end{bmatrix} = -\int_V \nabla q(\vec{r}, t) \, dV \quad 3.1.5
\]

Finally, if \( g \) is the rate of heat generation per unit volume per unit time then:

\[
\begin{bmatrix}
\text{rate of heat} \\
\text{generation in } V
\end{bmatrix} = \int_V g(\vec{r}, t) \, dV \quad 3.1.6
\]
Using these results (equations 3.1.3, 3.1.5, and 3.1.6) one can rewrite equation 3.1.2 in the limit where dV is very small:

\[
\rho c \frac{\partial T(\vec{r},t)}{\partial t} = -\nabla q(\vec{r},t) + g(\vec{r},t) \tag{3.1.7}
\]

Substituting Fourier's law we find:

\[
\frac{1}{\alpha} \frac{\partial T(\vec{r},t)}{\partial t} = \nabla^2 T(\vec{r},t) + \frac{g(\vec{r},t)}{K} \tag{3.1.8}
\]

where 1) the diffusivity \( \alpha = K/\rho c \)

and 2) the medium is assumed anisotropic

\( (i.e., K_x = K_y = K_z = K) \)

For living biological materials Pennes [40] derived an expression for heat generation:

\[
g = G_{\text{met}} - w c_{bl} (T - T_a) \tag{3.1.9}
\]

where 1) \( g \) is the net local heat generation

2) \( G_{\text{met}} \) is the metabolic heat generation

3) \( w \) is the perfusion rate,

4) \( c_{bl} \) is the specific heat of blood,

5) \( T \) is the baseline temperature of the tissue,

and 6) \( T_a \) is the temperature of the incoming arterial blood.
One notes that in the steady state \((g = 0)\) the heat generated by metabolic processes is exactly equal to the heat carried away by the blood. Further one sees that Pennes' expression for heat generation neatly accounts for the transfer of thermal energy by convection (i.e. perfusion).

If one considers that energy may be absorbed from an external source, \(G_{\text{ext}}\), and adds this term to equation 3.1.8 one obtains an expression known as the "Bio-heat" equation:

\[
K \nabla^2 T + G_{\text{met}} + G_{\text{ext}} - w c_{\text{bl}} (T - T_a) = \rho c \frac{\partial T}{\partial t}
\]

3.1.10
Figure 3.1 From the consideration of the conservation of thermal energy within a control volume of tissue one can derive the Bio-heat equation.
Chapter 3.2 Steady-state Solution to the Bio-heat Equation in one Cartesian dimension

Before proceeding with the detailed solution to the coupled probe-tissue heat transfer problem an overview of the problem and solution method will be presented. In the introduction to this chapter it was stated that the goal of the thermal modeling was to find an expression relating perfusion, supplied power and imposed temperature increment. It is known that power is supplied to the flake thermistor so that the volume average temperature of the thermistor is maintained constant.

Solution of the coupled probe-tissue heat transfer problem will yield the temperature in the flake, \( T_f \), as a function of supplied power, \( p \), time, \( t \), temperature increment, \( \Delta T \), and perfusion, \( w \). Thus let \( T_f(p,t,w) \) be the notation used to denote the temperature in the flake thermistor. Therefore, the volume average temperature increment of the heated thermistor, denoted by \( \Delta T \), is defined by:

\[
\Delta T = \frac{1}{\text{flake volume}} \int \frac{T_f(p,t,w) - T_0}{V} \ dv
\]

3.2.1

Because 1) \( \Delta T \) is pre-determined, 2) power is measured, 3) the initial baseline temperature of the thermistor, \( T_0 \), is known, and 4) the volume of the thermistor flake is known, the only unknown in equation 3.2.1 is perfusion, \( w \). Thus from equation 3.2.1 an expression for perfusion as a function of supplied power can be obtained.
3.2.1 The Governing Equations

In order to determine the temperature profile in the flake thermistor and in the abutting medium the probe-tissue system was modeled as shown in Figure 3.2. One should note that the flake extends from \( x=0 \) to \( x=a \) and the abutting tissue medium extends from \( x=a \) to \( x=\infty \). In order to determine the heat transfer properties of this system one must write a governing equation for each region. Thus writing the heat conduction equation for the flake thermistor and the Bio-heat equation for the tissue one gets:

\[
\nabla^2 T_f + \frac{G_f}{K_f} = \frac{1}{\alpha_f} \frac{\partial T_f}{\partial t} \quad \text{in the flake} \quad \text{3.2.1.1}
\]

\[
\nabla^2 T_m + \frac{G_m}{C_m} = \frac{1}{\alpha_m} \frac{\partial T_m}{\partial t} \quad \text{in the medium} \quad \text{3.2.1.2}
\]

Where

1) \( T_f \) is the temperature in the flake thermistor

2) \( T_m \) is the temperature in the abutting medium,

3) \( G_f \) is the heat generated in the flake, and

4) \( G_m \) is the heat generated in the abutting medium,
Consider the following:

1) steady-state conditions, that is \( t = \infty \),

2) \( G_f = \Gamma \),

3) \( G_m = G_{\text{met}} - w c_{b1} (T_m - T_a) \),

4) \( V_f = T_f - T_o \),

5) \( V_m = T_m - T_o \),

and 6) \( G_{\text{met}} = w c_{b1} (T_o - T_a) \).

Conditions 2, 4, and 5 are notational definitions. Condition 3 is credited to Pennes [40]. Condition 6 follows from the argument that in the steady-state all heat generated by metabolic processes is carried away by perfusion. Condition 1 will be used to find, first run, steady-state, solution to the heat transfer problem.

Given the above conditions one can rewrite equation 3.2.1.1 and 3.2.1.2:

\[
\frac{\partial^2 v_f}{\partial x^2} + \frac{\Gamma}{K_f} = 0 \quad a \leq x \tag{3.2.1.3}
\]

\[
\frac{\partial^2 v_m}{\partial x^2} - w c_{b1} \frac{v_m}{K_m} = 0 \quad x \geq a \tag{3.2.1.4}
\]
3.2.2 Boundary Conditions

In order to solve equations 3.2.1.3 and 3.2.1.4 four boundary conditions must be considered. Continuity of temperature and heat flux is required at the probe-tissue interface. Thus:

$$\#1 \quad V_f = V_m \quad \text{at} \ x = a$$

3.2.2.1

$$\#2 \quad K_f \frac{\partial V_f}{\partial x} = K_m \frac{\partial V_m}{\partial x} \quad \text{at} \ x = a$$

3.2.2.2

Note: it is assumed that any thermal contact resistance is negligible. It is assumed that far away from the probe, at $x = \infty$, the medium is unperturbed by the heated thermistor flake. Thus:

$$\#3 \quad V_m = 0 \quad \text{at} \ x = \infty$$

3.2.2.3

Finally, because 1) the probe consists of two flake thermistors mounted back-to-back, and 2) both thermistors are heated to the same temperature, an adiabatic boundary exists at $x = 0$. Thus:

$$\#4 \quad \frac{\partial V_f}{\partial x} = 0 \quad \text{at} \ x = 0$$

3.2.2.4
3.2.3 Solution of the Ordinary Differential Equation

The general solution to equation 3.2.1.3 is:

\[ v_f(x) = -\frac{\Gamma}{2K_f} x^2 + Ax + B \]  \hspace{1cm} 3.2.3.1

The general solution to equation 3.2.1.4 is:

\[ v_m(x) = Ce^{nx} + De^{-nx} \]  \hspace{1cm} 3.2.3.2

where

\[ n = \sqrt{\omega \frac{c_{bl}}{K_m}} \]  \hspace{1cm} 3.2.3.3

Boundary condition 3 requires that \( C = 0 \).

Boundary condition 4 requires that \( A = 0 \).

Applying boundary condition 1 and 2 one finds that:

\[ V_f = -\frac{\Gamma x^2}{2K_f} + \frac{\Gamma a^2}{K_m} \left[ \frac{K_m}{\omega c_{bl} a^2} + \frac{K_m}{2K_f} \right] x < a \]  \hspace{1cm} 3.2.3.5

\[ V_m = \frac{\Gamma a}{\sqrt{\omega c_{bl} K_m}} e^{(a-x)\sqrt{\omega c_{bl} / K_m}} \]  \hspace{1cm} x > a  \hspace{1cm} 3.2.3.6
3.2.4 Results

Given the solution of the steady state heat transfer problem one can now find a theoretical expression for perfusion. First, one knows that power is applied to the thermistor so as to maintain a volume average temperature, $\Delta T$, within the flake thermistor. Thus:

$$\Delta T = \frac{1}{a b^2} \int_{0}^{a} b^2 V_f(x) \, dx \quad \text{3.2.4.1}$$

Using equation 3.2.3.5 and solving the integral one finds:

$$\Delta T = -\frac{\Gamma a^2}{6 K_f} + \frac{\Gamma a^2}{K_m} \left[ \frac{K_m}{\sqrt{w} c_{b1} K_m} + \frac{K_m}{2K_f} \right] \quad \text{3.2.4.2}$$

solving for $w$:

$$w = \frac{1}{K_m c_{b1}} \left[ \frac{3 \Gamma a K_f}{3 K_f \Delta T - \Gamma a^2} \right]^2 \quad \text{3.2.4.3}$$

Thus assuming we know $K_m$, $a$, $K_f$, and $c_{b1}$ we can quantify perfusion from a measurement of steady-state power for a given applied $\Delta T$.

Solving equation 3.2.4.3 for $\Gamma$ one finds:

$$\Gamma = \frac{3 K_f \Delta T \sqrt{w} c_{b1} K_m}{3 a K_f + a^2 \sqrt{w} c_{b1} K_m} \quad \text{3.2.4.4}$$
Figure 3.3 shows how power varies with perfusion. Note the sensitivity, the slope of the curve in Figure 3.3, is greatest for low perfusions. Using the relationship between perfusion and power, equation 3.2.4.3, and the equation for $V_f(x)$, equation 3.2.3.5, and $V_m(x)$, equation 3.2.3.6, the exact calculation of temperature profiles is possible. Figure 3.4 shows the effect of various perfusion rates on the temperature profile within the perfused tissue. Note that, depending upon the perfusion level, at 0.5 cm the temperature is approximately 25% to 35% of the value at the thermistor surface. Thus in order to maintain a condition with one-dimensional heat flow the thermistor probe size must be much greater than 0.5 cm. Another way to view this situation is to recognize the spatial decay constant in equation 3.2.3.6,

$$\delta \sim \sqrt{\frac{K_m}{m c_{bl}}}$$ \hspace{1cm} 3.2.4.5

Thus a constraint of a typical thermistor probe dimension, $x$, is that,

$$x \gg \delta$$ \hspace{1cm} 3.2.4.6

in order to have one-dimensional heat flow.
Figure 3.5 shows the effect of various perfusion rates on the temperature profile within the thermistor. Note that the surface temperature (the temperature at $x = 0.01$ cm) is a strong function of perfusion. Prior to Bowman and Balasubramanium, investigators using self-heated thermistors assumed the thermistor to be a lumped thermal mass implying that the temperature profile within the heated thermistor was flat. This assumption apparently relegated thermal methods for the measurement of perfusion to that of qualitative methods. It was not until Bowman and Balasubramanium considered the thermistor as a distributed thermal mass, thus accounting for the temperature gradients which exist within the thermistor, that perfusion could be quantified using the self-heated invasive thermistor probe technique [25,26].
Figure 3.2 Schematic of the one-dimensional Cartesian heat flow problem.
Figure 3.3 The relationship between the perfusion in the underlying tissue and the steady-state power requirement of the heated noninvasive thermistor. Notice that the sensitivity is greatest at low perfusion rates.
Figure 3.4 The effect of various perfusion rates on the temperature profile within the perfused tissue. Notice that approximately 0.5cm into the tissue the temperature is approximately 25-35% of the temperature at the thermistor surface.
Figure 3.5 The effect of various perfusion rates on the temperature profile within the heated thermistor. The thermistor extends from 0.0 to 0.01cm.
Chapter 3.3 Transient Solution to the Bio-heat Equation in one Cartesian Dimension

This section deals with the complete solution to the coupled probe-tissue heat transfer problem. The preceding section detailed the steady-state solution to this problem. It was shown that from knowledge of the steady-state power requirement, quantification of perfusion was possible. However, one cannot always wait for steady-state conditions to be met; thus this section details a solution which yields the time shape of the applied power and thus an analytic means by which to calculate the steady-state power requirements from a transient measure of applied power.

The transient solution of the coupled probe-tissue model involves six major steps: 1) consideration of the governing equations, 2) description of boundary and initial conditions, 3) Laplace transform of the governing equations, 4) solution of the ordinary differential equations, 5) inverse Laplace transform, and 6) the $\Gamma$ versus $\beta$ relationship.
3.3.1 The Governing Equations

The governing equations were derived in chapter 3.1 and presented in chapter 3.2. They are repeated here for the sake of clarity.

\[ \nabla^2 T_f + \frac{G_f}{K_f} = \frac{1}{\alpha_f} \frac{\partial T_f}{\partial t} \quad \text{in the flake} \]

(3.3.1.1)

\[ \nabla^2 T_m + \frac{G_m}{K_m} = \frac{1}{\alpha_m} \frac{\partial T_m}{\partial t} \quad \text{in the medium} \]

(3.3.1.2)

3.3.2 Boundary and Initial Conditions

The boundary conditions for the transient problem are the same as those for the steady-state problem:

1. \[ V_f = V_m \quad \text{at } x = a \]

(3.3.2.1)

2. \[ K_f \frac{\partial V_f}{\partial x} = K_m \frac{\partial V_m}{\partial x} \quad \text{at } x = a \]

(3.3.2.2)

3. \[ V_m = 0 \quad \text{at } x = \infty \]

(3.3.2.3)

4. \[ \frac{\partial V_f}{\partial x} = 0 \quad \text{at } x = 0 \]

(3.3.2.4)

The initial conditions are initial rest conditions:

\[ V_m = 0 \quad \text{at } t = 0 \]

(3.3.2.5)

\[ V_f = 0 \quad \text{at } t = 0 \]

(3.3.2.6)
3.3.3 The Laplace transform

In order to solve this heat transfer problem, first the governing equations are converted from second order partial differential equations to second order ordinary differential equations using the unilateral Laplace transform. One recalls the definition of the unilateral Laplace transform:

\[ \mathcal{L}\{v(t)\} = \mathcal{L}\{v(t)\} = \int_0^a e^{-st} v(t) \, dt \]  

(3.3.3.1)

Thus from equations (3.3.1.1) and (3.3.1.2) one derives:

\[ \frac{d^2 \tilde{v}_f(x,s)}{dx^2} + \frac{\Gamma}{K_f} + \frac{\beta}{K_f} F(s) = \frac{1}{\alpha_f} [s\tilde{v}(x,s) - v_f(t=0^+)] \]

(3.3.3.2)

\[ \frac{d^2 \tilde{v}_m(x,s)}{dx^2} = \frac{W \, c_p \, \tilde{v}_m(x,s)}{K_m} = \frac{1}{\alpha_m} [s\tilde{v}_m(x,s) - v_m(t=0^-)] \]

(3.3.3.3)
3.3.4 Solution of the Ordinary Differential Equations

Using the initial conditions one finds that the general solution to equations (3.3.3.2) and (3.3.3.3) is:

\[ v_f(x,s) = c_{f1} e^{+ x q_f(s)} + c_{f2} e^{- x q_f(s)} + \frac{\alpha_f}{K_f s^2} \left[ \Gamma + 3 s F(s) \right] \]  
\[ (3.3.4.1) \]

\[ v_m(x,s) = c_{m1} e^{+ x q_m(s)} + c_{m2} e^{- x q_m(s)} \]  
\[ (3.3.4.2) \]

where

1) \( q_f(s) = \frac{\sqrt{s}}{\alpha_f} \)  
\[ (3.3.4.3) \]

and 2) \( q_m(s) = \frac{\sqrt{\omega}}{c_{bl}/K_m + s/\alpha_m} \)  
\[ (3.3.4.4) \]

Application of the four boundary conditions completes the solution to the ordinary differential equation. One finds:

\[ c_{f1} = c_{f2} = \frac{-X(s)}{\cosh[a q_f(s)] + \frac{q_f(s) K_f}{q_m(s) K_m} \sinh[a q_f(s)]} \]  
\[ (3.3.4.5) \]

\[ c_{m1} = 0 \]  
\[ (3.3.4.6) \]

\[ c_{m2} = \frac{X(s) \frac{q_f(s) K_f}{q_m(s) K_m} e^{a q_m(s)} \sinh[a q_f(s)]}{\cosh[a q_f(s)] + \frac{q_f(s) K_f}{q_m(s) K_m} \sinh[a q_f(s)]} \]  
\[ (3.3.4.7) \]

where

\[ X(s) = \frac{\alpha_f}{s^2 K_f} \left[ \Gamma + s \beta F(s) \right] \]  
\[ (3.3.4.8) \]
In order to simplify the \( \psi_f \) expression let:

\[
\psi(x, s) = 1 - \frac{\cosh[a \ q_f(s)] + \frac{q_f(s)}{q_m(s)} \ \frac{K_f}{K_m} \ \sinh[a \ q_f(s)]}{\cosh[a \ q_f(s)]}
\]  

(3.3.4.9)

Thus

\[
\psi_f(x, s) = \left[ \frac{\alpha_f}{K_f} \ \frac{s}{\Gamma} + \frac{\alpha_f \ \beta}{K_f} \ F(s) \right] \ \psi(x, s) \ \text{for} \ x \leq a
\]  

(3.3.4.10)

3.3.5 **Inverse Laplace Transform**

The most difficult step in the solution to the coupled probe-tissue heat transfer problem is finding the inverse Laplace transform. Inverse transforms of \( \psi(s, x) \) cannot be found in standard tables of Laplace transforms [41,42]. For the case of the spherical \((4\pi\ \text{geometry})\) probe-tissue heat transfer problem, Balasubramaniam and Bowman obtained the inverse transform by preforming a contour intergration [25,26]. This method yielded an exact solution, however, one that was left in the form of an integral. More desirable is a closed-form solution. Valvano and Bowman obtained such a solution by expanding the hyperbolic functions in a power series, then performing a term-by-term inverse Laplace transform [30,31], perhaps at the suggestion of Carslaw and Jaeger [37 pg. 264]. This section details this latter method as applied to the Cartesian one-dimensional heat transfer problem.
In order to simplify the algebraic manipulations, the scaling property of Laplace transforms is invoked:

\[ \mathcal{L} \left[ \gamma_f v_f(\gamma_f t) \right] = \tilde{v}_f(s/\gamma_f) \quad (3.3.5.1) \]

Thus let

\[ \gamma_f = a^2/\alpha_f \quad (3.3.5.2) \]

and one finds:

\[ q_f(s/\gamma_f) = \sqrt{s}/a \quad (3.3.5.3) \]

\[ q_m(s/\gamma_f) = \sqrt{\alpha_f \alpha_m} \frac{\sqrt{z + s}}{a} \quad (3.3.5.4) \]

where

\[ z = \frac{w c b l a^2}{K_m} \frac{\alpha_m}{\alpha_f} \quad (3.3.5.5) \]

Therefore

\[ \psi(s/\gamma_f, x) = 1 - \frac{\cosh \frac{x}{a} \sqrt{s}}{\cosh \sqrt{s} + \sqrt{\frac{K_m}{K_f}} \frac{K_m}{K_f} \frac{s}{z + s} \sinh \sqrt{s}} \quad (3.3.5.6) \]
\( \psi(s/\gamma_f, x) \) will be expanded in a series of the form:

\[
\psi(s/\gamma_f, x) = \sum_{n=0}^{N} \psi_n(x) s^{n/2}
\]  \hspace{1cm} (3.3.5.7)

let

\[
\psi(s/\gamma_f, x) = 1 - \beta(s)
\]  \hspace{1cm} (3.3.5.8)

where

\[
\beta(s) = \frac{\sqrt{z+s} \cosh \frac{x}{a} \sqrt{s}}{\sqrt{z+s} \cosh \sqrt{s} + \frac{K_f}{K_m} \sqrt{\frac{\alpha_m}{\alpha_f}} \sqrt{s} \sinh \sqrt{s}}
\]  \hspace{1cm} (3.3.5.9)

or

\[
\beta(s) = \frac{\sqrt{z+s} A(s)}{\sqrt{z+s} B(s) + D(s)}
\]  \hspace{1cm} (3.3.5.10)

where

\[
A(s) = \cosh \frac{x}{a} \sqrt{s} = 1 + \frac{c_2}{2!} s + \frac{c_4}{4!} s^2 + \ldots
\]  \hspace{1cm} (3.3.5.11)

\[
B(s) = \cosh \sqrt{s} = 1 + s/2 + s^2/4! + \ldots
\]  \hspace{1cm} (3.3.5.12)

\[
D(s) = c_1 \sqrt{s} \sinh \sqrt{s} = c_1 s + \frac{c_1}{3!} s^2 + \frac{c_1}{5!} s^3 + \ldots
\]  \hspace{1cm} (3.3.5.13)

where

\[
c_1 = \frac{K_f}{K_m} \sqrt{\frac{\alpha_m}{\alpha_f}}
\]  \hspace{1cm} (3.3.5.14a)

\[
c_2 = x/a
\]  \hspace{1cm} (3.3.5.14b)
Eliminating the $\sqrt{s + z}$ term from the denominator

$$\beta(s) = \frac{(z + s) A(s) B(s) - \sqrt{z + s} A(s) D(s)}{(z + s) B^2(s) - D^2(s)}$$  \hspace{1cm} (3.3.5.15)

Equation 3.3.5.15 is next reduced from a ratio of series to the sum of two series:

$$\beta(s) = \frac{E(s) + \sqrt{z + s} F(s)}{G(s)}$$  \hspace{1cm} (3.3.5.16)

$$\beta(s) = \frac{E(s)}{G(s)} + \frac{\sqrt{z + s} F(s)}{G(s)}$$  \hspace{1cm} (3.3.5.17)

$$\beta(s) = H(s) + \sqrt{z + s} I(s)$$  \hspace{1cm} (3.3.5.18)

Given the notation:

$$\psi(s/\gamma F, x) = \psi_0 + \psi_1 \sqrt{z + s} + \psi_2 s + \psi_3 s \sqrt{z + s} + \ldots$$  \hspace{1cm} (3.3.5.19)

and remembering that

$$\psi = 1 - \beta(s)$$  \hspace{1cm} (3.3.5.20)
one finds that

$$\psi_0 = 1 - h_0 = 0$$  \hspace{1cm} (3.3.5.21)

$$\psi_1 = -i_0 = 0$$

$$\psi_2 = -h_1 = 1/2 - x^2/2a^2$$  \hspace{1cm} (3.3.5.22)

$$\psi_3 = -i_1 = c_1/z$$  \hspace{1cm} (3.3.5.23)

$$\psi_4 = -h_2 = \frac{x^2}{2a^2} - \frac{x^4}{24a^4} - \frac{5}{24} - \frac{x^2}{za^2}$$  \hspace{1cm} (3.3.5.24)

$$\psi_5 = -i_2 = \frac{c_1}{z} \left[ \frac{x^2}{2a^2} - \frac{5}{6} - \frac{1}{z} \right]$$  \hspace{1cm} (3.3.5.25)

Using the above coefficients one can write equation (3.3.4.10) in the form of a power series. The $\psi_2$ term of equation (3.3.4.10) can be written:

$$\bar{v}(s/\gamma_f, x) \psi_2 = \frac{\alpha_f}{K_f} \Gamma \gamma_f \frac{\psi_2}{s} + \frac{\alpha_f \gamma_f}{K_f} \beta \frac{F(s/\gamma_f)}{\psi_2}$$  \hspace{1cm} (3.3.5.27)
The inverse Laplace transform of the first term on the right-hand-side is found using

\[ \mathcal{L}^{-1}[1/s] = u_{-1}(t) \quad \text{(the step function)} \quad (3.3.5.28) \]

\[ \mathcal{L}[\gamma_f v_f(\gamma_f, t)] = \tilde{v}_f(s/\gamma_f) \quad (3.3.5.29) \]

One finds

\[ v_f(x, t) \psi_2, \Gamma = \frac{\Gamma a^2}{2 K_f} \left( 1 - \frac{x^2}{a^2} \right) u_{-1}(t) \quad (3.3.5.30) \]

The second term on the right-hand-side cannot be inverted until \( F(s) \) is known.

One can write the \( \psi_3 \) term of equation (3.3.4.10):

\[ \tilde{v}(s/\gamma_f, x) \psi_3 = \frac{\alpha_f}{K_f} \Gamma \gamma_f^2 \left[ \frac{1}{s^2} \psi_3 s \sqrt{z + s} \right] \]

\[ + \frac{\alpha_f \gamma_f \beta F(s/\gamma_f)}{K_f s} \psi_3 s \sqrt{z + s} \quad (3.3.5.31) \]

The first term on the right-hand-side can be inverted using [41]

\[ \mathcal{L}^{-1} \left[ \frac{\sqrt{z + s}}{s} \right] = \sqrt{z} + \frac{e^{-zt}}{\sqrt{\pi t}} \]

\[ + \sqrt{z} \left[ \text{erf}\sqrt{zt} - 1 \right] \quad (3.3.5.32) \]
Thus one finds:

\[ v_f(x,t) \psi_3, \Gamma = \sqrt{\frac{\Gamma}{\alpha_m}} w_c b_l \frac{\sqrt{\frac{w_c b_l \alpha_m}{K_m}}} e^{-\left( \frac{w_c b_l \alpha_m t}{K_m} \right)} \left\{ - \frac{w_c b_l K_m}{K_m} \text{erfc} \sqrt{\frac{w_c b_l \alpha_m t}{K_m}} \right\} \]

(3.3.5.33)

The second term on the right-hand-side of equation 3.3.5.31 cannot be inverted until \( F(s) \) is known.

The \( \psi_4 \) term of equation (3.3.4.10) is:

\[ -v_f(s/\gamma_f, x) \psi_4 = \frac{\alpha_f}{K_f} \Gamma \gamma_f^2 \psi_4 + \frac{\alpha_f \gamma_f \beta}{K_f} s F(s/\gamma_f) \psi_4 \]

(3.3.5.34)

but it is known that:

\[ \mathcal{L}^{-1}[1] = u_0(t) \quad \text{(the impulse function)} \]

(3.3.5.35)

Thus, because events that occur at time \( t = 0 \) are ignored let:

\[ v_f(x, t) \psi_4, \Gamma = 0 \]

(3.3.5.36)

Higher order terms \( \psi_5, \psi_6, \ldots \) are ignored because they represent less significant terms.
The contribution to $V_f$ of the constant application of power, $\Gamma$, is now known. In order to identify $f(t)$, or $F(s)$, $V_f(x,t)$ was divided into two parts: a steady-state part, $V_f(x,t)_{ss}$, and a transient part, $V_f(x,t)_{\text{trans}}$. Thus:

$$v_f(x,t)_{ss} = \frac{\Gamma}{2K_f} (a^2 - x^2) + \frac{\Gamma a}{\sqrt{w c b l m}}$$  \hspace{1cm} (3.3.5.37)

(which is exactly the same as that derived in chapter 3.2), and

$$v_f(x,t)_{\text{trans}} = \frac{\Gamma a}{\sqrt{\alpha_m \pi w c b l}} e^{-\frac{\alpha_m t}{K_m}} - \frac{\Gamma a}{\sqrt{w c b l m}} \text{erfc} \sqrt{-\frac{w c b l \alpha_m t^3}{K_m}}$$  \hspace{1cm} (3.3.5.38)

Let

$$\tau = \frac{K_m}{w c b l \alpha_m}$$  \hspace{1cm} (3.3.5.39)

Therefore one can write

$$v_f(x,t)_{\text{trans}} = \frac{\Gamma a}{w c b l \sqrt{\alpha_m \pi}} \left[ \frac{e^{-t/\tau}}{\sqrt{\tau}} - \sqrt{\pi} \text{erfc} \sqrt{t/\tau} \right]$$  \hspace{1cm} (3.3.5.40)
In order to find $f(t)$ it was noted that the volume average temperature step, $\bar{v}_f^{\text{total}}$, is composed of three parts (one steady-state, and two transient):

$$\bar{v}_f^{\text{total}} = \bar{v}_f^{\Gamma_{\text{ss}}} + \bar{v}_f^{\Gamma_{\text{trans}}} + \bar{v}_f^{\beta} \quad (3.3.5.41)$$

[Note, by definition:

$$\bar{v}_f^{\text{total}} = \frac{1}{a^2 b^2} \int_0^a \int_0^b v_f^{\text{total}}(x,t) \, dx$$

$$(3.3.5.42)$$]

In the steady-state one sees that

$$\bar{v}_f^{\text{total}} = \bar{v}_f^{\Gamma_{\text{ss}}} \quad (3.3.5.43)$$

Thus for all time

$$\bar{v}_f^{\Gamma_{\text{trans}}} = -\bar{v}_f^{\beta} \quad (3.3.5.44)$$

The time shape of the $\Gamma_{\text{trans}}$ term must therefore be the same as that for the $\beta$ term. From Equation 3.3.5.40 one sees that the functional form of the time shape of power application is:

$$f(t) \sim \frac{e^{-t/\tau}}{\sqrt{\pi}} - \sqrt{\frac{\pi}{\tau}} \text{erfc}\sqrt{t/\tau} \quad (3.3.5.45)$$
thus

\[ F(s) = \frac{\sqrt{\pi}}{\sqrt{s + 1/\tau}} - \sqrt{\frac{\tau}{s}} \left( \frac{\sqrt{s + 1/\tau} - \sqrt{1/\tau}}{s} \right) \]  

\[ (3.3.5.46) \]

or

\[ F(s) = \sqrt{\pi} \left[ \frac{\sqrt{s + 1/\tau} - \sqrt{1/\tau}}{s} \right] \]  

\[ (3.3.5.47) \]

Plugging equation (3.3.5.47) back into the \( \beta \) terms of equations (3.3.5.27) and (3.3.5.31) and after some algebra and a transformation from the Laplace domain to the time domain one finds:

\[ v_f(x, t)_\beta = \frac{a^2 \beta}{K_f} f(t) \left[ (1/2 - x^2/2a^2) - \frac{k_m}{a \sqrt{\pi} \cdot b_1 \cdot k_m} \right] \]  

\[ (3.3.5.48) \]

The inverse Laplace transform of equation (3.3.4.2) is found in a similar manner. That is, \( V_m(x, s) \) is expanded in a series resulting in the expression of \( V_m(x, s/y_m) \) as the product of three series:

\[ \tilde{V}_m(s/y_m, x) = c_1 \left[ \frac{a_f}{K_f} \frac{\gamma_m^2}{s^2} \left( \Gamma + \sqrt{\frac{\pi}{\gamma_m}} \beta \sqrt{s + \gamma_m / \tau} - \sqrt{\frac{\pi}{\tau}} \beta \right) \right] \]

\[ \cdot \left[ \frac{\sqrt{a_f}}{\sqrt{\gamma_m}} \frac{\sqrt{z}}{a} \left( 1 + \frac{b}{2 \sqrt{z}} s + \frac{b^2}{8 z^{3/2}} s^2 \right) \right] \]

\[ \cdot \left[ \frac{s \sqrt{z} + s}{z} - \frac{c_1 s^2}{z} + \frac{3 - z}{3 z^2} s^2 \sqrt{z} + s \right. \]

\[ + \frac{c_1 (2z + 3) s^3}{3 z^2} \left] \right. \]  

\[ (3.3.5.49) \]
where

\[ b = (a - x) \frac{1}{a} \sqrt{\frac{\alpha_f}{\alpha_m}} \]  

\[ c_1 = \frac{K_f}{K_m} \sqrt{\frac{\alpha_m}{\alpha_f}} \]  

\[ z = \frac{w \ c_{bl} \ a^2 \ \alpha_m}{K_m \ \alpha_f} \]  

\[ \tau = \frac{K_m}{w \ c_{bl} \ \alpha_m} \]  

\[ \gamma_m = \frac{a^2}{\alpha_f} \]  

\[ z = \gamma_m / \tau \]  

\[ V_m(x, s/\gamma_m) \text{ is next expressed as the sum of two parts} \]

\[ \tilde{v}_m(s/\gamma_m, x) = \tilde{v}_{m\Gamma}(s/\gamma_m, x) + \tilde{v}_{m\beta}(s/\gamma_m, x) \]
Each of these parts is transformed term-by-term from the Laplace domain to the time domain. Thus:

\[ v_{m_{\text{ss}}} = \Gamma_a e^{\frac{(a - x) \sqrt{w c_{bl}}}{K_m}} \]  \hspace{1cm} (3.3.5.57)

\[ v_{m_{\text{trans}}} = \Gamma_a e^{\frac{(a - x) \sqrt{w c_{bl}}}{w c_{bl} \sqrt{\alpha_m \pi}} f(t)} \]  \hspace{1cm} (3.3.5.58)

and

\[ v_{m_{\beta}} = \frac{-a \beta e^{b\sqrt{z}}}{\sqrt{K_m w c_{bl}}} f(t) \]  \hspace{1cm} (3.3.5.59)

Remember

\[ f(t) = \frac{1}{\sqrt{\pi}} e^{-\frac{w c_{bl} \alpha m t}{K_m}} - \sqrt{\frac{w c_{bl} \alpha m}{K_m}} \text{erfc} \sqrt{\frac{w c_{bl} \alpha m t}{K_m}} \]  \hspace{1cm} (3.3.5.60)

Note that for clarity the \( \Gamma \) term was expressed as the sum of two terms, a steady-state term and a transient term. Further, all terms containing powers of \( t^{-3/2} \) or less were discarded (e.g. \( t^{-3/2}, t^{-2}, t^{-5/2}, ... \) )
3.3.6 The $\Gamma$ versus $\beta$ Relationship

In order to complete the solution a relationship among $\Gamma$, $\beta$ and thermal properties must be found. From the solution of the steady-state problem an analytic expression for $\Gamma$ in terms of thermal properties was derived (see also equation 3.2.1.17):

$$
\Gamma = \frac{3K_f \Delta T \sqrt{w} c_{bl} K_m}{3a K_f + a^2 \sqrt{w} c_{bl} K_m}
$$

(3.3.6.1)

Further, it was shown (chapter 3.3.5) that:

$$
\ddot{\nu}_f_{\Gamma_{\text{trans}}} = - \ddot{\nu}_f_{\beta}
$$

(3.3.6.2)

from which a relationship between $\Gamma$ and $\beta$ can be found. Recall equation (3.3.5.40):

$$
\nu_f_{\Gamma_{\text{trans}}} (x,t) = \frac{\Gamma a}{w c_{bl} \sqrt{\alpha \pi}} \left[ \frac{e^{-t/\tau}}{\sqrt{\tau}} - \sqrt{\frac{\pi}{\tau}} \text{erfc}(\sqrt{t/\tau}) \right]
$$

(3.3.6.3)

Thus

$$
\ddot{\nu}_f_{\Gamma_{\text{trans}}} = \frac{\Gamma a}{w c_{bl} \sqrt{\alpha \pi}} f(t)
$$

(3.3.6.4)
Further recall equation (3.3.5.48):

\[ v_f(x, t)_\beta = \frac{a^2 \beta}{K_f} f(t) \left[ \frac{1}{2} - \frac{x^2}{2a^2} \right] - \frac{K_m}{a \sqrt{\omega c_{bl} K_m}} \]

(3.3.6.5)

Thus

\[ \tilde{v}_f = \frac{a^2 \beta}{K_f} f(t) \left[ \frac{1}{3} - \frac{K_f}{a \sqrt{\omega c_{bl} K_m}} \right] \]

(3.3.6.6)

From equations (3.3.6.2), (3.3.6.4), and (3.3.6.6) one can derive:

\[ \Gamma/\beta = \frac{\sqrt{\alpha m \pi}}{K_f K_m} \left[ 3 K_f \sqrt{\omega c_{bl} K_m} - a \omega c_{bl} K_m \right] \]

(3.3.6.7)
In conclusion, the approximate complete solution to the Cartesian one-dimensional coupled probe-tissue heat transfer problem is:

\[ v_f(x,t) = \frac{\Gamma}{2k_f} \left( a^2 - x^2 \right) + \frac{\Gamma a}{\sqrt{wc_bk_m}} \]

\[ + f(t) \left[ \frac{\Gamma a}{wc_b\alpha_m\pi} + \frac{a^2\beta}{2k_f} \left( 1 - \frac{x^2}{a^2} - \frac{2k_f}{a\sqrt{wc_bk_m}} \right) \right] \]

\[ 0 < x < a \]

(3.3.6.8)

\[ v_m(x,t) = \frac{ae^{(a-x)\sqrt{wc_bk_m}}}{\sqrt{wc_bk_m}} \left[ \Gamma + f(t) \left( \Gamma \sqrt{\frac{k_m}{wc_b\alpha_m\pi}} - \beta \right) \right] \]

\[ x > a \]

(3.3.6.9)

where

\[ f(t) = \frac{\sqrt{wc_b\alpha_m}}{e^{\frac{km}{k_m}}} t - \sqrt{\frac{wc_b\alpha_m\pi}{km}} \text{erfc} \sqrt{\frac{wc_b\alpha_m}{km}} t \]

(3.3.6.10)

\[ \Gamma = \frac{3K_f\Delta T}{3aK_f + a^2\sqrt{wc_bK_m}} \]

(3.3.6.11)

\[ \Gamma/\beta = \frac{\sqrt{\alpha_m\pi}}{K_fK_m} \left[ 3K_f\sqrt{wc_bK_m} - awc_bK_m \right] \]

(3.3.6.12)
3.3.7 The Limiting Case of an Unperfused Medium

An unperfused medium represents a limiting case where intuition does not necessarily yield correct answers. First, consider the limit of $\Gamma$ as perfusion approaches zero.

$$\lim_{w \to 0} \Gamma = \frac{\Delta T}{\sqrt{w} \ c_{b1} \ K_m} \frac{a}{1} = 0 \quad (3.3.7.1)$$

Thus as perfusion approaches zero the power required to maintain the thermistor at a constant temperature, $\Delta T$, is zero. Next consider,

$$\lim_{w \to 0} f(t) = t^{-1/2} \quad (3.3.7.2)$$

Thus as time increases one finds:

$$\lim_{w \to 0} \lim_{t \to \infty} v_f(x, t) = \frac{\Gamma a}{\sqrt{w} \ c_{b1} \ K_m} = \frac{\Delta T}{\sqrt{w} \ c_{b1} \ K_m} \frac{a}{1} = \Delta T \quad (3.3.7.3)$$

and

$$\lim_{w \to 0} \lim_{t \to \infty} v_m(x, t) = \frac{\Gamma a}{\sqrt{w} \ c_{b1} \ K_m} e^{(a - x) \sqrt{w} \ c_{b1} / K_m} \quad (3.3.7.4)$$

Thus in the steady-state, if the medium is unperfused then the entire region reaches a constant temperature, $\Delta T$. Consider a more familiar diffusion problem; an infinitely long, infinitesimally thin tank is filled with water. Dye is injected at one end, i.e. at $x = 0$. The dye diffuses through the unstirred water by a process similar to the
diffusion of heat through the unperfused tissue medium. The concentration of dye at \( x = 0 \) is held constant; with time the concentration of dye increases at every point \( x > 0 \). As time approaches infinity, the concentration of dye at each point approaches a maximum, i.e. the concentration at the point \( x_i \) approaches the concentration at the point \( x = 0 \). See Figure 3.6.

In conclusion, the derivation of an approximate closed-form solution to the Cartesian one-dimensional coupled probe-tissue heat transfer problem has been shown. The solution allows for the calculation of thermal profiles and power requirements as a function of the thermal properties and perfusion of the abutting tissue medium. One should remember that a closed-form solution was obtained using series expansion techniques and thus is not exact. The degree of mathematical accuracy required is naturally a function of the degree to which the model fits the physical system. In the following chapter initial test results and the correlation of those results with the above analytical model will be discussed.
Figure 3.6 The relationship between dye concentration and linear distance at various times. For time < 0 the concentration of the dye is everywhere zero. At time t=0 the concentration of the dye at X=0 is fixed. As time increases the increases at every point X > 0 within the tank. Thus the concentration at every point X > 0 slowly approaches the concentration at X=0.
Chapter 4 Initial Noninvasive Probe Testing

In the preceding chapter a theoretical basis was presented with which to analyze the results of experiments. In this chapter these initial experimental findings will be presented and analyzed. First, however, in order to offer a basis of comparison the experimental results obtained using the invasive probe will be discussed.

4.1 Review of Invasive Probe Results

Both an exact open-form solution [25,26] and an approximate closed-form solution [30,31] have been obtained for the invasive probe thermal model. From these solutions the calculation of thermal conductivity, thermal diffusivity, and perfusion can be made from the measurement of supplied power. In particular, it has been shown that:

$$K_{\text{eff}} = \frac{1}{4 \pi \Delta T a_b R_h V_{ss}^2 - 0.2/K_b}$$  \hspace{1cm} (4.1.1)

where $K_{\text{eff}}$ = effective (measured) thermal conductivity,
$\Delta T$ = applied temperature step,
$a_b$ = probe radius,
$R_h$ = heating resistance,
$V_{ss}$ = steady-state applied power, and
$K_b$ = probe thermal conductivity.

Further, it was shown by Valvano and Bowman [30,31] that the time shape of the applied power is:

$$f(t) = e^{-z''t} \sqrt{\frac{t}{\pi}} - \sqrt{\frac{z''t}{\pi}} \text{erfc}\sqrt{z''t}$$  \hspace{1cm} (4.1.2)
where

\[ \zeta'' = \frac{w c_{bl} \alpha_m}{K_c} \]  \hspace{1cm} (4.1.3)

Finally, it was shown [25,26,30,31] that a quantification of perfusion was possible from a measure of \( K_{\text{eff}} \):

\[ w = \frac{(K_{\text{eff}} - K_m)^2}{K_m c_{bl} a_b^2} \]  \hspace{1cm} (4.1.4)

where \( w = \) perfusion,

\( K_{\text{eff}} = \) effective (measured) thermal conductivity,

\( K_m = \) intrinsic tissue thermal conductivity,

\( c_{bl} = \) specific heat of blood, and

\( A_b = \) probe radius.

Thus by monitoring the time course of the power supplied to the invasive probe the quantification of thermal conductivity and perfusion is possible. Figure 4.1 shows a typical plot of power versus time \(-1/2\): one experiment was conducted in a perfused liver at \( w = 0.02 \, \text{gm/ml-s} = 100 \, \text{ml/100gm-min} \), the other experiment was conducted using the same probe with the same \( \Delta T \), in the same location, after the perfusion was interrupted. Note 1) the perfectly linear relationship for the unperfused liver and the nearly linear relationship for the slightly perfused liver; and 2) the perfusion induced increase in the steady-state power requirement of the probe. Data reduction is relatively straightforward. Referring to equation 4.1.1 one sees that the only parameter that is altered by the change in perfusion is \( V_{ss} \). Thus, increasing perfusion implies increasing \( V_{ss} \), which implies increasing \( K_{\text{eff}} \) which implies (see equation 4.1.4) increasing calculated perfusion.
The measurement procedure for a noninvasive probe would be the same; that is, monitor the probe power requirements for a relatively short period of time, calculate the steady-state voltage and power requirement, then calculate the perfusion from equation 3.2.4.3.
Figure 4.1 A plot of $voltage^2$ versus time$^{-1/2}$ for an invasive thermistor probe. Note that more power is required in the presence of perfusion. Also note the perfectly linear relationship in the no flow case and the slight deviation from linearity in the presence of perfusion.
4.2 Noninvasive Probe Tests

Initial noninvasive probe tests were conducted on probes of two different sizes, see Figure 4.2. One probe was fairly large with a typical thermistor size of approximately 0.6 cm by 0.6 cm; the other probe was smaller with a typical thermistor size of 0.1 cm by 0.1 cm. As one recalls from chapter 3.2, the solution of the one-dimensional thermal model indicated that a probe approximately 2 cm by 2 cm was necessary to insure one-dimensional heat flow. Thus the larger probes, when heated, may yield results conforming to the one-dimensional heat flow model. However, when these probes were tested it was found that the present instrumentation [29] could not supply the power necessary to instantaneously heat the thermistor to the required constant volume average temperature. Appendix B reveals that a quick theoretical calculation could have easily predicted this experimental finding. The smaller noninvasive probes were therefore tested. As one would expect (again see Appendix B) heating these probes in a step-like fashion does not take much power; however, these probes are much too small to approximate the Cartesian one-dimensional heat flow model; thus, the model presented in chapter 3 is invalid for these smaller probes.

The results of the initial tests with the smaller probes are however very enlightening. Figure 4.3 shows a typical plot of the power requirements of the smaller flake thermistor probes. A nonlinear relationship between power and time $^{-1/2}$ seems quite apparent. However, if one plots the exact same data using a different time window, see Figure 4.4, then one sees a quite linear relationship between power and time $^{-1/2}$. The result shown in Figure 4.4 is remarkably similar to that shown for the invasive probe in Figure 4.1. That is, after the
noninvasive probe has been heated for a period of time the power
requirements of the noninvasive probe are temporally identical to the
power requirements of a spherical invasive probe.

In order to understand this result, a spherical model for the
operation of the noninvasive flake thermistor probe was developed, see
Figure 4.5. The model hypothesis is that the surface thermistor heats
the right-half semi-infinite medium and the guarding flake heats the
left-half semi-infinite medium. The thermal wavefront that propagates as
a result of heating the thermistors is initially a planar wavefront;
however, with increasing time the wavefront evolves into a spherical
shape. Thus, the power required to heat the thermistor approaches the
time shape of that required to heat a truly spherical thermistor. That
is, with increasing time the power requirement becomes more proportional
to time$^{-1/2}$.

From a scaling argument point of view one can assert that as one
gets far from the probe the probe looks like a point source of heat,
thus, the thermal wavefront will be spherical. Or more rigorously, using
standard finite difference methods [43] one can show that the actual
wavefront approaches a spherical shape. See Figure 4.6. Appendix A
gives a brief outline of the method of finite difference analysis;
implementation considerations and raw data are also presented. Valvano
and Hayes using finite element analysis recently independently confirmed
the spherical nature of the propagating wavefront [54].

The results of these initial investigations indicated that there
were two basic routes that could be pursued.

1) The larger noninvasive thermistor probes could be used. These
probes would presumably provide one-dimensional heat flow, or
2) The smaller probes, which develop a spherical heat flow pattern, could be used.

The former route would require 1) building and debugging a system to power the larger probes, and 2) debugging the measurement transducer itself. The latter route would allow the use of the present instrumentation and data collection and reduction protocols to debug this new type of transducer. It was felt that utilization of previous efforts to aid the development of a transducer was of primary importance; thus, the latter route was chosen.
Figure 4.2 A sketch of an "overhead" view of the two different sizes of noninvasive flake thermistor probes. 

(Scale x10).
Figure 4.3 A plot of $V^2$ versus $t^{-1/2}$ for a noninvasive thermistor probe.
Figure 4.4 A plot of voltage^2 versus time^{-1/2} for a noninvasive flake thermistor probe. Note that if a time window is selected to exclude the first 15 seconds of data then a good fit of voltage^2 versus time^{-1/2} can be obtained.
Figure 4.5 Schematic of the proposed spherical model for the noninvasive probe. Note, because of the adiabatic boundary on the $X=0$ plane, flake FLO4 effectively heats only the right-half semi-infinite medium.
Figure 4.6 As derived using finite difference methods, the thermal wavefront produced by the heated noninvasive thermistor probe is plotted for various times. The actual wavefront is indicated by the dashed lines; a true spherical wavefront is indicated by the solid lines. Wavefront propagation was calculated using standard finite difference methods. Note, probe temperature is 4.0°C, wavefront temperature is 0.4°C.
Chapter 5 Evaluation of the Noninvasive Thermal Probe

The steps taken in the evaluation of the noninvasive thermal probe are evaluated in this chapter. In brief these steps are:

1) Probe design,
2) Resistance versus temperature calibration,
3) Thermal properties calibration,
4) Testing of the calibration, and
5) Testing of the perfusion quantification ability.

5.1 Probe Design

As mentioned in Chapter 2, the noninvasive probe consists of two thermistor flakes mounted back-to-back separated only by a thin dielectric film. This ensemble is further mounted on a supporting ceramic substrate, see Figure 2.1. [Manufactured by Thermometrics Inc., Edison, N.J. See also reference 44.] Figure 5.1 indicates the design used to stabilize the leads and the thermistors to the supporting base. A simple thermal test was employed to experimentally verify that this wiring pattern was used. The test was based on a measurement of the thermal time constant of each thermistor. Eloquent theory is not needed to recognize that if the entire probe is subjected to a sudden change in ambient temperature then because of the thermal mass of the supporting substrate the temperature of the guarding thermistor will change more slowly than that of the surface thermistor. Figure 5.2 shows the response for noninvasive probe FLR17/18.

The most critical part of the probe design was the protection of the probe from the environment. In brief, the insulation of the probe is vital because these probes are to be used in aqueous, ionic media.
Any conduction between the thermistors and the surrounding medium or between the thermistors themselves will impair the performance of the probe. Figure 5.3 shows a voltage $^2$ versus time $^{-1/2}$ plot of a well insulated probe; Figure 5.4 shows the results of a poorly insulated probe.

Several types of insulation were tested. The manufacturer applied RTWl12 (an electrical insulator) to one set of probes and an epoxy to the other set. This effort reduced the noise levels but not adequately. The epoxy used with the invasive probes [45] was then tried. Several techniques were investigated to achieve the best application of epoxy. Best results were obtained when the epoxy was diluted with acetone (3:1 acetone:epoxy). Each coat was smooth, clean, and thin (approximately 0.02 mm). Approximately five coats were applied to each probe by dipping the entire probe into the acetone-epoxy mixture. Ten minutes of drying time was allowed between application of each coat; twenty-four hours at approximately 100°F was allowed for a final cure. Application of several coats seems to eliminate the effect of pin-point holes. Separate tests indicated the only noxious effect of this insulation method was slight deterioration of the dielectric film by acetone. The resistance versus temperature characteristics of the thermistor flakes were unchanged by the insulation; thus, apparently the thermistors themselves were unaffected by the procedure.

This insulation functioned quite well and progress in the evaluation of the probe proceeded through steps 2, 3, and 4, as outlined. However, it was found that if a probe was left in an aqueous medium for greater than six hours then the probe function would deteriorate (noise would become a serious problem). Further, it was
discovered that the insulation cracked slightly with time near the edges of the supporting substrate. Thus it was concluded that a thin layer, 0.05cm, of latex (Manufacturer: Trenton Rubber Co., Trenton, NJ) stretched over the end of the probe would be useful. In addition, a desiccant, \( \text{CaSO}_4 \), was placed inside the latex sheath, far enough from the probe so as not to interfere with the measurement, yet close enough to absorb any water that may penetrate through the latex. This latter step seemed to adequately insulate the noninvasive probe. Figure 5.6 shows a cross-section of the probe in its final configuration.
Figure 5.1 A cross-section of the noninvasive probe showing the design used to stabilize the lead wires.
Figure 5.2 The temperature response of each thermistor in the noninvasive probe due to a step change in ambient temperature. Note that the surface thermistor, FLR18, responds more rapidly than the guarding thermistor, FLR17.
Figure 5.3 A plot of voltage$^2$ versus time$^{-1/2}$ for a minimally noisy flake thermistor probe.
Figure 5.4 A plot of voltage$^2$ versus time$^{-1/2}$ for a noisy flake thermistor probe.
Figure 5.5 A schematic cross-section of the fully insulated noninvasive flake thermistor probe.
Chapter 5.2 Resistance versus Temperature Calibration

The essence of the noninvasive thermal diffusion probe is a negative temperature coefficient (NTC) flake thermistor [44]. NTC thermistors are electrically resistive devices whose resistance varies inversely with temperature. Resistance is an electrical property of a material that can be easily and accurately measured. Thus, given the relationship between resistance and temperature for a given thermistor one can accurately determine the thermistor temperature from measured resistance. For NTC thermistors the resistance versus temperature curve can be well fit by a third order logarithmic equation:

\[
\frac{1}{T + 273.15} = H_0 + H_1 \ln(R) + H_3 [\ln(R)]^3
\]

5.2.1

where \( T \) is temperature in degrees Celsius, \( R \) is resistance in ohms, and \( H_0, H_1, \) and \( H_3 \) are empirically determined coefficients.

A probe is calibrated by immersing it in a well-stirred water bath and recording the water bath temperature and thermistor resistance at increments of 1°C between 15°C and 45°C. Temperature is measured with a Hewlett Packard quartz thermometer with precision of better then 0.001°C [HP Model #2804A]. Resistance is measured with the Thermal Diffusion Probe [29,31] with accuracy of 0.1 ohms. Independent studies have shown that thermal gradients in a water bath are eliminated by stirring. A chi square nonlinear regression is used to determine the coefficients \( H_0, H_1, \) and \( H_3 \). Table 5.1 and Figure 5.6 show the relationship between resistance and temperature for flake thermistor FLR18.
Table 5.1.

The Resistance versus Temperature Calibration for Thermistor FLK18

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Resistance (ohms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.513</td>
<td>2214.0</td>
</tr>
<tr>
<td>16.434</td>
<td>2149.3</td>
</tr>
<tr>
<td>18.064</td>
<td>2041.1</td>
</tr>
<tr>
<td>19.304</td>
<td>1963.4</td>
</tr>
<tr>
<td>20.735</td>
<td>1877.8</td>
</tr>
<tr>
<td>22.092</td>
<td>1800.5</td>
</tr>
<tr>
<td>23.105</td>
<td>1745.4</td>
</tr>
<tr>
<td>24.328</td>
<td>1680.7</td>
</tr>
<tr>
<td>25.635</td>
<td>1614.7</td>
</tr>
<tr>
<td>26.698</td>
<td>1564.2</td>
</tr>
<tr>
<td>27.741</td>
<td>1516.1</td>
</tr>
<tr>
<td>28.910</td>
<td>1465.5</td>
</tr>
<tr>
<td>30.380</td>
<td>1403.1</td>
</tr>
<tr>
<td>31.202</td>
<td>1369.4</td>
</tr>
<tr>
<td>32.640</td>
<td>1313.5</td>
</tr>
<tr>
<td>33.368</td>
<td>1285.9</td>
</tr>
<tr>
<td>34.840</td>
<td>1233.2</td>
</tr>
<tr>
<td>35.966</td>
<td>1194.3</td>
</tr>
<tr>
<td>37.008</td>
<td>1159.2</td>
</tr>
<tr>
<td>38.252</td>
<td>1119.4</td>
</tr>
<tr>
<td>39.208</td>
<td>1089.9</td>
</tr>
<tr>
<td>40.483</td>
<td>1052.2</td>
</tr>
<tr>
<td>41.653</td>
<td>1018.2</td>
</tr>
<tr>
<td>42.731</td>
<td>988.5</td>
</tr>
<tr>
<td>44.760</td>
<td>935.7</td>
</tr>
</tbody>
</table>

\[ H_0 = 7.7848753 \times 10^{-3} \]

\[ H_1 = 3.3592798 \times 10^{-4} \]

\[ H_3 = 2.1503811 \times 10^{-7} \]

Data taken on: July 8, 1982
Figure 5.6 Resistance versus temperature calibration for thermistor F1R18.
Chapter 5.3 Thermal Properties Calibration

5.3.1 Theory

In order to accurately measure the thermal properties of a medium using the solution of the spherical thermal model, the values of probe conductivity, \( K_f \), and radius, \( a_f \), must be known. However, because these constants are not known a priori, calibration experiments must be conducted. The model predicts that by heating the thermistors, the intrinsic thermal conductivity of a medium, \( K_m \), can be measured. In particular:

\[
K_m = \frac{1}{4\pi SP \ a_f - 0.2/K_f} \quad (5.3.1.1)
\]

where

\[
SP = \frac{\Delta T \ R_h}{V_{ss} \ \frac{2}{2}} \quad (5.3.1.2)
\]

\( \Delta T \) is the applied temperature step, \( R_h \) is the thermistor resistance after heating, and \( V_{ss} \) is the voltage applied in the steady state. Therefore, if \( SP \) is measured and the \( K_m \) for two different media are known, then the determination of \( K_f \) and \( a_f \) can be made.

Let

- \( \text{SPAGAR} = \) the average measured \( SP \) in agar
- \( \text{SPGLY} = \) the average measured \( SP \) in glycerine
- \( \text{KMAGAR} = \) the known \( K_m \) in agar
- \( \text{KMGLY} = \) the known \( K_m \) in glycerine
Substituting these values into equation (5.3.1.1), one finds:

\[
\frac{1}{4 \pi \text{SPAGAR} \ a_f - 0.2/K_f} \quad (5.3.1.3)
\]

and

\[
\frac{1}{4 \pi \text{SPGLY} \ a_f - 0.2/K_f} \quad (5.3.1.4)
\]

Solving for \( K_f \) and \( A_f \) one finds:

\[
K_f = \frac{(\text{SPGLY} - \text{SPAGAR}) \ \text{KMAGAR} \ \text{KMGLY}}{5 \ (\text{KMGLY} \ \text{SPGLY} - \text{KMAGAR} \ \text{SPAGAR})} \quad (5.3.1.5)
\]

and

\[
A_f = \frac{\text{KMAGAR} - \text{KMGLY}}{4 \pi (\text{SPGLY} - \text{SPAGAR}) \ \text{KMAGAR} \ \text{KMGLY}} \quad (5.3.1.6)
\]
5.3.2 Experimental Procedure

The thermal conductivity of water (6.234 X 10^-3 watts/cm-K at 37°C) and glycerine (2.894 X 10^-3 watts/cm-K at 37°C) are known [46,47]. Water, however, cannot be used in its liquid form as a calibration medium. If a heated thermistor were placed on the water surface, the density of the heated water would be less than that of the surrounding water and free convection would result, thereby violating the constraints already established for the thermal model. However, independent tests (see Appendix C) have demonstrated that the addition of modest amounts of agar to water does not measurably alter the thermal properties of water; consequently, an agar gel is used for calibration experiments. The preparation of the agar gel requires that 200 ml of water be heated to 100°C in a 250 ml flask. Three (3.00) grams of agar are added to the heated water. The mixture is cooled to room temperature. The noninvasive probe can then be placed on the mixture surface.

Glycerine has a higher viscosity than water; thus, when heated, thermally induced free convection does not occur in the time of measurement to an extent which alters the measurement. The preparation of glycerine simply entails the placement of the noninvasive probe on the surface of 200 ml of glycerine in a 250 ml flask.

Because the ultimate goal of this research is to measure perfusion in a physiologic environment, the calibration must be done at physiologic temperature. Therefore, the flask containing the agar or glycerine is placed in a water bath and maintained at 37°C. After temperature stabilization (stability is defined as less than a .005°C change in 15 seconds) between 10 and 20 experiments are conducted.
Each experiment consists of:

1) Measuring the initial baseline temperature,

2) Independently heating each of the thermistors to a known pre-set temperature,

3) Recording the power required to heat each thermistor,

4) Calculating $V_{ss}$,

5) Calculating SP.

The SP values from all experiments are then used to calculate the average SP for each thermistor. Thus, for each thermistor, an $a_f$ and $K_f$ is obtained.

One recalls that the steady-state voltage requirement, $V_{ss}$, is calculated by extrapolation of the transient measurements of voltage. Figure 5.3 shows in graphical form one such calculation. Using the voltages measured from the 30 second point to the 98 second point a least-squares linear regression is used to calculate the ordinate-intercept ($V_{ss}^2$). The 30 second point was selected empirically — prior to 30 seconds the spherical nature of the expanding wavefront and the $t^{-1/2}$ nature of the power have not been reached. The 98 second point was also empirically selected. If a longer time interval is selected then baseline temperature fluctuations may begin to corrupt the signal. One remembers that according to the spherical model for the noninvasive probe, see Figure 4.5, the surface thermistor heats the left-half semi-infinite medium and the guarding thermistor heats the right-half semi-infinite medium. However, empirically it was observed that the guarding flake is also somewhat sensitive to changes in the properties of the abutting medium. Thus, for both thermistors an effective characteristic dimension, $a_f$, and an effective thermal conductivity, $k_f$, can be
determined.

The results of probe FLR17/18 calibration are shown in Tables 5.2 and 5.3. The calculated $K_f$ and $a_f$ are:

<table>
<thead>
<tr>
<th>FLR17</th>
<th>FLR18</th>
</tr>
</thead>
<tbody>
<tr>
<td>(guard)</td>
<td>(surface)</td>
</tr>
</tbody>
</table>

\[
a_f = 0.33858 \text{ cm} \quad a_f = 0.01978 \text{ cm}
\]

\[
K_f = 1.6597 \times 10^{-3} \quad K_f = 3.2234 \times 10^{-3}
\]

(watt/cm·°C) \quad (watt/cm·°C).
Table 5.2. Noninvasive probe FLR17/18: Calibration data for the guarding thermistor FLR17. SP recorded as the mean of 10 experiments ± one standard deviation.

<table>
<thead>
<tr>
<th>Medium</th>
<th>$K_m$ (mW/cm·°C)</th>
<th>Measured SP (°C/W)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water (Agar)</td>
<td>6.234</td>
<td>326.0±2.8</td>
</tr>
<tr>
<td>Glycerin</td>
<td>2.894</td>
<td>370.2±1.3</td>
</tr>
</tbody>
</table>

Table 5.3. Noninvasive probe FLR17/18: Calibration data for the surface thermistor FLR18. SP values are recorded as the mean of 10 experiments ± one standard deviation.

<table>
<thead>
<tr>
<th>Medium</th>
<th>$K_m$ (mW/cm·°C)</th>
<th>Measured SP (°C/W)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water (Agar)</td>
<td>6.234</td>
<td>868.0±16.1</td>
</tr>
<tr>
<td>Glycerin</td>
<td>2.894</td>
<td>1590.5±45.0</td>
</tr>
</tbody>
</table>
Chapter 5.4 Test of Calibration

After determination the characteristic dimension, $a_f$, and thermal conductivity, $k_f$, the next step is to test the accuracy with which the probe can noninvasively measure the thermal properties of a medium of known thermal properties. This is an important step because for a heated thermistor in spherical geometry the accurate quantification of perfusion follows directly from the accurate measurement of thermal conductivity. Equation 5.4.1, derived by Balasubramaniam and Bowman, shows that perfusion, $w$, is calculated from the difference between the thermal conductivity in the perfused, $k_{\text{eff}}$, and unperfused, $k_m$, states.

\[
\frac{(k_{\text{eff}} - k_m)^2}{K_m c_b l a_b^2}
\]

(5.4.1)

To assess the ability of the noninvasive probe to quantify thermal conductivity, the probe was placed on the surface of media of known thermal conductivity. These media include several mixtures of water/agar and glycerin as well as solutions of pure water/agar and glycerin. The thermal conductivity of the mixture is calculated from the mass fraction of its constituent ingredients.
Thus:

\[ K_m = \frac{M_{\text{water}}}{M_{\text{total}}} K_{\text{water}} + \frac{M_{\text{glycerin}}}{M_{\text{total}}} K_{\text{glycerin}} + \frac{M_{\text{agar}}}{M_{\text{total}}} K_{\text{agar}} \] (5.4.2)

where \( M_i \) is the mass of the "i" th component. Table 5.4 shows results obtained using probe FLR17/18. Note that both thermistors can quantify thermal conductivity within 5% error; however, the thermal conductivity as calculated by averaging the results of thermistor FLR17 and the results of thermistor FLR18 yield values within 2% error [48]. Figure 5.7 shows a plot of measured thermal conductivity versus known thermal conductivity for this probe. Close inspection of the data reveals that, in general, if FLR17 slightly overestimated the conductivity the FLR18 slightly underestimated the conductivity, and vice versa. Thus, in general, the average of the two measurements of the thermal conductivity was more accurate than either measurement alone.

A major question, however, is why is the guarding thermistor so sensitive to the thermal properties of the abutting medium? First, one should note that when the noninvasive probe is pressed against the medium, the surface of the medium is not rigid and therefore molds about the probe. For the surface thermistor (i.e. FLR18), the face (area = 0.1cm x 0.1cm) and the four edges (4 x 0.1cm x 0.02cm) contact the medium; and for the guarding thermistor (i.e. FLR17), only the four edges (4 x 0.1cm x 0.02cm) contact the medium. Thus, the guarding thermistor has only 44% less contact area than the surface thermistor.
Consequently, it is not surprising that both thermistors are sensitive to the thermal properties of the abutting medium. The observation that even the guarding thermistor was sensitive lead to the hypothesis that a single thermistor placed on the surface of a medium may be sensitive to the thermal properties of the abutting medium. Appendix F briefly explores this hypothesis.

The results in Table 5.4 and Figure 5.7 were obtained using a probe insulated with several thin (0.02mm) coats of acetone diluted epoxy. The results shown in Table 5.5 and Figure 5.8 were obtained using the same probe further insulated with a latex sheath. Note that in both cases accurate quantification of thermal conductivity is possible.

Further, contrast the thermal conductivity, \( k_f \), and the characteristic dimension, \( a_f \), of each thermistor for each case, see Table 5.6.

The calibration coefficients of the surface thermistor, FLR18, are more greatly effected than the coefficients of the guarding thermistor, FLR17. This effect is to be expected - the latex sheath more directly abuts the surface thermistor. The characteristic dimension of the surface thermistor is almost four times greater in the presence of the latex; the thermal conductivity is approximately thirteen times smaller in the presence of the latex - the latex is certainly a thermal insulator. The guarding thermistor, FLR17, is also effected, however, not as greatly. The effective thermal conductivity of FLR17 is lower and the effective size is also slightly diminished.

In conclusion, in this section data has been presented that demonstrates the ability of the noninvasive probe to quantify thermal conductivity. The data, therefore, also indicates the validity of the
spherical model for the noninvasive probe; that is, as predicted by the spherical thermal model there is a linear relationship between the thermal conductivity of the medium and $\Delta T$/power, see equation 4.1.1.
Table 5.4
The ability of noninvasive probe FLR17/18 to measure thermal conductivity was tested in six media of known thermal conductivity. The noninvasive probe was only insulated with thin coats of epoxy. Notice that the average error of \( K_m \) is better than the \( K_m \) measured by either FLR17 or FLR18.

<table>
<thead>
<tr>
<th>Medium (Gly/agar)</th>
<th>( K_m )</th>
<th>( SP_{FLR17} )</th>
<th>( SP_{FLR18} )</th>
<th>( K_{mFLR17} )</th>
<th>( K_{mFLR18} )</th>
<th>( K_{m17/18} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>100% : 0%</td>
<td>2.894</td>
<td>370.2±1.3</td>
<td>1641.5±58.0</td>
<td>2.872±0.077</td>
<td>2.878±0.156</td>
<td>2.875±0.098</td>
</tr>
<tr>
<td>75% : 25%</td>
<td>3.532</td>
<td>350.9±0.7</td>
<td>1342.1±16.4</td>
<td>3.664±0.43</td>
<td>3.638±0.080</td>
<td>3.651±0.035</td>
</tr>
<tr>
<td>50% : 50%</td>
<td>4.302</td>
<td>342.4±2.5</td>
<td>1129.6±50.3</td>
<td>4.174±1.74</td>
<td>4.558±0.261</td>
<td>4.366±0.061</td>
</tr>
<tr>
<td>25% : 75%</td>
<td>5.114</td>
<td>328.4±0.5</td>
<td>1069.0±17.4</td>
<td>5.401±0.059</td>
<td>4.887±1.05</td>
<td>5.144±0.068</td>
</tr>
<tr>
<td>25% : 75%</td>
<td>5.300</td>
<td>327.0±2.1</td>
<td>1053.9±39.5</td>
<td>5.582±2.51</td>
<td>4.988±2.40</td>
<td>5.285±0.53</td>
</tr>
<tr>
<td>0% : 100%</td>
<td>6.234</td>
<td>326.0±2.8</td>
<td>868.0±16.1</td>
<td>5.710±3.38</td>
<td>6.501±1.74</td>
<td>6.106±1.91</td>
</tr>
</tbody>
</table>

Average Error = 4.5%

Calibration Coefficients

\[
a_f \quad K_f
\]

| FLR17 | .31222       | .18126         |
| FLR18 | .02011       | 3.0578         |

Units Key:

- \( a_f \) - cm
- \( K_f \) - mW/cm\(^{-}\)°C
- \( K_m \) - mW/cm\(^{-}\)°C
- \( SP \) - °C/W

\[
K_{m17/18} = \frac{K_{mFLR17} + K_{mFLR18}}{2}
\]

Data taken: September 15, 1983
Figure 5.7 Thermal conductivity as measured by the noninvasive probe is plotted versus the true thermal conductivity. The six media are glycerin, water and four glycerin/water mixtures. The true thermal conductivity of a mixture is determined from the mass fraction of water and glycerin. This noninvasive probe was only insulated with thin coats of epoxy. The measured conductivity is the average of that measured by thermistor FLR17 and FLR18. The average measurement error is 1.4%. 
Table 5.5
The ability of noninvasive probe FLR17/18 to measure thermal conductivity was tested in five media of known thermal conductivity. The noninvasive probe was insulated with thin coats of epoxy and a latex sheath.

<table>
<thead>
<tr>
<th>Medium (Gly/agar)</th>
<th>$K_m$</th>
<th>$SP_{FLR17}$</th>
<th>$SP_{FLR18}$</th>
<th>$K_{mFLR17}$</th>
<th>$K_{mFLR18}$</th>
<th>$K_{m17/18}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>100% : 0%</td>
<td>2.894</td>
<td>462.1±1.0</td>
<td>1232.0±7.1</td>
<td>2.958±.031</td>
<td>2.917±.058</td>
<td>2.937±.004</td>
</tr>
<tr>
<td>75% : 25%</td>
<td>3.82</td>
<td>440.5±1.3</td>
<td>1155.8±5.2</td>
<td>3.815±.062</td>
<td>3.722±.069</td>
<td>3.769±.042</td>
</tr>
<tr>
<td>50% : 50%</td>
<td>4.77</td>
<td>426.1±0.9</td>
<td>1100.6±5.1</td>
<td>4.741±.048</td>
<td>4.692±.079</td>
<td>4.716±.055</td>
</tr>
<tr>
<td>25% : 75%</td>
<td>5.30</td>
<td>417.4±1.0</td>
<td>1071.1±3.5</td>
<td>5.521±.105</td>
<td>5.375±.100</td>
<td>5.448±.087</td>
</tr>
<tr>
<td>0% : 100%</td>
<td>6.234</td>
<td>409.4±0.9</td>
<td>1043.5±3.6</td>
<td>6.282±.137</td>
<td>6.528±.133</td>
<td>6.405±.111</td>
</tr>
</tbody>
</table>

Average Error = 1.58%

Calibration Coefficients

<table>
<thead>
<tr>
<th></th>
<th>$a_f$</th>
<th>$K_f$</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLR17</td>
<td>0.2790</td>
<td>0.156</td>
</tr>
<tr>
<td>FLR18</td>
<td>0.0776</td>
<td>0.233</td>
</tr>
</tbody>
</table>

Units Key:

- $a_f$ - cm
- $K_f$ - mW/cm°C
- $K_m$ - mW/cm°C
- $SP$ - °C/W

\[
K_{m17/18} = \frac{K_{mFLR17} + K_{mFLR18}}{2}
\]

Data taken: March 20, 1983
Figure 5.8 Thermal conductivity as measured by the noninvasive probe is plotted versus the true thermal conductivity. The six media are glycerin, water and four glycerin/water mixtures. The true thermal conductivity of a mixture is determined from the mass fraction of water and glycerin. This noninvasive probe was insulated with thin coats of epoxy and a latex sheath. The measured conductivity is the average of that measured by thermistor FLR17 and FLR18. The average measurement error is 2.2%. 

Probe: FLR17/FLR18
Table 5.6 Comparison of calibration coefficients of a noninvasive probe before and after insulation with a latex sheath.

<table>
<thead>
<tr>
<th></th>
<th>$a_f$(cm)</th>
<th></th>
<th>$K_f$(mW/cm–°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>without latex</td>
<td>with latex</td>
<td>without latex</td>
</tr>
<tr>
<td>FLR17</td>
<td>0.31222</td>
<td>0.279</td>
<td>0.18126</td>
</tr>
<tr>
<td>FLR18</td>
<td>0.02011</td>
<td>0.076</td>
<td>3.0578</td>
</tr>
</tbody>
</table>
Chapter 5.5 The Isolated Rat Liver Perfusion Experiments

The final step in the evaluation of the noninvasive probe is the assessment of the ability of the noninvasive probe to quantify perfusion. Vital to this effort is an independent method of quantifying perfusion. The rat liver perfusion apparatus [31, 49], adapted from Brunengraber [50] allows for the independent quantification of perfusion by the method of radiolabeled microspheres and venous collection. In this section an overview of the perfusion apparatus will be presented, the results of experiments will be discussed, and conclusions will be drawn.
5.5.1 The Experimental Apparatus

The primary objective of this research is to develop a technique to quantify tissue perfusion noninvasively. Therefore, the ability to quantify perfusion must be tested against a standard. Such a standard exists in the form of the rat liver perfusion model. Figure 5.9 shows a schematic of the rat liver perfusion apparatus. Within this apparatus, temperature is controlled to within 0.005°C, 100% humidity is maintained, and the rat liver is kept in a viable state by perfusing it with oxygenated glucose Ringers solution. The rate of perfusion can be controlled with a pinch valve and measured with a mass balance and a stop watch by collecting venous outflow. Further, radiolabeled microspheres are used to quantify the spatial distribution of perfusion and the shunt fraction.

Three hours prior to surgery 37°C water begins to circulate through the water jacketed components (i.e. the two heat exchangers, the oxygenator, and the liver holder); thus, the thermal mass of the system is raised to physiologic temperature. A thermomix circulation pump (model #1460, B. Braun Instruments 805 Grandview Dr., S. San Francisco, CA 94080) is used to pump the 37°C water. One hour prior to surgery, the perfusate (see Appendix E) begins circulating from the reservoir (4 liter Erlenmmyer flask) through the pump (Harvard Apparatus Co. Model #1203, Millis, MA 02054) then through the filter (Swinnex-47 filter holder containing a 47mm diameter Millipore filter with pore size 1.2μm, Millipore Corp., Bedford, MA 01730), a heat exchanger, and oxygenator (manufactured by H. Vincent, 14 Lyndworth Close, Headington, Oxford OX39ER, England). Initially all of the perfusate returns to the reservoir either 1) via the overflow or 2) after passing the variable
pinch-valve, the second heat exchanger, the bubble trap, and the portal vein cannula (which before surgery discharges into the reservoir). Thus, at the start of surgery the entire apparatus is at 37°C and the perfusate is oxygenated and maintained at physiologic pH (i.e. pH = 7.4). Further, the constant pressure head has been established and the volume flow rate through the portal vein cannula can be controlled with the pinch-valve. After surgery all of the portal vein flow perfuses the liver and passes out via the inferior vena cava cannula. Any liquid oozing from the liver is also collected; however, livers that ooze are discarded because the effects of oozing on perfusion cannot be quantified. The flow rate is calculated using a mass balance (Satorus Model #1265 MP, Gottingen, W. Germany) and a stopwatch. Assuming a perfusate density of 1.0 gm/ml, the balance reading in grams is equivalent to a volume measurement in milliliters.

This fluid circulation pattern was chosen because 1) the closed-loop portion provides a reservoir of physiologic perfusate and maintains the constant pressure head, and 2) the open-loop portion allows indicators (e.g. microspheres) to be injected without contaminating the entire system. Note that in order to maintain temperature stability all components are water-jacketed; in addition, plastic wrap is placed around the liver holder to minimize convective liver cooling and 100% humidified air inside the cabinet minimizes evaporative liver cooling. Finally, a small fan circulates the air thus minimizing the thermal gradients within the cabinet.
Figure 5.9 Schematic of the rat liver perfusion apparatus. (Adapted from Valvano [31]).
Chapter 5.5.2 Experimental Procedure

The perfusion apparatus is prepared as described in section 5.5.1. Male rats of the Sprague-Dawley strain weighing approximately 250 grams were obtained from the Charles River Breeding Laboratories, North Wilmington, MA. For each experiment a rat is anesthetized (sodium pentobarbitol: 40mg/kg i.p. or 25mg/kg i.v.) and weighed. A large V-shaped incision from near the pubis to the costal boarders at the mid-axillary line exposes the abdominal contents. Ligatures are loosely placed around the portal vein, superior mesenteric vein and the inferior vena cava, see Figure 5.10. The superior mesenteric vein is located, an entrance hole is produced with microscissors, and the 18-gauge "portal vein" cannula is inserted. The cannula, through which approximately 30 ml/min of perfusate is flowing, is passed just beyond the splenic vein into the portal vein (but not cranially as far as the portal vein bifurcation). Immediately after cannulation, the inferior vena cava is severed rostral to the kidneys but caudal to the liver; this prevents pressure build-up in the hepatic venous system. The portal and superior mesenteric vein ligatures are pulled tightly, thus securing the cannula in place. A red to brown change in liver color indicates clearance of hepatic blood and that the liver is now being perfused by the Ringers solution. The liver is carefully separated from the stomach, spleen, pancreas, and intestines.

In order to expose the thoracic cavity one makes a V-shaped incision from the right and left lower costal margins to the sternal notch. Another 18 gauge plastic cannula is passed via the right atrium into the inferior vena cava. Thus holding the thoracic cannula in place. The cannula tip is positioned just rostral to the liver. A
ligature is tightened about the thoracic inferior vena cava. Next a piece of diaphragm is tied to the inferior vena cava cannula using the same thread. The abdominal inferior vena cava ligature is tightened and the abdominal inferior vena cava is cut caudal to this ligature. At this point all liver efflux should be via the inferior vena cava cannula.

The liver preparation is now carefully isolated from the heart, esophagus, and posterior diaphragm, placed within the liver holder, and suspended via the thoracic vena cava ligature. The noninvasive probe is placed upon the liver surface and the plastic wrap is carefully placed about the liver. Finally, the clear plexiglass door of the apparatus cabinet is closed. Boiling water raises the humidity within the cabinet to 100%. Liver temperature reaches equilibrium within approximately 30 minutes.

For the next 2.5 hours perfusion measurements are taken. Typically three perfusion levels are used (approximately 10, 20, and 30 ml/min of total liver flow). At each level four separate, independent measurements of perfusion are taken with the noninvasive probe. During each measurement period total liver flow is measured using the stopwatch and balance; prior to the third perfusion measurement radiolabeled microspheres are injected. Approximately 0.5 ml of a prepared microsphere solution \(10^6\) microspheres/ml of solution with an activity level of \(2 \times 10^{-5}\) curies/ml in physiologic saline produced by New England Nuclear, Billerica, MA) is mixed with 0.5 ml of saline in a 2.5 ml syringe. Three different labels are used, \(^{113}\)Sn, \(^{57}\)Co, \(^{103}\)Ru; each label is prepared in a separate syringe. At each of the three different perfusion rates one of the microsphere solutions is rapidly injected,
the cannula is then flushed with 2 ml of saline. The microspheres are used to determine the spatial distribution of the total liver flow. During microsphere injection, effluent perfusate is collected, the radioactivity level of this effluent is indicative of the shunt fraction (typically less than 1%).

After all perfusion measurements have been completed, flow to the liver is discontinued. The thermal conductivity of the unperfused liver can be determined as soon as the liver temperature stabilizes.

After measurements with the noninvasive probe are complete the liver is removed from the perfusion apparatus, and cut into seven or eight equal pieces. Each piece is weighed and placed in a small vial. The relative amount of radioactivity due to a specific isotope is indicative of the relative perfusion in that section at the time of isotope injection. Thus, for each liver section the activity due to each of the three isotopes is determined by placing each vial in a Na(I) deep well crystal detector connected to a multichannel analyzer (located in the MIT Radiation Protection Office). Gamma rays are detected in the 0 to 1280 KeV energy range and sorted into one of 512 channels. The counts in the 122 KeV Co$^{57}$ peak, 393 KeV Sn$^{113}$ peak, and the 497 KeV Ru$^{103}$ peak are recorded. All counts are time, background, and cross-talk corrected. This final correction, more thoroughly explained in appendix G, is dependent upon the spectrum which results from a pure sample of one radioisotope. Given the corrected counts for each isotope in each section of the liver the perfusion to that section can be quantified using the following equation:

$$w_1 = \frac{F \cdot N_i \cdot \rho_{\text{tissue}} \cdot \rho_{\text{perfusate}}}{60 \cdot N_t \cdot m_i} \quad (5.5.1)$$
where

\( w_i \) = perfusion in the "i"th piece (gm\textsubscript{perfusate}/ml\textsubscript{tissue} - sec),

\( F \) = total liver flow (ml\textsubscript{perfusate}/min),

\( N_i / N_t \) = activity in the "i"th piece relative to the activity in the total liver,

\( \rho_t \) = tissue density (gm\textsubscript{tissue}/ml\textsubscript{tissue}),

\( \rho_p \) = perfusate density (gm\textsubscript{perfusate}/ml\textsubscript{perfusate}),

\( m_i \) = mass of the "i"th piece of tissue (gm\textsubscript{tissue}).
Figure 5.10 Schematic of the abdominal region of the rat indicating the placement of the venous ligatures.
Chapter 5.5.3 Previous Validation Studies

Thus far the apparatus and experimental procedure used in the evaluation of thermal techniques to quantify perfusion have been discussed. In this section studies that were done to verify the ability with which perfusion can be independently and accurately quantified using the rat liver apparatus will be presented. A complete description of these studies can be found in references 31 and 49.

The rat liver perfusion apparatus was adapted from the well-tested system developed by Brunengraber [50], who demonstrated that the rat liver was biochemically viable for approximately three hours after initial cannulation. In order to quantify perfusion using this thermal method, the establishment and maintenance of temperature stability is critical; thus, one of the major adaptations to the Brunengraber system was the addition of several constant temperature water-jacketted elements. This adaptation yielded a system in which the temperature of the perfusate, at constant flow rate, changes by less than 0.003°C/minute. Corresponding liver temperature changes are less than 0.01°C/minute. A second major adaptation was to change the source of the driving pressure for perfusion. Flow from a pump was too pulsatile, therefore a gravity-feed, constant-pressure-head source was introduced to yield constant flow. A pinch valve varies system resistance and thus allows flow rates to be changed. Once the pinch valve is set, the flow rate varies by less than 0.1%/minute.

As previously mentioned (chapters 2 and 5.5.2), the independent method for quantifying perfusion involves 1) determining the total flow rate by collecting venous effluent, and 2) determining the distribution of the total flow within the liver using radiolabeled microspheres. Equation 5.5.1 is then used to calculate regional perfusion. Errors in the
determination of any of the parameters in equation 5.5.1 lead to errors in
the calculated perfusion. Liver density is determined from liver weight
(typically known to within 0.1% error) and liver volume (typical error is
3%). The measurement of total flow is determined using a mass balance and
a stopwatch; thus total flow typically is known to within 1.5% error.
Errors can occur because 1) microspheres can stream – an unlikely source
of error given a Reynold's number of 2301 (see Appendix G), 2) microspheres block sinusoids thereby altering flow patterns – however,
typically less than 1% of the sinusoids are blocked per radioactive label
used, and 3) microspheres may be shunted through A-V anastomosis thus
bypassing the sinusoids – a minor problem because the shunt fraction is
typically less than 1% (as determined from the radioactivity in the venous
effluent). Experiments have shown [31,49] that at a set flow rate
microsphere distribution within the liver is reproducible to within ±3%.
Further, perfusion derived using microsphere distribution and venous
effluent collection correlated well (0.973) with perfusion derived using a
simple thermal washout method. The thermal washout method involves
perturbing the baseline liver temperature, then monitoring the liver
temperature recovery. Perfusion can be calculated from the time constant
of recovery.

In summary, the results of the validation studies indicated that the
rat liver system provided a thermally stable environment with a constant
total flow to a viable liver for approximately three hours. Using this
system, local perfusion could be quantified to within 8% error using the
microsphere method. Careful measurement technique allows for more
accurate quantification.
Chapter 5.5.4 Experimental Results

The ability to quantify perfusion noninvasively was studied using the rat liver system. In this chapter, the results of the rat liver perfusion study will be presented. In brief, six rats were utilized in this study; however, because of surgical complications (rat #101), apparatus malfunctions (rats #102 and 103) and eventual irreversible probe malfunction (rat #106) only the results from two rat liver experiments (rats #104 and 105) are analyzed.

The materials and methods for these two experiments were as described in Chapters 5.5.1 and 5.5.2. The true perfusion to each liver section was determined from the total flow and the microsphere distribution (see Appendix G). The work-up of this data is shown in Tables 5.7 and 5.8. The results of perfusion measurements for rat #104 are shown in Tables 5.9 and 5.10. Similarly, the results for rat #105 are shown in Tables 5.11 and 5.12. The calibration coefficients, $a_f$ and $K_f$, were determined as described in Chapter 5.3. The intrinsic thermal conductivity, $K_m$, was measured after flow to the liver was stopped.

Theoretically, several relationships between true perfusion and measured parameters should exist.

1) There should be an inverse monotonic relationship between $\Delta T$/power, a parameter called SP, and true perfusion. Figures 5.11, 5.12, 5.13, and 5.14 show this relationship.

2) Further, a monotonic relationship between effective conductivity and true perfusion should exist. Figures 5.15, 5.16, 5.17 and 5.18 show this relationship.

3) Finally, there should be a linear relationship between measured perfusion and true perfusion. Figures 5.19 and 5.20 show this
relationship; however, the slope of the best fit line through these points is not equal to one, as it ideally should be, and the intercept is not zero, as it ideally should be. However, the general pattern seen in Figures 5.11 through 5.20 does indicate that the noninvasive probe is sensitive to changes in perfusion.

Figures 5.11 through 5.20 show all the perfusion measurements made during experiments #104 and 105. Some of these measurements were taken under less than ideal conditions; such measurements are not expected to be an accurate quantification of the true perfusion. For example, as can be seen in Tables 5.9, 5.10, 5.11 and 5.12 the baseline temperature was not stable for experiments 38, 43, 44, 48, 49, 50, 64 and 66; thus, these experiments would not be expected to accurately quantify perfusion. Further, when experiment 77 was conducted it was noted that the effluxing liver perfusate was very "foamy"; this sign is indicative of a failing liver and thus potentially a liver with altered flow patterns. The perfusion measured during experiment 77 would not be expected to necessarily correlate well with microsphere corrected true perfusion. Finally, the microsphere distribution in rat #105 was quite unusual, see Table 5.8. In particular, when compared with the tin and cobalt distribution, the percent of ruthenium-labeled microspheres in liver section #1 (the section upon which the probe was placed) is low. Although temporal variations in perfusion are to be expected [31], an almost 50% variation is unexpected. Thus, the ruthenium distribution was "corrected" to be the average of the tin and cobalt distributions. In summary, before further work-up was done some points were discarded and the true perfusion was corrected. Figure 5.21 and 5.22 show the data points that were not discarded.
Using the relationship

\[ w = \frac{(K_{eff} - K_m)^2}{K_m c_{bl} a_f^2} \]  \hspace{1cm} (5.5.4.1)

and

\[ K_{eff} = \frac{1}{4\pi a_f \Delta T/power - 0.2/K_f} \]  \hspace{1cm} (5.5.4.2)

A least squares fit of the data was obtained to determine the optimal \( K_m, a_f, K_f \). Table 5.13 and Figures 5.23, 5.24 and 5.25 show the relationship between the "fit" measured perfusion and true perfusion. Notice that the average percent error for probe FLR17 (12.5%) and FLR18 (23.8%) is quite good; also, the average percent error for \( w_{m_{17+18/2}} \) (16.9%) is also quite good.

In Chapter 5.4 it was noted that the effective surface area for FLR17 is 0.008 cm\(^2\) and for FLR18 is 0.018 cm\(^2\). Thermistor, FLR17 has only 45% less exposed surface area than FLR18; therefore, it is not surprising that both thermistors are sensitive to changes in perfusion. However, it is somewhat surprising that the "guarding" thermistor, FLR17, is slightly more sensitive than the "surface" thermistor, FLR18. One possible explanation of this observation is that FLR17, while "guarding" FLR18, is also heating the supporting substrate. The supporting substrate is in contact with the tissue surface. Thus heat flows from the guarding thermistor into the supporting substrate then into the tissue. In other words, the substrate acts as a "fin" increasing the effective surface area of the guarding thermistor FLR17. This conclusion is supported by data presented in chapter 5.3, where it..
was shown that the characteristic dimension, $a_f$, of FLR17 was much
greater than that for FLR18. Therefore, although the "actual" surface
area of the guarding thermistor is less than that for the surface	hermistor, the guarding thermistor has a much greater effective surface
area and therefore is more sensitive to changes in perfusion in the
underlying tissue.
Table 5.7 This three page table contains the work-up of the microsphere data for rat experiment #104.

Table 5.7.a Cross talk data. Use pure sample counts to subtract cross talk.

<table>
<thead>
<tr>
<th></th>
<th>Peak region</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ru</td>
<td>Sn</td>
</tr>
<tr>
<td>Ru</td>
<td>82830</td>
<td>5261</td>
</tr>
<tr>
<td>Pure Sn</td>
<td>6510</td>
<td>108140</td>
</tr>
<tr>
<td>sample Co</td>
<td>0000</td>
<td>0000</td>
</tr>
</tbody>
</table>

Thus for every count in the Ru peak region
subtract 0.00000 counts from the Co sample
subtract 0.05144 counts from the Sn sample

for every count in the Sn peak region
subtract 0.00000 counts from the Co sample
subtract 0.06020 counts from the Ru sample

for every count in the Co peak region
subtract 0.00000 counts from the Ru sample
subtract 0.00000 counts from the Sn sample
Table 5.7.b Raw and corrected data

<table>
<thead>
<tr>
<th>Sample</th>
<th>Ru</th>
<th>Sn</th>
<th>Co</th>
</tr>
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<tr>
<td></td>
<td>low</td>
<td>peak</td>
<td>high</td>
</tr>
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<td>1</td>
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<td>91400.</td>
<td>0.</td>
</tr>
<tr>
<td>2</td>
<td>0.</td>
<td>354880.</td>
<td>0.</td>
</tr>
<tr>
<td>3</td>
<td>0.</td>
<td>327540.</td>
<td>0.</td>
</tr>
<tr>
<td>4</td>
<td>0.</td>
<td>232810.</td>
<td>0.</td>
</tr>
<tr>
<td>5</td>
<td>0.</td>
<td>131120.</td>
<td>0.</td>
</tr>
<tr>
<td>6</td>
<td>0.</td>
<td>7310.</td>
<td>0.</td>
</tr>
<tr>
<td>7</td>
<td>0.</td>
<td>61110.</td>
<td>0.</td>
</tr>
</tbody>
</table>

#chan 0 27 0 0 21 0 3 54 11

Corrected counts

BC = Background and time corrected
CC = Cross talk corrected

<table>
<thead>
<tr>
<th>Sample</th>
<th>Mass</th>
<th>Time</th>
<th>RuBC</th>
<th>RuCC</th>
<th>SnBC</th>
<th>SnCC</th>
<th>CoBC</th>
<th>CoCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.124</td>
<td>60.</td>
<td>1523.3</td>
<td>1401.3</td>
<td>2099.8</td>
<td>2027.7</td>
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<td>18175.5</td>
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<tr>
<td>2</td>
<td>2.012</td>
<td>60.</td>
<td>5914.7</td>
<td>5786.6</td>
<td>2425.5</td>
<td>2127.8</td>
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<td>63566.8</td>
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<tr>
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<td>1.457</td>
<td>60.</td>
<td>5459.0</td>
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<td>73645.4</td>
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<tr>
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<td>60.</td>
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<td>3544.8</td>
<td>5753.5</td>
<td>5571.1</td>
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<td>52493.5</td>
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<tr>
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<td>1.518</td>
<td>60.</td>
<td>2185.3</td>
<td>1976.4</td>
<td>3573.2</td>
<td>3471.5</td>
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<tr>
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<td>60.</td>
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<td>114.6</td>
<td>125.3</td>
<td>119.4</td>
<td>1793.2</td>
<td>1793.2</td>
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<tr>
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<td>60.</td>
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<td>943.1</td>
<td>1301.2</td>
<td>1252.7</td>
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<tr>
<td>Total</td>
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<td></td>
<td>18854.22</td>
<td>20741.25</td>
<td>272856.25</td>
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</tr>
</tbody>
</table>
Table 5.7.c The calculation of perfusion from the corrected counts and total liver flow in rat #104. Note that the noninvasive probe measured perfusion on the surface of liver sample #1.

Sn was injected at 11:45  
Ru was injected at 12:40  
Co was injected at 13:20.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Mass</th>
<th>Ru</th>
<th>Sn</th>
<th>Co</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.124</td>
<td>.074</td>
<td>.098</td>
<td>.067</td>
</tr>
<tr>
<td>2</td>
<td>2.012</td>
<td>.307</td>
<td>.103</td>
<td>.233</td>
</tr>
<tr>
<td>3</td>
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<td>.270</td>
<td>.298</td>
<td>.270</td>
</tr>
<tr>
<td>4</td>
<td>1.807</td>
<td>.188</td>
<td>.269</td>
<td>.192</td>
</tr>
<tr>
<td>5</td>
<td>1.518</td>
<td>.105</td>
<td>.167</td>
<td>.145</td>
</tr>
<tr>
<td>6</td>
<td>2.301</td>
<td>.006</td>
<td>.006</td>
<td>.007</td>
</tr>
<tr>
<td>7</td>
<td>1.435</td>
<td>.050</td>
<td>.060</td>
<td>.086</td>
</tr>
</tbody>
</table>

Exp#  F_{total}  W_{true}
38     27.610  31.810
39     38.160  43.965
40     36.460  42.008
41     36.061  41.546
42     34.760  40.049
43     34.561  39.818
44     34.279  39.495
45     18.280  19.069
46     17.560  18.318
47     17.310  18.057
48     16.780  17.504
49     16.320  17.024
50     13.200  16.441
51     13.170  16.404
52     12.480  15.544
53     12.410  15.457

where

\[ \rho_{\text{perfusate}} = 1.000 \text{ gm/ml} \]

\[ \rho_{\text{tissue}} = 1.050 \text{ gm/ml} \]
Table 5.8 This three page table contains the work-up of the microsphere data for rat experiment #105.

Table 5.8.a Cross talk data. Use pure sample counts to subtract cross talk.

<table>
<thead>
<tr>
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<th>Peak region</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ru</td>
</tr>
<tr>
<td>Ru</td>
<td>82830</td>
</tr>
<tr>
<td>Pure</td>
<td>6510</td>
</tr>
<tr>
<td>sample</td>
<td>0000</td>
</tr>
</tbody>
</table>

Thus for every count in the Ru peak region
subtract 0.00000 counts from the Co sample
subtract 0.05144 counts from the Sn sample

for every count in the Sn peak region
subtract 0.00000 counts from the Co sample
subtract 0.06020 counts from the Ru sample

for every count in the Co peak region
subtract 0.00000 counts from the Ru sample
subtract 0.00000 counts from the Sn sample
Table 5.8.b Raw and corrected data

Raw counts

<table>
<thead>
<tr>
<th>Sample</th>
<th>Ru</th>
<th>Sn</th>
<th>Co</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>low peak high</td>
<td>low peak high</td>
<td>low peak high</td>
</tr>
<tr>
<td>1</td>
<td>0. 117770. 0. 0. 233530. 0. 32324. 2129002. 86585.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0. 27200. 0. 0. 147770. 0. 10812. 685085. 26420.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0. 220. 0. 0. 290. 0. 25. 2316. 91.</td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>5</td>
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</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
<td>8</td>
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</tr>
</tbody>
</table>

Corrected counts

BC = Background and time corrected
CC = Cross talk corrected

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<tr>
<th>Sample</th>
<th>Mass Time</th>
<th>RuBC</th>
<th>RuCC</th>
<th>SnBC</th>
<th>SnCC</th>
<th>CoBC</th>
<th>CoCC</th>
</tr>
</thead>
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<td>1733.9</td>
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<td>27092.7</td>
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<td>2447.1</td>
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</tr>
<tr>
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<td>67.3</td>
<td>90.7</td>
<td>87.2</td>
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<td>432.3</td>
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<tr>
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<td>2607.7</td>
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<td>3225.5</td>
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<tr>
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<td>6222.0</td>
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<tr>
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<td>6094.6</td>
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<tr>
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<td>557.8</td>
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<td>1476.5</td>
<td>7193.4</td>
<td>7193.4</td>
</tr>
<tr>
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<td>17890.52</td>
<td>140831.96</td>
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</tbody>
</table>
Table 5.8c The calculation of perfusion from the corrected counts and total liver flow in rat #105. Note that the noninvasive probe measured perfusion on the surface of liver sample #1.

Sn was injected at 12:11
Ru was injected at 13:02.
Co was injected at 13:46.

### Zeta(i)

<table>
<thead>
<tr>
<th>Sample</th>
<th>Mass</th>
<th>Ru</th>
<th>Sn</th>
<th>Co</th>
</tr>
</thead>
<tbody>
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<td>.213</td>
<td>.192</td>
</tr>
<tr>
<td>2</td>
<td>0.298</td>
<td>.020</td>
<td>.137</td>
<td>.062</td>
</tr>
<tr>
<td>3</td>
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<td>.001</td>
<td>.001</td>
<td>.001</td>
</tr>
<tr>
<td>4</td>
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<td>.004</td>
<td>.005</td>
<td>.003</td>
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<td>.174</td>
<td>.180</td>
<td>.114</td>
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<td>.241</td>
<td>.348</td>
<td>.268</td>
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### Exp# F<sup>total</sup> w<sup>true</sup>

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<th>w&lt;sup&gt;true&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
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<td>62.659</td>
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<tr>
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<td>21.580</td>
<td>62.450</td>
</tr>
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<td>67</td>
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<td>59.880</td>
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<td>58.170</td>
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<td>69</td>
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<td>58.341</td>
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<tr>
<td>70</td>
<td>7.120</td>
<td>11.220</td>
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<tr>
<td>71</td>
<td>7.350</td>
<td>11.580</td>
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<tr>
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<td>9.740</td>
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<tr>
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<td>6.440</td>
<td>10.150</td>
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<td>74</td>
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<td>45.650</td>
</tr>
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<td>75</td>
<td>17.460</td>
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<td>45.390</td>
</tr>
<tr>
<td>77</td>
<td>17.380</td>
<td>45.340</td>
</tr>
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</table>

where

\[ \rho_{\text{perfusate}} = 1.000 \text{ gm/ml} \]

\[ \rho_{\text{tissue}} = 1.050 \text{ gm/ml} \]
Table 5.9 The results of perfusion experiments taken by probe FLR17 during rat experiment #104.

<table>
<thead>
<tr>
<th>Time</th>
<th>Exp#</th>
<th>$T_s_{17}$</th>
<th>$S_P_{17}$</th>
<th>$K_{ef_{17}}$</th>
<th>$w_{17}$</th>
<th>$w_{true}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(°C)</td>
<td>(°C/W)</td>
<td>(mW/cm$^{-1}$°C)</td>
<td>(gm/ml-s)</td>
<td>(gm/ml-s)</td>
</tr>
<tr>
<td>11:52</td>
<td>38</td>
<td>36.168</td>
<td>398.1</td>
<td>7.773</td>
<td>23.263</td>
<td>31.810</td>
</tr>
<tr>
<td>12:09</td>
<td>39</td>
<td>36.192</td>
<td>391.1</td>
<td>9.235</td>
<td>41.731</td>
<td>43.965</td>
</tr>
<tr>
<td>12:17</td>
<td>40</td>
<td>36.216</td>
<td>400.4</td>
<td>7.373</td>
<td>19.151</td>
<td>42.008</td>
</tr>
<tr>
<td>12:23</td>
<td>41</td>
<td>36.225</td>
<td>399.8</td>
<td>7.473</td>
<td>20.142</td>
<td>41.546</td>
</tr>
<tr>
<td>12:31</td>
<td>42</td>
<td>36.214</td>
<td>396.0</td>
<td>8.165</td>
<td>27.696</td>
<td>40.049</td>
</tr>
<tr>
<td>12:43</td>
<td>43</td>
<td>36.096</td>
<td>408.4</td>
<td>6.279</td>
<td>9.36</td>
<td>39.818</td>
</tr>
<tr>
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<td>44</td>
<td>36.076</td>
<td>397.8</td>
<td>7.814</td>
<td>23.716</td>
<td>39.495</td>
</tr>
<tr>
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<td>35.388</td>
<td>409.3</td>
<td>6.184</td>
<td>9.271</td>
<td>19.069</td>
</tr>
<tr>
<td>13:09</td>
<td>46</td>
<td>35.316</td>
<td>411.2</td>
<td>5.977</td>
<td>7.915</td>
<td>18.318</td>
</tr>
<tr>
<td>13:17</td>
<td>47</td>
<td>35.221</td>
<td>413.3</td>
<td>5.757</td>
<td>6.594</td>
<td>18.057</td>
</tr>
<tr>
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<td>1.916</td>
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</tr>
<tr>
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<td>4.972</td>
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<td>17.024</td>
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<td>2.626</td>
<td>15.457</td>
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</table>

$a_f = .23828$ cm

$K_f = 0.191$ mW/cm$^{-1}$°C

$K_m = 3.436$ mW/cm$^{-1}$°C

Data taken on: May 26, 1983
Table 5.10 The results of perfusion experiments taken by probe FL318 during rat experiment #104.

<table>
<thead>
<tr>
<th>Time</th>
<th>Exp#</th>
<th>$T_{s18}$ (°C)</th>
<th>$SP_{18}$ (°C/W)</th>
<th>$K_{ef18}$ (mW/cm°C)</th>
<th>$W_{18}$ (gm/ml-s)</th>
<th>$W_{true}$ (gm/ml-s)</th>
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</thead>
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<td>75.996</td>
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<td>269.928</td>
<td>43.965</td>
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<td>42.008</td>
</tr>
<tr>
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<td>1037.2</td>
<td>6.308</td>
<td>90.996</td>
<td>41.546</td>
</tr>
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<td>5.504</td>
<td>43.473</td>
<td>39.818</td>
</tr>
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<td>6.199</td>
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<td>39.495</td>
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<tr>
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</tr>
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<td>23.776</td>
<td>18.318</td>
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<td>35.411</td>
<td>1079.9</td>
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<td>26.570</td>
<td>18.057</td>
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<tr>
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<td>5.495</td>
<td>17.504</td>
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<tr>
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<td>4.303</td>
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</table>

$a_f = .06925 \text{ cm}$

$K_f = 0.2688 \text{ mW/cm°C}$

$K_m = 3.703 \text{ mW/cm°C}$

Data taken on: May 26, 1983
Table 5.11 The results of perfusion experiments taken by probe FLR17 during rat experiment #105.

<table>
<thead>
<tr>
<th>Time</th>
<th>Exp#</th>
<th>$T_{s_{17}}$</th>
<th>$SP_{17}$</th>
<th>$K_{ef_{17}}$</th>
<th>$W_{17}$</th>
<th>$W_{true}$</th>
</tr>
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<tbody>
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</tr>
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<td>27.353</td>
<td>58.170</td>
</tr>
<tr>
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<td>4.940</td>
<td>11.580</td>
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</tr>
<tr>
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<td>16.798</td>
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</tr>
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</tr>
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<td>409.7</td>
<td>6.140</td>
<td>7.216</td>
<td>45.340</td>
</tr>
</tbody>
</table>

$a_f = .23828 \text{ cm}$

$K_f = 0.191 \text{ mW/cm}^{-\circ C}$

$K_m = 3.669 \text{ mW/cm}^{-\circ C}$

Experiment #66 is not listed because microspheres were injected during this experiment - the solution in which the microspheres were suspended was 35°C thus altering the baseline temperature of the liver in an unquantifiable manner.

Data taken on: June 1, 1983
Table 5.12 The results of perfusion experiments taken by probe FLR18 during rat experiment #105.

<table>
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<th>Exp#</th>
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<th>$SP_{18}$</th>
<th>$K_{ef,18}$</th>
<th>$W_{18}$</th>
<th>$W_{true}$</th>
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</thead>
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<tr>
<td></td>
<td></td>
<td>(°C)</td>
<td>(°C/W)</td>
<td>(mW/cm°C)</td>
<td>(gm/ml-s)</td>
<td>(gm/ml-s)</td>
</tr>
<tr>
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<td>1034.6</td>
<td>6.096</td>
<td>64.745</td>
<td>62.659</td>
</tr>
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<td>149.490</td>
<td>62.450</td>
</tr>
<tr>
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<td>36.826</td>
<td>1039.8</td>
<td>6.221</td>
<td>72.172</td>
<td>59.880</td>
</tr>
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<td>1037.5</td>
<td>6.297</td>
<td>76.914</td>
<td>58.170</td>
</tr>
<tr>
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<td>36.807</td>
<td>1023.4</td>
<td>6.827</td>
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<td>58.341</td>
</tr>
<tr>
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<td>35.948</td>
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<td>5.934</td>
<td>55.744</td>
<td>11.220</td>
</tr>
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$a_f = 0.06925$ cm

$K_f = 0.2688$ mW/cm°C

$K_m = 3.854$ mW/cm°C

Experiment #66 is not listed because microspheres were injected during this experiment - the solution in which the microspheres were suspended was 35°C thus altering the baseline temperature of the liver in an unquantifiable manner.

Data taken on: June 1, 1983
Table 5.13 The results of perfusion experiments taken by probe FLR17/18 during rat experiments #104 and 105. Perfusion as measured by thermistor FLR17 and by thermistor FLR18 are determined by least squares fitting \( SP_{17} \) and \( SP_{18} \) to the true perfusion (see the text).

Note \( w_{m,17+18}^{17+18/2} \) is the average of \( w_{m,17} \) and \( w_{m,18} \).

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<tr>
<th>Exp#</th>
<th>( w_{m,17} )</th>
<th>( %error_{17} )</th>
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<th>( %error_{18} )</th>
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<td>39.991</td>
<td>11.9</td>
<td>45.390</td>
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</table>

Average error 12.5

Calibration Coefficients:

rat#104

\[ K_{m,17} = 3.425 \text{ mW/cm}\cdot\text{°C} \]

\[ A_{f,17} = 0.098 \text{ cm} \]

\[ K_{f,17} = 0.635 \text{ mW/cm}\cdot\text{°C} \]

rat#105

\[ K_{m,17} = 6.80 \text{ mW/cm}\cdot\text{°C} \]

\[ A_{f,17} = 0.041 \text{ cm} \]

\[ K_{f,17} = 2.35 \text{ mW/cm}\cdot\text{°C} \]

Note:

rat#104 = Exp#39-53

rat#105 = Exp#65-76
Figure 5.11 The relationship between SP and true perfusion in rat #104. SP was calculated from the power requirements of thermistor FLR17.
Figure 5.12 The relationship between SP and true perfusion in rat #105. SP was calculated from the power requirements of thermistor FLR17.
Figure 5.13 The relationship between SP and true perfusion in rat #104. SP was calculated from the power requirements of thermistor FLR18.
Figure 5.14 The relationship between SP and true perfusion in rat #105. SP was calculated from the power requirements of thermistor FLR18.
Figure 5.15 The relationship between effective conductivity and true perfusion in rat #104. Effective conductivity was calculated from the power requirements of thermistor FLR17.
Figure 5.16 The relationship between effective conductivity and true perfusion in rat #105. Effective conductivity was calculated from the power requirements of thermistor FLR17.
Figure 5.17 The relationship between effective conductivity and true perfusion in rat #104. Effective conductivity was calculated from the power requirements of thermistor FLR18.
Figure 5.18 The relationship between effective conductivity and true perfusion in rat #105. Effective conductivity was calculated from the power requirements of thermistor FLR18.
Figure 5.19 The relationship between perfusion as calculated from the
d power requirements of thermistor FLR17 and true perfusion.
The data from both rat #104 and 105 are included in this figure.
Figure 5.20 The relationship between perfusion as calculated from the power requirements of thermistor FLR18 and true perfusion. The data from both rat #104 and 105 are included in this figure.
Figure 5.21 The relationship between perfusion as calculated from the power requirements of thermistor FLR17 and true perfusion. The data from both rat #104 and 105 are included in this figure, however, discarded data points (see the text) are not included.
Figure 5.22 The relationship between perfusion as calculated from the power requirements of thermistor FLR18 and true perfusion. The data from both rat #104 and 105 are included in this figure, however, discarded data points (see the text) are not included.
Figure 5.23 The relationship between perfusion as calculated and fit from the power requirements of thermistor FLR17 and the corrected true perfusion. The data from both rat #104 and 105 are included in this figure.
Figure 5.24 The relationship between perfusion as calculated and fit from the power requirements of thermistor FLRL7 and the corrected true perfusion. The data from both rat #104 and 105 are included in this figure.
Figure 5.25 The relationship between perfusion as calculated and fit from the power requirements of thermistor FLR17 and FLR18 and the corrected true perfusion. The data from both rat #104 and 105 are included in this figure.
Chapter 5.6 Conclusions

In chapter 5 the critical steps in the evaluation of the noninvasive probe were presented. The resistance versus temperature calibration showed that a noninvasive probe could accurately and reproducibly measure temperature. The thermal properties calibration, and the test of that calibration, indicated that the conductivity of a medium could be measured to within approximately 2% error. The isolated rat liver perfusion experiments were conducted to determine the accuracy with which the noninvasive probe could measure perfusion and the sensitivity with which the probe could measure changes in perfusion. Figures 5.11 through 5.14 showed that the probe was sensitive to changes in perfusion. However, Figures 5.19 and 5.20 showed that given 1) the a priori $a_f$ and $K_f$, and 2) the measured intrinsic thermal conductivity, $K_m$, there was an apparent inability to accurately quantify perfusion. However, given a least squares fit of $a_f$, $K_f$ and $K_m$ the percent error between "measured" perfusion and true perfusion is encouragingly low. Other investigators, namely Castellana et. al. [36] and Valvano [31], found a similar low percentage error given a similar fit/"calibration". This percent error is, however, more an indication of the sensitivity of the noninvasive probe than of the absolute accuracy with which the probe can quantify perfusion. Therefore, the conclusion to be drawn from these rat liver perfusion experiments is that the sensitivity of the noninvasive probe to changes in perfusion is very good and that given a "fit/calibration" the ability of the noninvasive probe to accurately quantify perfusion is also excellent (typically within 15% error).
Chapter 6  *Suggestions for Further Research*

Clearly, the result of this research effort was not a transducer/instrument for everyday use in a clinical environment. Important steps were, however, taken toward this desired end. In taking these steps several critical problems were encountered; a few were not solved. First, it was noted that the noninvasive probes used were extremely fragile - a slight bump to two of the probes changed the room temperature resistance values from approximately 1K ohms to 10K ohms. Such fragility was previously encountered with the invasive spherical thermistors if they were left uninsulated. Thus perhaps the fragility was just one manifestation of the insulation problems previously mentioned (and see below) or perhaps fragility is a factor inherent to thin (0.02 cm thick) flake thermistors. Irrespective of the reason, thermistor fragility hindered this research and would hinder the transducer operation in most research and clinical environments.

A second major problem was protecting the thermistor from the environment. An isotonic, aqueous environment is a difficult one in which to conduct electrical experiments. Insulation of the electronics (i.e. thermistors) from the environment proved to be difficult and may have been the cause of the eventual malfunctioning of the noninvasive probes. Two thermistor noninvasive probes are more difficult to use than are one thermistor invasive probes because there is an increase in conductance between the two flake thermistors as ions leak through the insulation barrier. Such an increase in conductance seemed to be well correlated with the increases in noise seen on the voltage² versus time⁻¹/² plots. Insulation problems encountered were probably a result of two factors, first the thermistors in the noninvasive probe are
square. It is apparent that the sharp corners of these thermistors were
the nidus of tears in the insulation; perhaps disk-shaped flake
thermistors are more appropriate. Second, even in the absence of tears
the insulation used did not seem to adequately halt water and ion
fluxes; a better insulation is required.

The noninvasive measurement of perfusion was the goal of this
research. The approach documented in this thesis is just one of several
possible approaches. Appendix F presents preliminary data for another
viable approach - the placement of a single spherical thermistor on the
surface of the medium of interest. An approach which was not completely
evaluated is to use larger flake thermistors - see Chapter 4.2. Such an
approach could yield a system that is a better approximation to true
one-dimensional heat flow. However, as noted in Appendix B, the power
requirements of such a probe would be much greater than can be provided
by the present instrumentation system.

One final comment, the ability of the thermal diffusion probe (TDP)
to measure perfusion, invasively or noninvasively, is strictly dependent
upon the ability to accurately quantify thermal conductivity and/or
thermal diffusivity. At present, the calibration media used to test the
probes have conductivities ranging from 2.89 mW/cm-°C (glycerin) to 6.23
mW/cm-°C (water); however, when measuring perfusion one often encounters
effective thermal conductivities on the order of 10 to 12 mW/cm-°C or
greater. Although it is not unreasonable to expect that the TDP can
measure thermal conductivity in the 10 to 12 mW/cm-°C range it is
unproven that the TDP is accurately measuring thermal conductivities in
this range. Thus, although this author could find no liquids with a
thermal conductivity between 6.23 mW/cm-°C and approximately 83 mW/cm-°C
(mercury) [46,47], such a substance is needed to 1) verify the accuracy of the TDP thermal conductivity calibration for measuring thermal conductivity greater than 6.23 mW/cm·°C, and 2) improve the accuracy with which the TDP can quantify perfusion.
Appendix A: Finite Difference Analysis

Theory

Finite difference analysis is based on the approximation that a differential equation can be written as a difference equation [43]. One can convert a differential equation into a difference equation using either a forward, backward, or central difference formulation. Because of the instabilities involved with the forward and backward formulations a central difference formulation was utilized in the calculation of the thermal wavefront produced by the heated noninvasive thermistor probe.

In general:

<table>
<thead>
<tr>
<th>Differential form</th>
<th>Difference form</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\frac{\partial f(x,y,z,t)}{\partial x}$</td>
<td>$\frac{f_{\ell+1,m,n,t} + f_{\ell-1,m,n,t}}{2 \Delta x} - \frac{f_{\ell,m,n,t}}{(\Delta x)^2}$</td>
</tr>
<tr>
<td>$\frac{\partial^2 f(x,y,z,t)}{\partial x^2}$</td>
<td>$\frac{f_{\ell+1,m,n,t} + f_{\ell-1,m,n,t} - 2f_{\ell,m,n,t}}{2 \Delta x}$</td>
</tr>
<tr>
<td>$\frac{\partial f(x,y,z,t)}{\partial t}$</td>
<td>$\frac{f_{\ell,m,n,t+1} - f_{\ell,m,n,t}}{\Delta t}$</td>
</tr>
</tbody>
</table>
Thus, for example, if we have the differential equation

\[
\frac{\partial f}{\partial x} = c \frac{\partial f}{\partial t}
\]

the corresponding difference equation is

\[
\frac{f_{\ell+1,m,n,t} + f_{\ell-1,m,n,t}}{\Delta x} = \frac{c}{\Delta t} \left( f_{\ell,m,n,t+1} - f_{\ell,m,n,t} \right)
\]

In this way the value of \( f \) at \( x,y,z \) at time \( t+1 \) can be calculated from values at time \( t \) using the equation

\[
f_{\ell,m,n,t+1} = \frac{\Delta t}{c \Delta x} \left( f_{\ell+1,m,n,t} + f_{\ell-1,m,n,t} \right) + f_{\ell,m,n,t}
\]

Application of the difference equation to a particular problem requires that the system under consideration be subdivided into regions called nodes, where the value of the parameter \( f \) is assumed constant throughout the region. Thus for each time \( t \) the parameter \( f \) has a value assigned to it. One then uses the governing difference equation(s) and the boundary conditions to compute the value of \( f \) at each node for all times. Initial conditions determine the value of \( f \) at all nodes at time \( t=0 \).
Application to the noninvasive probe

A finite difference analysis of the coupled tissue - noninvasive probe system was implemented to determine the spatial and temporal nature of the developing isotherms. The thermistor probe was assumed to achieve a spatially and temporally constant temperature at time \( t=0 \). The abutting medium was assumed to be initially at rest (i.e. \( T_{t=0} = 0 \)). It was further assumed that no thermal resistance exists between the flake and the medium; thus at the interface the temperature of the flake and the medium are equal.

The 'Bio-heat' equation governs the transport of heat in the tissue. For this case one writes the 'Bio-heat' equation as

\[
\frac{\partial^2 V_m}{\partial t^2} - \frac{w c_{bl} V_m}{K_m} = \frac{1}{\alpha_m} \frac{\partial V_m}{\partial t}
\]

A.7

where
1) \( V_m = T_{\text{medium}} - T_{\text{initial}} \)
2) \( w \) is perfusion,
3) \( c_{bl} \) is the specific heat of blood,
4) \( K_m \) is the intrinsic thermal conductivity of the medium and
5) \( \alpha_m \) is the intrinsic thermal diffusivity of the medium.
Using the central difference formulation and solving for $V_{m,n,l,t+1}$ one finds:

$$V_{\ell,m,n,t+1} = \frac{\alpha_m \Delta t}{(\Delta x)^2} \left[ V_{\ell+1,m,n,t} + V_{\ell-1,m,n,t} + V_{\ell,m+1,n,t} + V_{\ell,m-1,n,t} + V_{\ell,m,n+1,t} + V_{\ell,m,n-1,t} \right]$$

$$- \left[ 1 - \frac{6 \alpha_m \Delta t}{(\Delta x)^2} \right] V_{\ell,m,n-1,t}$$

$$- \omega c_{bl} \Delta t \frac{\alpha_m}{K_m} V_{\ell,m,n,t}$$

A.8

This equation can be simplified by letting

$$n = \frac{(\Delta x)^2}{\alpha_m \Delta t} = 6$$

A.9
Therefore

\[ V_{\ell,m,n,t+1} = \frac{1}{6} \left[ V_{\ell+1,m,n,t} + V_{\ell-1,m,n,t} \right. \]
\[ + V_{\ell,m+1,n,t} + V_{\ell,m-1,n,t} \]
\[ + V_{\ell,m,n+1,t} + V_{\ell,m,n-1,t} \]
\[- ( w c_{bl} a_m \Delta t/K_m ) V_{\ell,m,n,t} \] \hspace{1cm} (A.10)

In the limit where perfusion, \( w \), is zero this equation implies that the future value of the temperature, \( V \), at some node is simply the average of the present temperature of the six surrounding nodes.

Implementation

The software written to implement the finite difference analysis takes advantage of several symmetry conditions that exist in this particular system. The flake is modeled as a set of four nodes on the surface of a 20 X 20 X 20 matrix of nodes. See Figure A.1. Planes of symmetry exist where \( Z=0 \), i.e. the XY plane, and where \( Y=0 \), i.e. the XZ plane; the \( X=0 \) plane, i.e. the ZY plane is modeled as an adiabatic boundary. For \( X \), \( Y \), or \( Z \) greater than 20 the temperature, \( V \), is zero for all time; that is, it is assumed that far away from the thermistor, the heating has no effect. Thus in effect the thermistor probe is a set of nine nodes, a 3 X 3 square, on the surface of a semi-infinite medium modeled by a 20 X 40 X 40 matrix of nodes, refer to Figure A.2.
Figure A.1 A schematic of the finite difference model used to analyze the heat flow from the flake thermistor. Note that the flake is modeled as a set of 4 nodes on the surface of a 20 x 20 x 20 matrix of nodes.
Figure A.2 A schematic of the finite difference model used to analyze the heat flow from the flake thermistor. Note that because of symmetry the flake is actually a set of 9 nodes on the surface of a 20 x 40 x 40 matrix of nodes.
Appendix B Initial Power Requirements of the Flake Thermistor

A simple first-order estimation of the initial power requirements of a self-heated thermistor can determined as follows.

Let:

\[ \rho = \text{the density of the thermistor (gm/ml)} \]
\[ c = \text{the specific heat of the thermistor (W-s/gm\textdegree C)} \]
\[ V = \text{the volume of the thermistor (ml)} \]

thus \( \rho c V = \text{the thermal mass of the thermistor (W-s}/\text{°C)} \).

Further let:

\[ \Delta T = \text{the desired temperature step (°C)} \]
\[ P_m = \text{the maximum power that can be applied to the thermistor (W)} \]
\[ \tau_h = \text{the time needed to reach the desired heated temperature (s).} \]

Therefore \( \rho c V \Delta T = P_m \tau_h \)

In general, one knows that \( \rho c = K/\alpha \). For an invasive thermistor probe it has been found that [31]:

\[ \alpha = 0.958 \times 10^{-3} \text{ cm}^2/\text{s} \]

and \( K = 1.31822 \times 10^{-3} \text{ W/cm\textdegree C.} \)

Thus, \( \rho c = 1.4 \text{ W-s/cm}^3\textdegree \text{C}. \) This value is assumed typical for thermistor probes, both invasive and noninvasive. Thus to estimate the heating time constant for the large, 0.65 cm X 0.65 cm X 0.04 cm, noninvasive probes first one calculates:

\[ V = .017 \text{ cm}^3. \]

The applied temperature step, \( \Delta T \), is typically 4.0°C and the maximum power, \( P_m \), is approximately

\[ (15 \text{ volts})^2/10^3 \text{ ohms} = .225 \text{ Watts} \]
Thus:

\[ \tau_h = 0.4 \text{ seconds} \]

Remember that this time constant is calculated without considering heat flux from the thermistor. If heat flux were considered then the time constant would certainly be greater than 0.4 seconds.

In order to utilize the results of the thermal model, which assumes a step change in the volume average temperature of the thermistor, \( \tau_h \) must be on the order of 50 milliseconds or less.

Note that for the invasive probe:

\[ V = (0.05)^3 4 \pi / 3 = 5.24 \times 10^{-4} \text{ cm}^3 \]

thus: \( \tau_h = 13.0 \text{ milliseconds} \).

And for the small noninvasive probes:

\[ V = 0.1 \times 0.1 \times 0.02 = 2 \times 10^{-4} \text{ cm}^3 \]

thus: \( \tau_h = 5.0 \text{ milliseconds} \).

In order to heat the large noninvasive probes, for example, in 50 milliseconds, \( P_m \) must be at least

\[ P_m = \rho c V \Delta T / \tau_h = 1.9 \text{ Watts} \]

Therefore, for a 1000 ohm thermistor the supply voltage must be

\[ V = \sqrt{PR} = 44 \text{ volts} \]

In order to heat a 2cm x 2cm x 0.04cm thermistor flake for example, in 50 milliseconds, \( P_m \) must be at least

\[ P_m = \rho c V \Delta T / \tau_h = 18 \text{ Watts} \]

Therefore, for a 1000 ohm thermistor the supply voltage must be

\[ V = \sqrt{PR} = 135 \text{ volts} \]
Appendix C

The Effects of Agar on the Thermal Conductivity of Water

Introduction

In the process of calibrating the noninvasive probes, two media of known thermal conductivity must be used, glycerin and water. The true thermal conductivity of these media are well known [46,47]; however, water cannot be used in its liquid form because of the unquantified effects of free convection. Thus an agar gel of water is made. The purpose of this appendix is to present the results and conclusions of an experiment done to assess the effects of varying the concentration of agar in water on the measured thermal conductivity of water-agar gels.

Experimental Method

Each water-agar gel was prepared as follows:

- 200 ml of distilled water was brought to a boil in a stoppered 250 ml Erlenmeyer flask,
- the appropriate amount of agar (e.g. for 1.5 wg% agar - 3.000 gms) was slowly added over approximately a 1 minute period to the stirred boiling water,
- the mixture was then allowed to cool to room temperature.

Note: 0.25 wg% to 1.75 wg% agar was used because if less than 0.25 wg% agar is used then a gel does not form and if more than 1.75 wg% agar is used then the agar does not completely dissolve in the water. (Standard calibration procedures call for the use of 1.5 wg% agar.)

Precalibrated invasive probes were inserted into the gel and used to measure the thermal conductivity of the water-agar gels at 37°C.
Results

Table C.1 and Figure C.1 show the measured thermal conductivity of each water-agar gel. Note that all points are recorded as the mean of ten experiments ±1 standard deviation. These results seem to indicate that over the range of 0.25 wg% to 1.75 wg% agar there is no measurable difference in the thermal conductivity of the water-agar gels. Thus, although the thermal conductivity of a pure water solution was not measured, extrapolation of these results to the 0.0 wg% agar point would seem to indicate that thermal conductivity of pure water is the same as the thermal conductivity of a water-agar gel.
Table C.1: The measured thermal conductivity of various water-agar gel mixtures. Note that there is no statistically significant difference between the measured thermal conductivity of any of these mixtures. (All measurements were taken at 37°C and are recorded as the mean ± S.D. for N = 10 experiments.)

<table>
<thead>
<tr>
<th>wg% agar</th>
<th>Measured K (mW/cm°C)</th>
<th>Probe B32GH</th>
<th>Probe B317H</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>6.410±.048</td>
<td>6.491±.037</td>
<td></td>
</tr>
<tr>
<td>0.50</td>
<td>6.401±.027</td>
<td>6.552±.037</td>
<td></td>
</tr>
<tr>
<td>0.75</td>
<td>6.403±.041</td>
<td>6.498±.031</td>
<td></td>
</tr>
<tr>
<td>1.00</td>
<td>6.372±.036</td>
<td>6.516±.028</td>
<td></td>
</tr>
<tr>
<td>1.25</td>
<td>6.402±.028</td>
<td>6.482±.029</td>
<td></td>
</tr>
<tr>
<td>1.50</td>
<td>6.394±.050</td>
<td>6.499±.027</td>
<td></td>
</tr>
<tr>
<td>1.75</td>
<td>6.424±.029</td>
<td>6.535±.036</td>
<td></td>
</tr>
</tbody>
</table>
Figure C.1 The relationship between the thermal conductivity as measured by an invasive thermistor probe and the weight percent agar of the medium in which the thermistor probe was placed.
Appendix D Some Unilateral Laplace Transforms

The following is a listing of some unilateral Laplace transform identities that were used to solve the heat transfer problem of Chapter 3. For a more complete listing see [41, 42].

The definition of the unilateral Laplace transform is:

\[ \mathcal{L}[v(t)] = \bar{v}(s) = \int_0^\infty e^{-st} v(t) \, dt \]

Transform Identities

1) \( v(t) \quad \bar{v}(s) \)

2) \( \partial v(t)/\partial t \quad s \bar{v}(t) - v(t=0) \)

3) \( \gamma v(\gamma t) \quad \bar{v}(s/\gamma) \)

4) \( u_{-1}(t) \quad 1/s \)

5) \( u_0(t) \quad 1 \)

6) \( u_1(t) \quad s \)

7) \( e^{-at}/\sqrt{t} \quad \sqrt{\pi}/\sqrt{s+a} \)

8) \( \frac{e^{-zt}}{2 \sqrt{\pi}} \quad \sqrt{s+z} \)

9) \( e^{-zt} \quad \sqrt{z + \frac{\sqrt{\pi}}{\sqrt{zt}} + \sqrt{z} \left( \text{erf}\sqrt{zt} - 1 \right)} \quad \sqrt{s+z}/s \)
10) \( \text{erfc}(\sqrt{st}) \)

Note:

\[
\text{erfc}(x) = 1 - \text{erf}(x) \\
\text{erf}(x) = \frac{2}{\sqrt{\pi}} \int_{0}^{x} e^{-\phi^2} d\phi
\]
Appendix E  The Ringer's Solution

The Ringer's bicarbonate buffer solution is prepared as follows:

Into 4 liter of distilled water add:

27.76 g NaCl
1.416 g KCl
1.524 g CaCl₂
0.648 g KH₂PO₄
1.176 g MgSO₄
3.60 g glucose

then bubble CO₂ into the water for 10-15 minutes,
stop the CO₂ and add:

8.40 g NaHCO₃.

During the liver perfusion 95% O₂ and 5% CO₂ are bubbled into the Ringer's solution. Thus the liver is perfused with an isotonic, buffered (pH = 7.4), fully oxygenated, nutritive medium.
Appendix F The Spherical Noninvasive Probe

The results shown in Chapters 5.3 and 5.4 suggested that the guarding thermistor, FLR17, was sensitive to the thermal properties of the medium upon which the noninvasive probe rested. Thus, even though some of the heat leaving this thermistor was not entering the medium, but was in fact diffusing "up" the probe stem, there was enough heat flow into the medium for the thermistor to be sensitive to the thermal properties of the medium. Consequently, it was hypothesised that if an "invasive" spherical thermistor probe was placed on the surface of a medium, it too would be sensitive to the thermal properties of the medium.

To test this hypothesis a spherical thermistor was epoxied to a plastic base, see Figure F.1, in order to minimize convective heat flow into the environment. This "noninvasive" probe was then placed on the surface of several media of known thermal conductivity, as in Chapter 5.4. The thermistor was heated and the power requirement monitored in the usual manner. The steady-state power requirement was calculated from a linear regression of the power versus time\(^{-1/2}\) relationship over the period between \(t=30\) seconds and \(t=98\) seconds. The results of this experiment are shown in Table F.1 and Figure F.2. Note that a perfectly linear relationship between true and measured thermal conductivity does not exist, however, the thermistor is sensitive to the thermal properties of the abutting medium. This nonlinearity may be due to a miscalculation of the true thermal conductivity of the mixtures of glycerin and agar. One possibility is that the nonlinearity can be accounted for using an empirically expression for the thermal conductivity of a mixture of two mediums [53]:
\[ K_{\text{mix}} = K_g X + K_w (1-X) + 1.4X(X-1)(\Delta K - 0.2) \\
- 1.4X(X-1)(T-20^\circ C) \times 10^{-3} \]

where

- \( K_g \) = thermal conductivity of glycerin at temperature \( T \),
- \( K_w \) = thermal conductivity of water at temperature \( T \),
- \( X \) = mass fraction of glycerin,
- \( \Delta K = K_w - K_g \),
- \( T \) = the temperature of the measurement.

Further investigation of this method is encouraged.
Table F.1 Results of an experiment in which spherical thermistor BOODH was placed on the surface of media of known thermal properties (at 37°C). Note the less than 5% error in measured thermal conductivity. Results reported as mean S.D. N=10.

<table>
<thead>
<tr>
<th>K_{m_{true}}</th>
<th>SP BOODH</th>
<th>K_{measured}</th>
<th>%ERROR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.894</td>
<td>520.0 2.0</td>
<td>2.988 .022</td>
<td>3.2</td>
</tr>
<tr>
<td>3.82</td>
<td>473.7 0.6</td>
<td>3.596 .007</td>
<td>5.86</td>
</tr>
<tr>
<td>4.77</td>
<td>424.3 1.3</td>
<td>4.594 .033</td>
<td>2.69</td>
</tr>
<tr>
<td>5.30</td>
<td>398.6 0.8</td>
<td>5.369 .028</td>
<td>1.30</td>
</tr>
<tr>
<td>6.234</td>
<td>368.1 0.6</td>
<td>6.712 .036</td>
<td>7.67</td>
</tr>
</tbody>
</table>

Average error = 4.4

Note: the calibration coefficients were determined from the least squares fit of SP versus K_{m_{true}}:

a_f = .097283 cm

K_f = 0.6644 mW/cm-°C

Date of experiment: March 18, 1983.
Figure F.1 Schematic cross section of the single spherical thermistor noninvasive probe. This design was selected to 1) stabilize the thermistor, and 2) maximize heat flow into the tissue (the low thermal conductivity of the plastic minimizes heat flow in the direction toward the plastic).
Figure F.2 The relationship between thermal conductivity as measured by the single spherical thermistor probe and the true thermal conductivity of the medium upon which the probe was placed. The average percent measurement error is 4.4%. 

\[ \text{K}_{\text{measured}} \] 
\[ (\text{mW/cm}^\circ\text{C}) \] 
\[ 6.5 \] 
\[ 5.5 \] 
\[ 4.5 \] 
\[ 3.5 \] 

True thermal conductivity (mW/cm$^\circ$C)
Appendix G

Radiolabeled Microspheres - The Theory and Practice of Their Use

The purpose of this research is to develop a system to noninvasively measure tissue perfusion. In order to prove that the system accurately quantifies perfusion, an independent method must exist to simultaneously quantify perfusion. This independent method must be accepted as an accurate and reproducible means of quantifying perfusion. A method involving the use of radiolabelled microspheres meets these criterion.

In general, if an organ has only one efferent vessel then the total flow to that organ can be determined by collection of the effluent. However, without knowledge of the spatial distribution of the total flow, the perfusion to any particular region is essentially unknown. Microspheres can be used to quantify the spatial distribution of flow given 4 critical assumptions [6]:

1) the microspheres must be trapped within the microvasculature as they pass through an organ,
2) the microspheres must be well mixed within the perfusate,
3) the microspheres must distribute according to whole blood flow, and
4) the microspheres must not alter the normal blood flow.

For the rat liver perfusion experiments, the microspheres are $15 \pm 3$ microns in diameter; this size allows passage of the microspheres through arterioles while ensuring trapping in the hepatic sinusoids. The microspheres are injected at a rate of approximately $1$ ml/sec through a portal vein cannula 800 microns in diameter. Assuming a viscosity of 6.9 millipoise and a density of 1.0 gm/ml the Reynolds
number is 2301. Given this transitional range Reynolds number and that the microspheres are injected orthogonal to the flow, one can assume that the microspheres are well mixed. The latter two assumptions were investigated by Valvano et. al. [49] whose work, summarized in Chapter 5.3, indicated that these assumptions are generally valid.

As was discussed in Chapter 1.3.2.1, there are two methods of quantifying the spatial distribution of perfusion using microspheres, see Figure 1.3. The rat liver system has one afferent and one efferent vessel, therefore method #2 is used. In order to determine the temporal variation of perfusion, three different labels were injected at three different times.

Data Work-up

Background

After the microspheres are injected and trapped in the liver sinusoids, the liver is sectioned and the activity in each section is determined. Each radio-isotope used in these experiments emits a gamma ray (photon). These photons were detected using a Na(I) deep well counter [51]. In general when a photon enters the detector one of 3 events can occur [51]:

1) the energy of the photon is completely transferred to an electron (the photoelectric effect),
2) the photon energy is incompletely absorbed by an electron (the Compton Effect) thus liberating a lower energy electron and scattered photon, or
3) the photon will Compton-scatter off of the aluminum surrounding the Na(I) thus if later absorbed via the photoelectric effect will yield lower energy electrons (called Backscatter). Schematically
the results of these three effects are shown in Figure G.1.

The Na(I) detector "collects" the electrons produced by the above effects and produces an output pulse with a voltage proportional to the energy of the "collected" electrons. A multichannel analyzer (MCA) then "examines" the voltage of the pulse, determines which of 512 energy bins the pulse falls into, and increments the counter for the corresponding bin. Thus the output is a histogram of the number of detections at a certain energy level versus the energy of the photon detected.

Ideally, for a isotope emitting a gamma ray at only one energy level, the MCA output should show only one peak, see Figure G.2.a. However, detection is not perfect therefore the peak is spread over several channels, see Figure G.2.b. Thus to determine the intensity of the peak one must "integrate" to find the area under the peak. The relative intensity of two peaks is then the ratio of their areas.

The effects of peak asymmetry and backscatter also alter ones ability to accurately quantify peak intensity. As Figure G.2.c indicates, the total area under a peak can be considered the sum of the background and the "true" peak.

Finally, the area under a peak can be altered by the presence of other isotopes. Figure G.3 shows that the Ru$^{103}$ Compton plateau (from approximately 50 KeV to 295 KeV) effects the Co$^{57}$ peak at 122 KeV. The effects of crosstalk can be accounted for by determining the energy spectrum for a pure sample of an isotope.

Actual Data Work-up

Thus the data work-up proceeds as follows:

1) obtain an energy spectrum for

   a) all liver samples, and
b) a sample of each pure isotope.

2) for each spectrum find the number of counts in the peak corresponding to each isotope then identify the number of counts in the low and high region of each peak (see Figure G.2.c),

3) for the pure isotope (see also Figure G.3)

   a) time correct: change all counts to counts per minute

   b) background correct: find the number of "true" counts in each peak region

   c) determine the cross-talk correction factors: for example, using the spectrum of pure Ru$^{103}$ one can calculate the number of counts in the Co peak due to Ru cross-talk. Thus, for every count in the Ru peak there are N counts in the Co peak due to Ru$^{103}$ activity, where:

   \[
   \frac{\text{cpm in the "true" Co peak due Ru cross-talk}}{N} = \frac{\text{cpm in the "true" Ru peak}}{\text{ counts in the Co peak due to Ru cross-talk}}
   \]

   d) repeat part c for all isotopes.

4) for the liver samples:

   a) do a time-correction, thus all counts are now in cpm,

   b) do a background correction,

   c) cross-talk correct using the factors determined in part 3c above, (For example, for every count in the Ru peak subtract N count from the Co peak, where N is as calculated in part 3c.)

5) for each liver sample determine the true perfusion:

   \[
   \omega_{\text{true}} = \frac{F^{\text{CC}_i}}{60 \text{ CC}_{\text{total} m_i}} \rho_{\text{tissue}} \rho_{\text{perfusate}}
   \]
where

\[ w_{\text{true}} = \text{true perfusion (gm perfusate/ml tissue - sec)}, \]
\[ F = \text{collected flow (ml/sec)} \]
\[ CC_i = \text{crosstalk corrected counts in the } i^{th} \text{ piece (cpm)}, \]
\[ CC_{\text{total}} = \sum_{i=0}^{N} CC_i, \text{ for } N = \text{total number of liver samples (cpm)}, \]
\[ \rho_{\text{tissue}} = \text{density of tissue (gm/ml)}, \]
\[ \rho_{\text{perfusate}} = \text{density of perfusate (gm/ml)}. \]
\[ m_i = \text{mass of the } i^{th} \text{ piece (gm)} \]

For the work presented in Chapter 5 a small alteration in this data work-up procedure was made. Because a Na(I) detector, not a Ge(Li) detector, was used for gamma ray counting the ability to separate the Sn$^{113}$ (395 KeV) and the Ru$^{103}$ (495 KeV) peaks was more difficult. Thus, at the suggestion of Dr. D. Hnatowich of the University of Massachusetts Medical Center Department of Nuclear Medicine, the scheme illustrated in Figure G.4 was used. Note, that there is no background correction for the Ru and Sn peaks. Other than this small change the microsphere data work-up was conducted exactly as described above.
Figure G.1 Graphical representation of the three major effects encountered when detecting photons: a) main peak, b) main peak + Compton effect, c) main peak + backscatter, and d) all three effects.
Figure G.2 Graphical representation of the effects of photon detection imperfections: a) an ideal single line output, b) peak spread due to detector imperfections, and c) the effects of peak asymmetry and backscatter. Note that the number of counts in the "true" peak = the total number of counts in the entire peak region minus the counts in the background region, where:

$$\text{Background counts} = \frac{1}{2} \left( \frac{\text{Low counts}}{\# \text{ low channels}} - \frac{\text{Hi counts}}{\# \text{ Hi channels}} \right) \# \text{ peak channels}$$
Figure G.3 The energy spectrum of a pure sample of Ru$^{103}$. Note that 1) the Ru peak is at approximately 498 KeV, and 2) a Co$^{57}$ peak at 122 KeV would fall within the Compton plateau which extends from 53 KeV to 297 KeV.
Figure G.4 Schematic illustration of the technique used to determine the activity in each peak region. Remember that for each liver section the number of counts in a peak region relative to the total number of counts in the entire liver in that peak is more important for the determination of regional perfusion than the absolute number of counts in the "true" peak. Note that only the Co peak can be background corrected.
REFERENCES


