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THE IMPLEMENTATION AND EVALUATION OF TWO THERMAL TECHNIQUES
FOR MEASURING LOCAL TISSUE PERFUSION

by

Chris John Diederich

A Thesis Submitted to the Faculty of the
DEPARTMENT OF ELECTRICAL AND COMPUTER ENGINEERING
In Partial Fulfillment of the Requirements
For the Degree of
MASTER OF SCIENCE
WITH A MAJOR IN ELECTRICAL ENGINEERING
In the Graduate College
THE UNIVERSITY OF ARIZONA

1986
STATEMENT BY AUTHOR

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This thesis has been approved on the date shown below:

Robert B. Roemer
Professor of Aerospace and Mechanical Engineering

12/9/86 Date
ACKNOWLEDGEMENTS

The author wishes to thank Dr. Kenneth C. Mylrea and Dr. Robert B. Roemer for their advice and assistance during this project. The author would like to extend his gratitude to the following colleagues who have provided technical, as well as friendly, support: Dennis Anhalt, Scott Clegg, Eugene Gross, Charles Johnson, Reid Kress, Peggy Kundrat and Eduardo Moros. He would also like to offer thanks to Dr. Kullervo Hynynen and Dr. Tom Cetas.

The author would like to express his most sincere thanks to his parents, Daniel and Ann Diederich, for all of their love and encouragement. Most of all, the author offers his deepest appreciation to his wife, Robin, for her constant support and enduring love.
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ABSTRACT

Two techniques for measuring local blood perfusion have recently been developed: the thermal pulse-decay method and the thermal diffusion probe method. These techniques were implemented in such a way as to allow for the sequential operation of each method using the same thermistor probe. Comparative experimental evaluations were performed to investigate the feasibility of their use during hyperthermia treatments. This included testing in both in vivo and in vitro dog kidney preparations with controllable flows to the organs. The results indicate that both techniques are able to linearly track changes in blood flow and to also map perfusion gradients throughout a region of tissue.

Also, a theoretical study on the accuracy of two mathematical models that describe the pulse-decay system was undertaken. This study shows that both thermal-pulse decay solutions are inaccurate at blood flows less than 5-10 Kg/m^3-s, and an experimental protocol is suggested to minimize these errors.
CHAPTER 1

INTRODUCTION

Knowledge of the thermo-physical and related physiological properties of biological materials is critical to the accurate modeling of the bioheat transfer characteristics of specific regions of tissue. This is important in the clinical treatment of malignant tissues where the use of hyperthermia would benefit from the ability to accurately estimate the temperature field during a treatment. These important parameters of the tissue include the specific heat, density, energy absorption due to external sources, thermal conductivity, and local blood perfusion flow fields and magnitudes. Of the above parameters, the blood perfusion is considered the most important in determining the temperature distributions achieved in the tumors and the surrounding normal tissue [1]. The ability to measure and map tumor and normal blood flow, before and during a hyperthermia treatment, could improve the accuracy of the treatment modeling and thereby provide for a more effective treatment.

There are numerous methods now in use to determine the blood perfusion to various organs and regions of tissue such as tumors. Indicator dilution methods use radioactive or diffusible gases to quantify the net transport into the region of interest and yield an estimate of perfusion. Trapped indicator methods such as
radiolabeled microspheres are utilized, where the distribution of these spheres trapped within the capillary beds gives a direct indication of the regional flow rate. Also, thermal clearance methods are often utilized and, due to their simplicity, are more ubiquitous. A summary of the various types of indicator and thermal clearance techniques has been presented by R. Eberhart, A. Shitzer, and E. Hernandez [2]. An overall review of measurements of the thermal properties of biological materials has been presented by J. Chato [3]. Of the above methods mentioned, the thermal pulse-decay method and the thermal diffusion probe methods show the most promise in future usage in the clinic. The measurements are made with a small, invasive probe, and they do not require post-mortem analysis as the microsphere method does.

1.1 The Thermal Pulse-Decay Method

The thermal pulse-decay method (TPD) was developed by M. Chen and K. Holmes and is capable of simultaneously determining the local tissue perfusion and thermal conductivity [4-6]. The method has been shown to be able to estimate thermal conductivities with small error in non-perfused media [4]. Similar tests were performed to assess the ability of this method to estimate perfusion in the dog and rabbit kidney as compared to simultaneous measurements by microspheres [5]. A theoretical analysis and sensitivity study of this
method that describes an optimal experimental protocol to minimize the measurement error has been presented by H. Arkin [7-8].

This method utilizes a small thermistor probe (0.3 mm diameter [6]), imbedded within the tissue of interest, as both a constant power source and a temperature sensing element. To obtain a measurement, a pulse of constant power and known duration is electrically applied across the thermistor bead. Nominally, a power pulse of 5 mW is applied for a duration of 3 seconds. This power is dissipated throughout the immediate region of tissue surrounding the probe tip and thereby elevates the temperature above that of the initial steady state. After cessation of the power pulse, the resulting transient temperature decay is then measured by the thermistor, used now as a temperature sensing element, as the probe temperature and the tissue temperature fall back toward steady state. The maximum temperature rise reached during the power pulse is approximately 4°C. Typical temperature decay curves for perfused and non-perfused tests in our lab are illustrated in Figure 1. This transient temperature decay data is fit to an analytical model of the temperature decay process to yield the local tissue perfusion and the thermal conductivity.
Figure 1. Typical Temperature Decay Traces of the TPD.
The temperature decay process of the pulse-decay is described by the two following equations. A complete derivation of these expressions, as derived from the bioheat transfer equation, is found in Appendix A. The thermal conductivity of a non-perfused media is determined from the following expression:

$$k = \left(\frac{\rho c}{\pi}\right)^{1/3} \left[ P((t_m - t_p)^{1.5} - t_m^{1.5})/4T_0 \right]^{2/3}$$  \hspace{1cm} (1.1)

where:

- $k$ = thermal conductivity
- $\rho$ = density
- $c$ = specific heat
- $P$ = power
- $t_m$ = measurement time
- $t_p$ = pulse length
- $T_0$ = temperature rise at time $t_m$

A single temperature measurement, $T_0$, at time $t_m$ during the decay process, allows one to calculate the thermal conductivity. The values used for the specific heat and density are obtained from the literature and the power and pulse length are chosen experimental constants. In a perfused environment the temperature field is described by the following integral expression:

$$T_0(t) = \frac{P(\rho c)^{1.5}}{8\pi^{1.5}k^{1.5}} \int_0^{t_p} (t-s)^{-1.5} e^{-w/p(t-s)} \, ds$$  \hspace{1cm} (1.2)
where:

\[ w = \text{perfusion} \]

\[ s = \text{dummy variable of integration} \]

The parameters \( k \) and \( w \) are optimized to fit this expression to the temperature data. The optimized values are the estimated values of thermal conductivity and perfusion.

This technique is enhanced by two salient features: the effective measurement volume of the probe can be varied and the proximity of the probe to non-ideal perfused regions such as large vessels and highly directional flow fields can be determined. These non-ideal regions are defined as those that do not adhere to the assumptions of the bio-heat transfer equation: these assumptions include homogeneous tissue properties within the field of measurement and a uniform, non-directional perfusion [9]. The effective volume is defined as the volume of tissue that is thermally perturbed at the time of measurement and increases in proportion to the measurement time [6]. At long measurement times this volume is sufficiently larger than the probe traumatized tissue volume thereby allowing these adverse effects to be neglected [6]. This method nominally uses a 6 second interval of the temperature decay data in the fitting algorithm to obtain an average measurement radius of roughly 15 times the radius of the thermistor bead [4]. For the probes under current use, with a radius of 0.178 mm, the effective radius is roughly 2.7 mm and the effective volume is \( 80 \text{ mm}^3 \). Since the effective measurement radius increases proportionally to the
square root of the measurement time [6], the effective volume can be controlled by fitting temperature data in either earlier or later intervals. This control adds flexibility to the technique. For instance, if the probe tip is located near a large blood vessel or non-homogeneous region, the effective volume can be limited to not include this region.

The closeness of the probe to non-ideal regions can be determined from traces of the apparent conductivity versus the measurement time, as computed from the non-perfused formula (Equation 1.1). In this case, a non-ideal region is defined as the tissue volume surrounding the probe with characteristics that do not adhere to the assumptions of the bioheat transfer equation; i.e., non-homogeneous tissue properties, directional flow fields, and the proximity of large blood vessels. The time dependence of the thermal conductivity from Equation 1.1 is specific to tissue regions that strictly adhere to the assumptions of the bioheat transfer equation. As suggested by Chen and Holmes [4], the comparison of these experimental curves to nominal predicted curves indicates the goodness of the probe position and data collected. In other words, if a large error exists between the two traces then the theoretical model used is not adequate to predict the thermal conductivity or perfusion.

1.2 The Thermal Diffusion Probe Method

The thermal diffusion probe method (TDP) was initially developed by H. Bowman, T. Balasubramanium, and M. Woods to predict
the thermal diffusivity and effective thermal conductivity of small
tissue volumes [10-11]. In the absence of perfusion this technique
can be used to give a direct measure of the thermal conductivity and
thermal diffusivity of that medium. In a perfused tissue, the
predicted thermal conductivity is an effective value and from the
deviation of this from the intrinsic conductivity of the non-
perfused tissue the local tissue perfusion can be extracted. The
analytical solutions that describe the system were later improved by
H. Bowman, J. Allen, and J. Valvano to give a more accurate
prediction of the perfusion [12]. This technique was evaluated by
the principal authors in non-perfused media and found to predict
thermal conductivity to within 1% [10-11]. Similar evaluations were
performed in isolated canine hindlimbs and rat kidney preparations
by comparing measurements of the thermal diffusion probe to
simultaneous microsphere measurements and it was found that the
predictions of perfusion correlate well with those determined from
microsphere trapping methods [12-13]. Also, Valvano, Cochran and
Diller used this technique to determine the thermal conductivities
and diffusivity of various biomaterials [14].

This method also utilizes a small thermistor probe (.75 mm
diameter [10]) imbedded in the medium of interest to monitor the
temperature. But, instead of applying a short pulse of constant
power similar to the TPD method, it is used to apply the transient
power necessary to maintain the probe temperature at a fixed
elevation above the initial steady state. This temperature
increment, usually 4°C, is prolonged for approximately 30 seconds. An analog controller circuit regulates the power over time to keep the probe at a constant temperature. As the surrounding tissue temperature rises toward the fixed probe temperature the surrounding temperature gradient in the tissue is reduced and less power is dissipated, thereby causing a slight heat up of the bead. The controller subsequently lowers the power applied in order to maintain the preset increment. Eventually, after long periods of time, the probe temperature and the surrounding tissue would reach steady state and the power required would also reach a steady state. The electrical power required is dependent on the characteristics of the surrounding medium where the presence of blood flow increases the power requirements. The model uses the time dependent characteristics of the transient power to determine the effective thermal conductivity and diffusivity as well as the blood perfusion. Typical transient power responses for perfused and non-perfused tests in our lab are shown in Figure 2. Normally, the interval from 4 to 20 seconds of the transient power response is used. For a complete explanation and the derivation of the analytical expressions used to determine the perfusion and the effective thermal conductivity and thermal diffusivity see Appendix A. To begin computation of the above parameters the transient power applied to the probe is curve fit to the following linear relation with $w$ initially set to zero:
Figure 2. Typical Power Response of TDP.
\[
\frac{V_p^2(t)}{R_f^{\frac{4}{3}} \pi^3} = \Gamma + \beta f(t)
\]

where the transient portion of the volumetric power requirements is

\[
f(t) = \exp\left\{-\frac{w_c b a_m t}{k_m}\right\} - \sqrt{\frac{w_c b a_m}{k_m}} \text{erfc} \sqrt{\frac{w_c b a_m t}{k_m}}
\]

Once the values of \(\Gamma\) and \(\beta\) are determined, the initial estimates of the desired parameters are determined directly from the following expressions:

\[
k_{\text{eff}} = \left(\frac{3\Delta T}{\Gamma a^2} \frac{0.2}{k_p}\right)^{-1}
\]

\[
\alpha_{\text{eff}} = \left[\frac{a}{(\pi \beta/\Gamma)(1 + 0.2 k_m/k_p)}\right]^2
\]

\[
w_1 = \left(\frac{k_{\text{eff}}}{k_m} - 1\right)^2 \frac{k_m}{\rho b c_b a^2}
\]
The transient power data is again curve fit to Equation 1.3 but this time the previous estimate of \( \omega \) from Equation 1.7 is substituted in Equation 1.4. This iterative procedure is continued until the solutions for \( k_{eff} \) and \( w_1 \) converge. The effective probe radius and thermal conductivity are specific to each probe and are determined prior to experimentation according to the calibration procedure described in Appendix C.

This method can also be used to predict the intrinsic thermal conductivity of a tissue region in the presence of blood perfusion.
This requires the sequential measurements of two probes, of different sizes, located within the same region. By eliminating \( w_1 \) in Equation 1.7 and setting the expressions for each probe equal, it is possible to obtain \( k_m \) from the following expression:

\[
\left( \frac{k_{\text{eff}1}}{k_m} - 1 \right)^2 \frac{1}{a_1^2} = \left( \frac{k_{\text{eff}2}}{k_m} - 1 \right)^2 \frac{1}{a_2^2}
\]  

1.9

Also, the proximity of large vessels or discontinuities in tissue properties can be discerned using this technique by comparing the non-linearities of the power response trace to those that are nominally linear. The effects of the significant vessels can be avoided by adjusting the measurement time, since the effective measurement volume increases with time. For most situations the effective volume has a radius that is 5 to 10 times the effective probe radius [14]. The probes used in our lab have an effective bead radius of 0.4 mm which yields an effective measurement volume ranging from 30 mm\(^3\) to 260 mm\(^3\) in the measurement interval from 5 to 60 seconds.

1.3 Description of Experimental Evaluation

A comparative evaluation of these two thermal techniques for measuring blood perfusion was performed to investigate the feasibility of their future use in our laboratory. Each of these methods were implemented, as described by the principal investigators, with modifications made in the controlling circuitry and data acquisition circuit, as well as in the construction of the thermistor probes.
The experimental apparatus allowed for the two techniques to be sequentially tested using the same probe, where a switch determined which method was used.

A set of experiments was designed to validate that the systems were operating correctly. Each method was used in media of known thermal conductivity and material properties to give an indication of how accurately they each predicted zero perfusion and the intrinsic thermal conductivity for that media. These results are compared to similar results as previously reported from each of the principle investigators, to establish that the methods, as implemented, were working correctly.

In the next set of experiments, these two techniques were evaluated in vitro using an alcohol fixed dog kidney preparation [15]. The kidneys were isolated in a constant temperature water bath and the total flow to the kidney was controlled by a pump and measured by an ultrasonic doppler flowmeter. The highly controlled nature of these experiments allowed for a more accurate statistical analysis and gave a better understanding of the accuracy and repeatability of each method, as well as its limitations in an "ideal" environment. Also, due to the lack of the constraints normally imposed on in vivo experiments, accurate perfusion mappings were able to be performed using a micro-manipulator to control the probe positions.

Finally, the ability of these techniques to predict perfusion was tested by measurements made in an in vivo dog kidney preparation.
and in the dog tongue. For the kidney preparations the kidney of an
anesthetized dog was isolated and a renal occluder and ultrasound
doppler flowmeter were placed around the renal artery. This allowed
the total flow to the kidney to be regulated by the occluder and
measured by the flowmeter. A series of perfusion measurements were
made using each technique, as the flow rate to the kidney was
varied. From these experiments, the ability of each of these
methods to monitor changing blood flow levels within the tissue of
the organ, as compared to changes in the total organ flow, was
determined. Also, the ability of these methods to yield adequate
perfusion field mappings was tested by measuring the magnitude of
perfusion at various positions within the kidney. In a separate set
of experiments the TPD method was tested in the tongue of an
anesthetized dog to test the ability of this technique to work in a
different type of tissue than the kidney.

1.4 Theoretical Study of Thermal Pulse-Decay

In addition to the experimental studies on the above tech­
niques, a theoretical analysis of the thermal pulse-decay method was
performed. The interactions between the measurement probe and the
surrounding tissue are described by two mathematical formulations--
the point source model as derived by Chen and Holmes [4] and the
spherical source model, derived by S. Clegg [16], as presented later
in this paper. These solutions are only approximations of the
complete description and therefore tend to exhibit inherent errors
or inaccuracies in their predictions of the temperature fields and
the corresponding estimations of perfusion. The sensitivity of these errors and their magnitudes were determined from a comparison to simulated transient temperature decay data that more accurately described those interactions. From this analysis an optimal measurement protocol and a better understanding of the inherent errors and limitations of the describing models is presented.
CHAPTER 2

EXPERIMENTAL APPARATUS AND PROCEDURES

2.1 Development of Apparatus

2.1.1 Probe Development

The measurement probes consisted of small thermistor beads fixed on the end of a piece of silica tubing, as shown in Figure 3. The silica tubing supported the thermobead and provided the rigidity needed to facilitate insertion into the tissue of interest. Also, the low thermal conductivity of this tubing limited conduction down the probe length.

The thermobeads used were Thermometrics type BR14, with a 0.356 mm outer diameter and a nominal resistance of 2000 ohms+/-5% (\(\angle25^\circ C\)) [17]. Two different size probes were constructed, depending on the diameter of the silica tubing used: For the 0.7 mm outer diameter silica tubing the platinum leads of the thermistor were soldered to either 3 mil teflon coated copper wire or 2 mil lacquer coated copper wire, and for the tubing with an outer diameter of 0.4 mm only the 2 mil copper wire could be used. The beads were fixed to the tip of the silica tubing with medical grade silicone rubber adhesive, with the lead wires passed through the core. A 60 cm length of polyethylene tubing (0.6 mm internal diameter, 0.96 mm outer diameter) was
Figure 3. Thermistor Blood Perfusion Probe.
inserted over the wires and partially over the end of the silica tubing, to provide insulation and durability, or protection, of lead wires during implantation. The ends of the leads were soldered to connectors and then the probes were resistance/temperature calibrated according to the procedure outlined in Appendix B. A more thorough explanation of the probe design and materials is found in Appendix D.

2.1.2 Implementation of The Thermal Pulse-Decay Technique

The thermal pulse-decay method requires that a short pulse of constant electrical power be applied to the thermistor bead and then the subsequent temperature field decay is measured. The original circuit implemented by M. Chen and K. Holmes utilized a wheatstone bridge to determine the probe resistance and a NE555 IC timer chip to regulate the duration of the pulse of voltage across the probe. This set up involved continuous adjustments of the bridge balance arm and calibration of the timing of the power pulse. To minimize the number of external adjustments prior to each measurement, the circuit in Figure 4 was implemented. The duration of the pulse was controlled by TTL trigger pulses to the flip-flop, which either turns on or off the transistor switch that drives the relay. In this case, mercury wetted relays were used to minimize switching delays and transients. When the relay was closed, a voltage \( V_h \) was applied across the thermistor probe in series with a variable resistor \( R_h \).
Figure 4. Circuit Diagram for TPD Method.
This variable resistor was used, when necessary, to adjust the power level applied to the probe. For example, to maintain a large enough temperature decay signal in a highly conductive region, the power level should be raised a few milli-watts above the level used for the low conduction case.

The above circuit was controlled by the system in Figure 5. The overall system consisted of an Hp 9836 desk top computer, Hp 3497a data aquisition unit, and an Hp 3456a digital voltmeter. The data aquisition unit controled the timing of the trigger pulses and the closing of the analog measurement channels. The voltages and the 4-wire resistance measurements were determined directly by the digital voltmeter, allowing the removal of bridge circuitry. All of the above processes were controlled by software on the 9836 desktop computer.

The software to control and process the data for the TPD method was written in HP BASIC 3.0. The general outline of the program and its various functions can be discerned from the flow chart in Figure 6.

After the system was initialized, the steady state temperature of the probe was monitored. When the temperature drift was below a minimum, the operator initiated a branching by depressing a softkey. This branching initiated the measurement cycle which began by measuring the initial probe resistance and then starting the constant power pulse. The length of the pulse could be varied but for most experimental situations it was set at 3 seconds.
Figure 5. Overall System for TPD and TDP Methods.
Figure 6. TPD Software Flow Chart.
During the middle of the pulse sequence the voltage across the probe thermistor ($V_s$) was measured. From this and the prior knowledge of $R_h$ and the measurement of $V_h$, the power to the probe was computed as follows:

$$P = \frac{(V_h - V_s)}{R_h}V_s$$  \hspace{1cm} (2.1)

After the duration of the power pulse a trigger command was sent to open the relay switch and turn the power off. Next, the transient temperature decay of the probe was monitored by recording resistance measurements for 15 seconds in intervals of 0.5 second. This measurement interval could be made as small as 0.1 seconds to as large as desired.

The resulting transient temperature decay was then determined from the above resistance measurements according to the following Equation [17] :

$$T = [A1 + A2 \log(R_p) + A3(\log(R_p))^3]^{-1}$$ \hspace{1cm} (2.2)

The coefficients $A1$, $A2$, and $A3$ are specific to each probe and are determined as shown in Appendix B. This calibration procedure was accurate to within 0.003°C. The parameters of the point source model were then optimized to curve fit the temperature data, giving simultaneous predictions of thermal conductivity and perfusion. Also, the apparent thermal conductivity was predicted from the non-perfused equation and the trace was displayed graphically. This gave an indication of the possible presence of large vessels or non-homogeneities in the region of the probe and, as compared to normal
traces, an idea of the overall goodness of the test. The optimization routine used the gauss method of minimization [18], with a convergence criteria of $1 \times 10^{-5}$.

2.1.3 Implementation of Thermal Diffusion Probe Technique

The Thermal Diffusion Probe method required that the transient power level in the thermistor be regulated so as to maintain a constant, preset, temperature or by direct correspondence, a preset resistance. This preset temperature increment had to be adjustable prior to experimentation. The complete circuit consisted of two sections: one for switching and the other for the controller. The circuitry suggested by H. Bowman and T. Balasubramanium [10] was modified to adapt to the Hp data acquisition system, except for the controller segment which was used as shown. This involved removing the wheatstone bridge circuitry and measuring the voltages and resistances directly with the data acquisition system as before. A complete circuit diagram, as implemented in this study, is shown in Figure 7.

The switching circuit was designed to control the double pole-triple throw relay switch when initiated by TTL trigger pulses from the Data Acquisition System. The trigger changed the logic level in the flip-flop, which when high drove the darlington pair transistor switch to apply the necessary current to close the relay. Again, mercury wetted relays were used to minimize bounce and transients. If the logic was low, the relay switch was open and the power circuit was off and the probe resistance was isolated.
Figure 7. Circuit Diagram for TDP Method.
The feedback control circuit consisted of an integrator and gain stage, with the difference between the voltages across $R_b$ and the probe used as feedback to adjust the current to maintain the preset temperature increment. This increment was set by a manual adjustment of the variable resistor to a value lower than the steady state probe resistance. This difference in resistance corresponded to a temperature increase. The controller drove the thermistor resistance toward that of the lower preset resistor by applying the current necessary to heat the thermistor and thereby decreased the resistance. Note that the thermistors used were negative coefficient variable resistances, so that resistances decreased as their temperatures increased.

The overall data acquisition system, as previously illustrated in Figure 5, was used to measure the transient voltages and the initial 4-wire resistance measurements of the probe and set value. The TTL trigger pulses to the switching circuitry were used to initiate and stop the transient application of power. All of these measurements and timing commands were controlled from the software on the Hp 9836 Desk Top computer.

The program that controlled the experiment, data acquisition, and the data reduction was written in Hp BASIC 3.0 and was run on the desk top computer. The flow chart of this program is shown in Figure 8.
Figure 8. TDP Software Flow Chart.
Initially, before the onset of the heating sequence, the initial resistances of the set point resistor and the probe were measured and the corresponding temperature difference between the two was displayed. At this point, if necessary, the set point resistor was altered to change the temperature increment to the desired value. Due to differences of the resistances between probes and the varying initial temperatures, adjustments were frequently made through an accessible potentiometer. The changes were continually monitored by the system and, when finished, the final set temperature increment was computed. At this point, if the increment was acceptable, the steady state temperature of the probe was monitored, and if the drift was below a minimum, the measurement sequence was initiated by depression of the appropriate softkey.

The next phase of the measurement cycle consisted of a final measurement of the initial probe resistance and once the temperature increment was established the power on sequence began. The TTL trigger pulses initiated the transient power application and then the voltage across the probe was recorded from 5 to 25 seconds after the start. The data was usually taken in an interval of 0.5 seconds but the system had the capacity to record a measurement every 0.1 seconds. After 30 seconds of time, TTL pulses reverted the system back to steady state. The resulting voltages were squared and plotted versus the inverse square root of time to give an indication of the validity of the data, as determined by any non-linearities, etc.
In the data reduction phase, the transient power response data was used to calculate the steady state and volumetric heat generation rate, as in Equation 1.3, by a least squares linear regression of the voltage squared versus the inverse square root of time. The parameter \( \beta \) was determined from the slope of this fit divided by the volumetric resistance of the probe given as follows:

\[
R_{\text{vol}} = \frac{R_f}{4/3\pi a^3}
\]

where \( a \) was the effective radius of the probe and \( R_f \) was the set point resistance. Similarly, the steady state parameter was determined from the intercept \( V_{ss}^2 \), the steady state voltage squared, divided by the volumetric resistance. These initial values were calculated for a zero perfusion situation using Equation 1.4, with \( w = 0. \), to give only an estimate of the correct values.

From these initial estimates, approximate values of \( k_{\text{eff}} \) and \( w \) were determined using Equations 1.5 and 1.7. Next, the transient voltage data was repeatedly fitted to Equations 1.3 and 1.4 but with \( w \) set to the most current estimate. At this step, after each linear regression of data, the values of \( k_{\text{eff}} \) and \( w \) were recalculated, and resubstituted into the fitting routine. After approximately 8 iterations the determinations of \( \Gamma \) and \( \beta \) converge and the final values of the effective thermal conductivity and diffusivity and the perfusion were calculated using Equations 1.5-1.8.
2.2 Experimental Methods

2.2.1 In Vitro Dog Kidney Experiments

These in vitro kidney preparations provided a perfused phan­tom with similar flow distributions and properties as those in the in vivo dog kidney preparations, but without the associated experimental variability. For this set of experiments the dog kidneys were fixed in alcohol using the method suggested by K. Holmes and associates [13]. A complete description of the alcohol fixation process can be found in Appendix F. The resulting flow field within these fixed kidney preparations is illustrated in Figure 9, a cross section photograph of a preparation that was perfused with blue dye.

During these experiments the fixed kidneys were isolated in a constant temperature water bath to essentially eliminate the transient temperature fluctuations as a source of error. The total flow of water to the preparation was controlled by a peristaltic pump and measured by an ultrasonic doppler flowmeter attached to the tubed extension of the renal artery. The water circulated through the kidney was degassed and the output from the renal vein was not monitored but it was recirculated. The fluid pressure drop across the kidney was monitored throughout the experiment to insure that the pressure values remained within the physiological limits to avoid damage or physical changes to the micro-structure. For an overall diagram of the system and experimental set-up, see Figure 10.
Figure 9. Cross Section Photograph of Alcohol Fixed Kidney Preparation.
Figure 10. Experimental Set-up for In Vitro Tests.
The silica probes were placed at various locations within the cortical and medullary regions of the kidney and fixed in place. These positions were approximate and determined by the distance of the probe tip from the surface of the kidney and a measurable presence of perfusion. Initially the probes were placed approximately 0.5 cm within the kidney, hopefully near the cortex. Then, the position of each probe was varied until large measurements of perfusion were recorded, thereby signifying that the probes were in the high flow region of the kidney, presumably the cortex. The total flow to the kidney was varied from normal \textit{in vivo} flow rates to zero in small increments. At each flow level a total of six measurements by each method were taken in an alternating fashion using the same probe. This process was repeated for numerous probes and locations throughout the kidney.

In another set of experiments the kidney position within the bath was fixed by suturing the exterior surface to a plastic template. The probe was attached to a micro-manipulator, where the distance of the probe tip from the external surface of the kidney was known. With the flow rate to the preparation maintained at a constant value, a series of perfusion measurements were made by each method as the location of the probe was varied. Again, the sequence of measurements was alternated between methods, with a total of 3 measurements for each technique.
2.2.2 **In Vivo** Dog Kidney Experiments

These *in vivo* dog kidney preparations allowed the probes to be tested in an *in vivo* environment where the total kidney flow surrounding the probe could be controlled and monitored. To implement the kidney preparation, the kidney of an anesthetized dog was surgically exposed and the vascular occluder and the ultrasound doppler flow probe were placed around the renal artery and were fixed with sutures. The flow probe transducer was then acoustically coupled to the vessel wall by insertion of a methyl paraben based gel between them, and then the area was wrapped in gauze to help maintain the coupling. At this point, the probe tracks through the kidney were made with needles and then the catheters were introduced through these into the anterior and posterior lobes of the kidney, and exited out the body wall. The above experimental set-up is illustrated in Figure 11. After the catheters were fixed in place the incision was closed with hemostats, a procedure which would allow for later access to the kidney from inside the abdomen.

The silica probes were placed through the catheters along the tracks, and with the thermistor tips visually placed at the medial surface of the kidney, the catheters were retracted, leaving only the measurement probes in the kidney. With the probe location known, the next step was to locate the highest region of flow—preferably the cortex. The high flow region was important since it yielded the largest changes in perfusion as the total organ flow was
varied. The probes were pulled back through the kidney toward the body wall in small increments, with perfusion measurements taken at each position. Once the position of high flow was determined, the position was fixed. The total flow to the kidney was then varied and approximately 10 perfusion measurements were made by each technique for each level of flow, alternating techniques between each of the measurements.

Next, the probes were pulled back from the above fixed position in increments of approximately 0.25 cm. For this procedure the total flow to the kidney was maintained at a constant, normal operating value. At each position the TDP method was used to determine the perfusion and as a result, mappings of perfusion versus the distance from the original position in the dog kidney were obtained.
Figure 11. Experimental Set-up for In Vivo Tests.
2.2.3 *In Vivo* Dog Tongue Experiments

This set of tests was performed in a tissue other than the kidney to further insure that the TPD method was properly developed and determine whether or not it was accurately measuring values of blood perfusion as well as thermal conductivity. At the time of these tests the TDP method was still under development and so was not tested concurrently. Two of the silica thermistor probes were placed in different locations within the dog tongue, with the probe tips being placed as far from either exposed surface as possible. Once the probe temperatures were at equilibrium with the surrounding tongue tissue, multiple measurements were made using both probes. The exact depth of the probe into the tissue, as well as the tongue dimensions and proximity to large vessels, were not recorded.

2.2.4 Validation in Known Media

To determine that either measurement system was accurately operating, the methods were tested in materials of known thermal properties and in the absence of perfusion. The ability of each technique to predict the intrinsic thermal conductivity and a value of zero perfusion was determined. For these tests the silica probes were positioned in the medium which in turn was isolated within a temperature regulated water bath. Special care was taken to insure that temperature drifts were kept to a minimum and that the probe tip was sufficiently surrounded by the medium of interest and far from the boundaries of the glass container. The TPD and TDP methods
were each tested in solutions of silicone oil, ethylene glycol, glycerin, and a 1.5% agar/water mixture. The results and discussion of these tests are presented in Appendix F.
CHAPTER 3

EXPERIMENTAL RESULTS

3.1 In Vitro Tests

The results of the in vitro comparisons using the alcohol fixed kidney preparations are shown in Figures 12-15. The first two plots are of the perfusion, as predicted by each method (Equations 1.2 and 1.5), versus the total flow into the preparation. Each of these plots corresponds to a different location within the kidney preparation. Here the TPD predictions were calculated from both the simultaneous determinations and a fixed thermal conductivity determination, in which the intrinsic value of the tissue was used in the solution. This fixed K solution solves Equation 1.2 for a value of perfusion while the thermal conductivity is held at a constant value. The intrinsic values of thermal conductivity were determined by each technique, under zero flow conditions, for the same position and are specific to each method. The TPD determination for thermal conductivity was $0.544 \text{ W/m}^\circ\text{C}$ and for the TDP it was $0.575 \text{ W/m}^\circ\text{C}$. Figure 14 is a plot of the thermal conductivity, as determined from the simultaneous TPD solution, versus the total organ flow for each of the probe locations. The probes were located 0.5 cm from the external surface of the kidney.
Figure 12. In Vitro TDP and TPD Perfusion Predictions - Location 1.

Linear least squares fit: (---) TDP, (-----) TPD Forced K, (----) TPD simultaneous.
Figure 13. In Vitro TDP and TPD Perfusion Predictions -- Location 2.

Linear least squares fit: (---) TDP, (----) TPD Forced K, (-----) TPD simultaneous.
Figure 14. In Vitro TPD Thermal Conductivity Predictions.

Thermal conductivity as determined in the presence of perfusion using the simultaneous determination (Equation 1.2). Linear least squares fit: (——) Location 1, (----) Location 2.
Figure 15. In Vitro TPD and TDP Perfusion Mapping.
Figure 15 is a perfusion mapping of the *in vitro* preparation, as determined by both methods. The TPD predictions were from both the simultaneous and fixed thermal conductivity formulations, again with the fixed value equal to the intrinsic value. The position was measured from the external surface of the kidney and controlled by the micro-manipulator. The flow was maintained at a constant rate of 125 ml/min.

3.2 TPD and TDP Tests in The In Vivo Dog Kidney

The results of the TPD simultaneous predictions in an *in vivo* dog kidney preparation are shown in Figure 16, where the calculated perfusion is plotted against the total flow to the kidney. The silica probe was fixed within the medullary region of the kidney. The pulse power was 12 milli-watts and applied for a length of 3 to 5 seconds. The total kidney weight was 35. grams, after dissection.

The results of the comparative evaluations using the *in vivo* dog kidney preparation are shown in Figure 17 and Figure 18. This first figure is a plot of perfusions as calculated by each method, with the probe fixed at one location near the cortex of the kidney. The total flow to the kidney was regulated by the pressure cuff to vary from normal physiological flow to zero in small increments, with multiple measurements made at each level. For these tests the TDP temperature increment was maintained at 4°C and the TPD pulse of power was set at 10 milli-watts for a duration of 3 seconds.
Figure 16. *In Vivo* TPD Perfusion Predictions.

Linear least squares fit; (—) TPD simultaneous.
Figure 17. In Vivo TPD and TDP Perfusion Predictions.

Linear least squares fit: (—) TDP, (---) TPD simultaneous.
Figure 18. In Vivo TDP Perfusion Mapping.

PERFUSION (kg/m**3 - s)

DISTANCE IN mm

0.0  5.0  10.0  15.0  20.0  25.0
5.0  10.0  15.0  20.0  25.0

0.0  5.0  10.0  15.0

0.0  5.0  10.0  15.0  20.0  25.0  0.0  5.0  10.0  15.0  20.0  25.0
Figure 18 is a perfusion mapping of the in vivo kidney preparation using the TDP method. It illustrates the flow values for various distances away from the initial position. With the total flow to the kidney held constant, the probe tip was pulled back in small increments toward the opposing cortical region on the distal side.

3.3 TPD Tests in The Dog Tongue

The results of the experiments using the TPD method in the dog tongue are shown in Table 1. These are the simultaneous predictions of the local thermal conductivity and perfusion as determined using two different silica probes in separate locations. A pulse length of 3 seconds and a constant applied power of 6 milliwatts was used for these tests.

As a separate point, the apparent thermal conductivity, as determined from the non-perfused formula (Equation 1.1), versus the measurement time for one test for each probe are plotted in Figure 19. This illustrates what typical traces of these curves are for various flow levels.
Table 1. Thermal Pulse-Decay Results--Dog Tongue

<table>
<thead>
<tr>
<th>PROBE</th>
<th>PERFUSION (kg/m³-s)</th>
<th>CONDUCTIVITY (w/m·°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP3</td>
<td>13.6</td>
<td>.528</td>
</tr>
<tr>
<td>SP3</td>
<td>17.0</td>
<td>.521</td>
</tr>
<tr>
<td>SP4</td>
<td>40.7</td>
<td>.474</td>
</tr>
<tr>
<td>SP4</td>
<td>32.5</td>
<td>.488</td>
</tr>
</tbody>
</table>

Tabulation of perfusion and thermal conductivity measurements made in the dog tongue using the TPD method. Two probes were used.
Figure 19. TPD Apparent Thermal Conductivity Traces.

Thermal conductivity as determined in the presence of perfusion using the non-perfused formula (Equation 1.1).
CHAPTER 4

DISCUSSION OF EXPERIMENTAL RESULTS

In the *in vitro* tests, the perfusion predictions of each method, including the TPD forced K solutions, were found to be linearly proportional to the total flow to the kidney preparation (Figures 12-13). Under these optimal experimental conditions the TDP and TPD forced K predictions of perfusion both correlate well with the changes in total flow and exhibit a small amount of data scattering. The TPD solutions from simultaneous evaluations of conduction and perfusion also yielded linear predictions of perfusion but appear lower and offset, thereby not tracking toward the origin as the flow is limited. In this low flow region the perfusion prediction prematurely became zero or negative.

These low perfusion values, from the TPD simultaneous solution were associated with large predictions of thermal conductivity. It is apparent from Figure 14 that the TPD simultaneous predictions of thermal conductivity increase linearly with respect to increases in the total organ flow. For the cases where the flow was decreased toward zero, the values did track toward that of the intrinsic conductivity of the tissue, 0.54 W/m-°C. This effect may be caused by a directional flow or large vessels.
Similar findings have been suggested by Chen and Holmes [5] for the immediate region surrounding the corticomedullary junction, where the probe tip was placed for these tests. Another possible explanation could be flow leakage along the probe surface due to the non-elastic properties of the fixed kidney preparation.

It is important to notice that, in situations where the TPD method cannot accurately determine the perfusion and thermal conductivity simultaneously, an alternate solution exists. By forcing the thermal conductivity to be fixed at the intrinsic value, a perfusion estimate that closely approximates those of the TDP method is obtained.

From further tests on the in vitro preparations, it is apparent that both of these methods exhibit the ability to map the perfusion field (Figure 15). The TDP method was better at tracking the sharp perfusion gradients within the kidney. This was most probably due to the difference in the size of the measurement volumes, which is smaller for the TDP method. These gradients are caused by the highly differentiated structures within the kidney and the perfusion differences between them.

From the results of the in vivo kidney test shown in Figure 16, it can be seen that the TPD method shows an ability to linearly track and accurately calculate and follow changing levels of blood flow in an in vivo situation. In this case, as the total flow to the kidney was varied from normal "full open" flow toward zero flow, the multiple measurements taken at each level indicate that the TPD
method linearly tracks the change in total blood flow toward the origin. The large scatter among the measurements was most likely due to temperature drift and fluctuations as well as physiological changes within the kidney that are encountered in vivo. Since the exact flow to the probe region was not known, the fact that the response was linear is a good indication of the efficacy of the TPD method in monitoring the blood flow.

These TPD predictions were found to be in good agreement with those reported by Chen and Holmes from tests in the in vivo dog kidney [5]. Due to the highly defined structures and regional nature of the kidney, the blood flow levels vary significantly with position. Values reported by Chen and Holmes ranged from 400 kg/m$^3$-s in the corticomedullary junction to 60 kg/m$^3$-s in the medulla, with a value of 125 kg/m$^3$-s reported for the cortex [5]. For these in vivo tests, the probe tip was located approximately in the cortex, therefore perfusion estimations were considered valid since they agreed with the previous measured values.

The sequential testing of the TPD and TDP techniques in the in vivo dog kidney preparation provided a second comparison of each of these methods in an environment similar to those expected during measurements in humans. The estimations of perfusion for each method in these kidney preparations were both in good agreement with each other for the various total organ flow levels (Figure 17). The TPD method did consistently give lower perfusions but this could be a result of the difference in measurement volumes and the proximity
of nearby large vessels. The TDP determinations had less scatter and were less susceptible to minor breathing artifacts and small temperature perturbations. The large deviations of the data and the non-linear correlations at the higher flows were most probably due to blood flow redistributions within the kidney preparation over the course of the measurements.

The TDP method was also used to map the perfusion field across the in vivo kidney preparation (Figure 18). The values measured at the positions along the probe track closely follow those expected for the actual anatomy. From the dimensions of the perfusion map, it was apparent that the probe was pulled back from the initial position within the cortex toward the pelvis and passed through the high flow region of the junction and into the moderately perfused medulla region. This is further supported by the fact that the dog kidney has a cortex region that is approximately 1 cm wide. This indicates that the TDP method shows promise in giving accurate descriptions of the blood perfusion and flow field descriptions in vivo and is in good agreement with the TPD and TDP mappings found in vitro (Figure 15).

The results from the testing of the TPD method in the dog tongue (Table 1) indicated that this method, as implemented, can determine both thermal conductivity and local blood perfusion levels at in vivo tissue sites other than the kidney. The values of thermal conductivity found here are in good agreement (with a maximum error of approximately 10%) with those reported in the
literature for muscle tissue of 0.545 W/m·°C [19]. The differences between the predictions by the two probes was due to separate locations within the inhomogeneous structure of the tongue.
CHAPTER 5

THEORETICAL ERROR ANALYSIS OF TPD METHOD

To augment the previous experimental evaluation of the thermal pulse-decay (TPD) method a theoretical evaluation was undertaken of the two models that describe the technique: The point source model (PSM) used by Chen and Holmes [4] and an improved spherical source model (SSM) developed by S. Clegg [16]. The purpose of this analysis was to determine the effectiveness of the point source thermal model in describing the actual thermal system and to introduce a second model with improved accuracy. To test these mathematical representations of the technique, transient temperature decay data was generated from a finite difference simulation of the probe/tissue system and used as a basis for the evaluations. The overall accuracy and sensitivity of each of these models to various parameters was also determined. A similar analysis of the TDP method has been presented by J. Valvano and L. Hayes [20].

The actual TPD system consists of a thermistor probe imbedded within the tissue region of interest. The thermistor is a non-uniform power source with finite dimensions and distinct, inhomogeneous material properties. The tissue that surrounds the probe has separate thermal properties from those of the probe and often has a non-homogeneous distribution of these properties within
the tissue region itself. The point source model, as used by Chen and Holmes [4], is an approximate solution to the above system in that it assumes that the probe is an infinitely small power source (point source) surrounded by an infinite, homogeneous tissue region. This representation does not account for the finite size and composition of the thermobead as a power source and as a temperature sensing device. The assumption of an infinite media is valid as long as the size of the tissue sample is significantly greater than the effective measurement volume. Also, since the actual measurement volume is small, the surrounding tissue that is sensed can be considered to approximate a homogeneous volume.

The spherical source model (SSM), as derived by S. Clegg (see Appendix A), more accurately describes the system by accounting for the size of the thermobead and assumes a power distribution of a spherical source with the same dimensions as the thermistor [16]. The SSM still assumes homogeneity of tissue parameters throughout the region, including the thermistor, thereby modeling the heated region with the same perfusion and thermal conductivity as the tissue. Neither model takes into account the separate thermal properties of the bead. From these descriptions it is apparent that a comparative analysis of the above models is necessary to determine if the assumptions in their derivations are valid and how accurate they are.

A sensitivity study of the above point source model was recently done by H. Arkin and associates [7-8]. The effect of experimentally derived errors (those errors propagated from errors
in the measurement data) on the overall error in the calculated values of perfusion and thermal conductivity was determined. From this information an ideal experimental protocol was established that limited the effects of the experimental errors on the parameter estimations. The optimal measurement protocol was shown to be dependent on the actual values of perfusion and thermal conductivity, and at low and moderate simulated perfusion rates the dominant error was in the prediction of perfusion. Throughout Arkins' analysis it was assumed that the point source model was an accurate representation of the system, therefore the analysis only illustrates the overall error due to the accumulated experimental errors for various experimental conditions. The theoretical assumptions of the point source model were justified by another analysis that verified that the effects of bead radius, non-homogeneity of the surrounding tissue region, and tissue trauma could be considered negligible [8].

The analysis of Arkin did not analyze the errors due solely to the inaccuracies of the model used to describe the system. The purpose of the study presented here is to introduce an improved model of the TPD system, the spherical source model (SSM), and compare this model's error with that of the point source model (PSM) under various simulated experimental conditions. These models are tested against temperature decay data generated by a finite difference model that more accurately depicts the thermobead/tissue system. Also, the ability of these models to predict low values of blood perfusion is investigated.
5.1 Finite Difference Simulations of Experiments

5.1.1 Thermobead/Tissue Description

The actual physical configuration of the thermistor bead consists of an inner, solid prolate spheroid composed of a resistive composite material, surrounded by an annular coating of glass. The power is generated electrically within the resistive region. The passive glass coating and the composite material of the bead each possess different thermal properties and no perfusion. The real tissue surrounding the bead is considered to be homogeneous within the small region of influence, except for differences due to probe induced tissue trauma at the thermistor-tissue interface. The effects of trauma can result in different thermal parameters for the damaged region other than those of the tissue homogeneous region.

5.1.2 Finite Difference Model Description

The simulation finite difference model used to generate the temperature decay data closely approximates the actual system as described above. This model was developed by S. Clegg [16] and allows for the different regions of thermal properties in the thermobead and the surrounding tissues. The resistive composite was modeled as a spherical power source and temperature sensing element, surrounded by a passive coating of glass. These two regions have separate thermal conductivities and a perfusion of zero. The tissue medium was modeled as a spherical annular region with concentric layers of thermal conductivity and perfusion surrounding the
thermistor bead. The number, size, and thermal properties of these
concentric regions were arbitrary and could be varied according to
the desired simulation design. To further adhere to the assumptions
of the bioheat transfer equation, the blood flow to the model was
assumed to be uniform and non-directional.

5.1.3 Finite Difference Simulations

This finite difference solution is solved from the transient
bioheat equation with variable thermal properties [9]:

\[
\rho(r)c(r)\frac{\partial \theta}{\partial t} - \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 k(r) \frac{\partial \theta}{\partial r} \right) + c_b(r)w(r)\theta = Q(r)
\]

5.1

where

\[ \theta = T - T_a \] and \( T_a \) is the arterial blood temperature and is
constant throughout the temperature field

\[ \rho = \text{density} \]
\[ c = \text{specific heat} \]
\[ k = \text{thermal conductivity} \]
\[ c_b = \text{blood specific heat} \]
\[ w = \text{blood perfusion rate} \]
\[ Q = \text{power deposition} \]

The above thermal properties are all constant with time. Equation
5.1, with spherical coordinates, is solved using a fully implicit
tridiagonal solver to calculate the one dimensional temperature
distribution. This yields the simulated temperature decay data used
in the evaluation and error comparison of the two models.
The thermistor was chosen to have an outer diameter of 0.5 mm and inner composite diameter of 0.2 mm. The specific thermal properties of the thermistor beads used in our lab were not known, so average values from the literature were used. The thermal conductivity of some common nickel-oxide and nickel-magnesium-oxide composites ranged in value from 2 to 14 W/m°C [21]. For this study, the thermal conductivity of the composite was generally chosen as 10 W/m°C, with a few comparisons made using a value of 3 W/m°C. The outer glass coating was chosen to have a thermal conductivity of 1.5 W/m°C. In experimental work with the TPD probe, a Thermometrics ruggedized thermobead, type BR14, was frequently used. Manufacturer’s specifications suggest that the outer bead diameter was 14 mils and the inner composite diameter ranges from 6 to 9 mils (note: This is an outside diameter of 0.356 mm and an inside diameter of 0.152 to 0.288 mm). Theoretical decay curves were also produced for beads with dimensions of the BR14. It should be noted that Chen and Holmes use thermistors with a diameter of 0.3 mm [4].

The tissue parameters used to generate data were chosen to bracket the expected physiological values. The tissue thermal conductivity was varied from 0.3 to 0.7 W/m°C, and the local perfusion values ranged from 1 to 50 kg/m³-s. The power delivered to the thermistor was chosen as 5 mW and the pulse length was varied from 1 to 5 seconds. The standard nominal experimental parameters as used in most comparisons, were as follows: a perfusion of 10 kg/m³-s, thermal conductivity of 0.5 W/m°C, and a pulse length of 3 seconds.
To generate the temperature decay data, the finite difference simulation program was run on a VAX 750 using double precision accuracy. To obtain a high degree of accuracy, the finite difference solution used a time step of 0.1 milli-seconds and a grid size of 4 microns. The outer spherical boundary of the tissue media was set at a radius of 2 cm. The transient temperature data were recorded in 0.1 second intervals for a total time of 20 seconds. A plot of a typical simulated temperature decay trace versus measurement time is shown in Figure 20.

The simulated temperature data were then used as a data base to evaluate the predictions of perfusion and thermal conductivity obtained from each model. An analysis program, also written on the VAX, was used to simultaneously optimize the perfusion and thermal conductivity to each set of transient temperature data using both of the mathematical models. Estimated values of perfusion and thermal conductivity were produced for each model. The optimization routine used the Gauss method of curve fitting and the solutions for the two models were solved using the romberg method of integration [18]. Equation 1.2 was used for the PSM and Equation a.9 was used for the SSM. In experimental applications of the TPD method, a 6 to 9 second interval of temperature data is used to generate a single determination of each parameter. To determine what region of this data produced the most error, the parameter estimations were
Figure 20. Typical Simulated Temperature Decay Curve.

Parameters: $W = 10 \text{ kg/m}^3\text{-s}$; $k = .5 \text{ w/m}^\circ\text{C}$; $t_p = 3 \text{ seconds}$; $p = 5 \text{ mW}$. 
computed for discrete moments of time. This was accomplished by analyzing the temperatures in an interval of 1.2 seconds centered at the measurement time. For example, since the temperature data was recorded in 0.1 second increments, the parameter estimations at the discrete time of 10 seconds were determined by optimizing the data from 9.4 to 10.6 seconds. The reason for these discrete evaluations was to illustrate how the effects of the inherent model errors varied with time over the course of the measurements. The errors were computed as the absolute value of the deviation of the parameter values predicted by each model from the corresponding input to the finite difference simulation program.

5.2 Results of Finite Difference Simulations

The prediction errors for each of the models for various perfusion rates, tissue thermal conductivity, pulse length, and dimensions and thermal properties of the thermistor bead were compiled into a series of figures to better illustrate the magnitude of the errors and the relative sensitivity to each of these parameters. Figures 21 and 22 are summations of the prediction errors of each model, the SSM and PSM, respectively, in determining perfusion for various measurement times as the simulated perfusion was varied from 1-50 kg/m$^3$-s. Similarly, a comparison of the errors of both models versus the actual perfusion is shown in Figure 23, as determined for discrete measurement times of 7, 11, and 16 seconds after cessation of the pulse.
Figure 21. Error of SSM in Perfusion Predictions.

Parameters: $k = 0.5 \text{ W/m}^\circ\text{C}$; $t_p = 3 \text{ seconds}$; $p = 5 \text{ mW}$. $W$ is varied from 1-50 kg/m$^3$-s.
Figure 22. Error of PSM in Perfusion Predictions.

Parameters: $k = 0.5 \text{ W/m}^\circ\text{C}$; $t_p = 3$ seconds; $p = 5 \text{ mW}$. $W$ is varied from 1-50 kg/m$^3$·s.
Figure 23. Comparison of SSM and PSM Errors in Perfusion.

Parameters: $k = 0.5 \text{ w/m}^{-\circ\text{C}}$; $t_p = 3$ seconds, $p = 5$ mW; $w = 10 \text{ kg/m}^3\text{-s}$. The measurement time is varied between 7, 11, and 16 seconds after the pulse ends.
The percent error of each model in predicting a simulated value of perfusion versus the thermal conductivity of the tissue is shown in Figure 24, where the time of measurement is a parameter. Figure 25 is a plot of the perfusion errors, for a discrete measurement time of 11 seconds, versus the tissue conductivity, as the level of perfusion is varied. The errors of the SSM in predicting the simulated value of thermal conductivity for various perfusions rates are shown in Figure 26. The perfusion error of each model was also plotted against the simulated pulse length, as the perfusion was varied, as shown in Figure 27. The measurement time was constant at 11 seconds.

Figure 28 is a plot of the perfusion predictions of each model versus the measurement time for various dimensions of the thermobead. The simulated radius of the thermistor was used for the SSM solutions while the PSM solutions were independent of this parameter. The inner diameter was varied from 0.2 mm to 0.4 mm and the outer from 0.356 mm to 0.5 mm. The other experimental values were held constant at the nominal values.

Next, to show the effects of tissue trauma due to needle insertion, the perfusion error of the SSM model is plotted against the measurement time in Figure 29 for cases where the non-perfused region surrounding the probe is varied from zero to a diameter of 0.712 mm. The bead diameter was held constant at 0.356 mm.
Figure 24. Perfusion Errors - Effects of Tissue Conductivity and Measurement Time.

Parameters: \( W = 10 \text{ kg/m}^3\text{-s}; t_0 = 3 \text{ seconds}; \rho = 5 \text{ mW}. \) \( K \) is varied between \(.3, .4, .5, \) and \(.7 \text{ W/m}^-\text{°C}\), and the measurement time is varied between \(7, 11, \) and \(16 \text{ seconds after the pulse ends. Both SSM and PSM solutions are used.}\)
Figure 25. Perfusion Errors - Effects of Tissue Conductivity and Simulated Perfusion.

Parameters: $t_p = 3$ seconds, $p = 5$ mW; measurement time = 11 seconds. $W$ is varied between 1, 10, and 50 kg/m$^3$-s, and $k$ is varied between 0.3, 0.5 and 0.7 W/m$^{-\circ}$C. Both SSM and PSM solutions are used.
Figure 26. Thermal Conductivity Error - Effects of Measurement Time and Simulated Perfusion.

Parameters: $k = 0.5$ w/m$^{-1}$°C; $t_p = 3$ seconds; $p = 5$ mW. $W$ is varied between 1, 3, 5, 10 and 50 kg/m$^{3}$-s. Solutions are from SSM only.
Figure 27. Perfusion Errors - Effects of Pulse Length and Simulated Perfusion.

Parameters: $k = 0.5 \text{ W/m}^{-\circ}\text{C}$; $p = 5 \text{ mW}$; $t_p$ is varied between 1, 3, and 5 seconds, and $W$ is varied between 1, 10, and 50 kg/m$^3$-s. Both SSM and PSM solutions are used.
Figure 28. Perfusion Error - Effects of Thermobead Dimensions.

Parameters: \( k = 0.5 \text{ W/m}^{-1}\text{C}; t_p = 3 \text{ seconds}, p = 5 \text{ mW}; W = 10 \text{ kg/m}^3\cdot\text{s}. \) Three different bead dimensions were tested using both SSM and PSM solutions. The following inner/outer diameters were used: 0.2 mm/0.5 mm; 0.4 mm/0.5 mm; 0.2 mm/0.36 mm.
Figure 29. Perfusion Error - Effects of Traumatized Tissue.

Parameters: $k = 5 \text{ W/m}^{-\circ\text{C}}$; $t_p = 3 \text{ seconds}$; $p = 5 \text{ mW}$; $W = 10 \text{ kg/m}^{-3}\cdot\text{s}$. The damaged tissue region was modeled as a spherical annulus surrounding the bead, with zero perfusion. The outer diameter of the trauma region was 2 times the bead diameter.
5.3 Discussion

For all of the conditions tested, the spherical source model more accurately predicted the local tissue perfusion and the thermal conductivity than the point source model. The ability of each model to predict local blood perfusion rates for various simulated perfusion levels and measurement times is illustrated in Figures 21-23. The prediction error is largest for low perfusion rates and short measurement times. This error is due to the dominant effect of the band size at these short measurement times. At these short times, the error in the PSM is due to the fact that the thermistor has a finite size and therefore is not a point source [7]. Similarly, the error in the SSM is due to the fact that the thermistor is surrounded by a passive glass coating and therefore is not a uniform power source. The longer measurement times produced acceptable results, within 10 percent for the moderate to high perfusions, but failed to adequately improve the predictions at low flow rates. Also, as both the simulated flow rate and the measurement time increases, the difference in errors between the two models decreases.

As suggested in Figure 22, from the time where the errors approach their minimum, and from the experimental protocol set up by Arkin, a measurement time interval centered at 11 seconds was chosen as the ideal measurement time to be used in later simulations. This time was found to be a trade off between too small of a measured temperature signal at long times and too large of a model error at
the shorter times. This is within the experimental measurement interval suggested by H. Arkin, and it also has an acceptable temperature signal.

The actual value of tissue thermal conductivity was found to have a significant effect on the prediction of perfusion, as shown in Figures 24 and 25. It is evident that larger values of tissue conductivity decrease the error in predicting perfusion. This effect is most noticeable at low values of perfusion and conductivity and then diminishes as the measurement time and perfusion are increased. This effect is due to the conductive matching at the thermobead-tissue interface. When the thermal conductivity of the tissue approaches that of the glass coating \( k = 1.5 \text{ W/m}\cdot\text{C} \), the thermistor more closely approximates a bead of a smaller size and a uniform power source. Since these conditions more closely approach those assumptions used in the initial derivations of each model, both solutions become more accurate. For very large perfusion rates, this effect is negligible.

The accuracy of these models in predicting the tissue thermal conductivity is high, with the spherical solution yielding slightly better results. In all cases the SSM estimations of thermal conductivity were a fraction of a percent closer than those of the PSM and each followed the same trends. Figure 26 shows how this error decreases as the perfusion is increased and that it is well below 2 percent in the time interval of interest.
The effects of the pulse length on the prediction of various perfusion rates is found in Figure 27. This effect is most noticeable at low perfusion levels, where the shorter pulse lengths produce better results. The shorter pulse lengths allow the effects of the finite bead size on the error to diminish at shorter measurement times as compared to the larger pulse lengths. At moderate to high perfusions, the pulse length has little effect.

The physical dimensions of the thermistor bead have a large effect on the prediction errors. For standard tissue parameters, the relative effect of the simulation bead properties are presented in Figure 28. The 0.2 mm inside diameter/0.356 mm outside diameter bead produced better results than the larger 0.2 mm inside diameter/0.5 mm outside diameter bead. Comparisons were also made between a 0.4 mm inside diameter/0.5 mm outside diameter and a 0.2 mm inside/0.5 mm outside diameter bead to illustrate the relative importance of the size of the inner composite material. The larger ratio of inner to outer diameters give better results, but the effect is not as significant as that of the outer diameter. As the thickness of the outer layer of the bead is decreased, the thermistor is more closely approximated as a uniform power source which is an assumption in the derivation of both models. Also, as the outer diameter is decreased the thermistor properties approach the properties of a point source. Further investigation showed that the internal bead conductivity values (from 3-10 W/m^3-°C) have a negligible effect. The above analysis
illustrates that the overall size, rather than the internal composite diameter, is the most significant bead property in limiting prediction errors.

The effect of tissue trauma in the immediate volume surrounding the thermistor bead is shown in Figure 29. The damaged region was modeled as a spherical annulus of tissue, without perfusion, surrounding the thermistor bead. For damage ranging from 0 to 2 bead diameters, the effect on the resulting perfusion predictions was noticeably small.
CHAPTER 6

SUMMARY AND CONCLUSIONS

The thermal pulse-decay and the thermal diffusion probe methods of determining local tissue perfusion have been implemented in our laboratory. A series of experiments in in vitro and in vivo dog kidneys was performed to evaluate each method. The thermal pulse-decay method was evaluated further by a theoretical analysis of the describing mathematical models used to determine the tissue parameters. This provided insight into the desirable features of the probe design, tissue conditions and the measurement protocol necessary to minimize the errors in the final estimations.

6.1 Summary

6.1.1 Summary of Experimental Evaluation

The experimental evaluations have shown that both of these techniques, which use a small invasive probe, are able to measure local blood perfusion and linearly track any changes in the corresponding magnitude. The values of perfusion and thermal conductivity determined by each technique correlated well with each other and agreed with values obtained from the literature for each specific region tested. Also, both of these methods showed an ability to map perfusion fields throughout a kidney, even in
regions of steep gradients. In this region the TDP method showed higher resolution. The above results are mainly indicative of the performance of each method in tissues with moderate to high blood flows. In this study, the behavior of each technique at low blood flow rates was not tested. It can be seen that at zero flow rates the determinations of perfusion by these methods becomes inaccurate (Appendix F), where for these cases non-zero values of perfusion were predicted.

In certain non-perfused media, each of these techniques can determine the intrinsic thermal conductivity to within 3%, with the TPD method giving slightly more accurate results (see Appendix F). It should be noted that in a perfused environment using a single probe, only the TPD method is capable of determining both the perfusion and thermal conductivity. The TDP method, as presently programmed, does require prior knowledge of the intrinsic thermal conductivity to compute the perfusion. Also, in tissue regions where the TPD method cannot determine k simultaneously, the optimization algorithm can be modified by fixing the intrinsic value of thermal conductivity and solving only for perfusion.

As far as ease of implementation for each technique, the experimental apparatus needed to operate the TPD method is simpler than that of the TDP method. Also, the TDP needs frequent resistance adjustments to maintain the preset temperature increment. This is necessary due to steady state temperature fluctuations over the course of the experiment and the variability of the resistances
between the different probes used. In contrast though, the computation algorithm to determine the tissue parameters is faster for the TDP and much less susceptible to minor temperature fluctuations during the measurement cycle. It was noticed during the evaluations that each of these methods are sensitive to very small drifts in the steady state temperature and this is a large source of error which could limit the usability of either of these systems at the present time. Valvano and associates [13] have stated that for accurate use of the TDP method, the drift should be less than 0.06°C/minute. A similar requirement has not been stated for the TPD method.

6.1.2 Summary of Theoretical Analysis of TPD

The point source and spherical source models used to describe the thermal pulse-decay system accurately predict moderate to high perfusion values. The spherical source model consistently yields significantly improved predictions for determining both the local tissue perfusion and thermal conductivity. Both of these mathematical models fail to adequately predict perfusion rates lower than approximately 5 to 10 kg/m^3-s. In this region, the relative error increases as the perfusion decreases.

The physical properties of the thermistor bead were found to have a large influence on the computational errors. The size of the outer diameter was found to be the most significant property, where the smaller the outer diameter of the bead, the less the inherent model error. Also, the thickness of the outer coating of glass was
the least significant parameter but still should be as thin as possible. The results presented above were for thermistor beads with either a 0.356 mm or 0.5 mm outer diameter. The resultant prediction errors for the smaller bead were substantially improved over the larger, but it still failed at low perfusion rates. In general, the effects of bead and tissue properties on the prediction errors diminish as the bead diameter decreases and become more pronounced as it increases. In present experimental situations, the smallest commercially available thermistor bead is limited to an approximate outer diameter of 0.25 mm. Although simulations were not undertaken for this size bead, it is assumed that the results would have been similar to the cases tested here, except with a diminished magnitude in the errors.

6.2 Conclusions

The thermal pulse-decay and thermal diffusion probe techniques are quite comparable, and the measurements of perfusion and thermal conductivity produced by these methods correlate well with each other. Both are able to linearly track changes in the levels of perfusion at a particular site and can also be used to obtain accurate mappings of the perfusion field throughout a region of interest. The author personally preferred the TPD method over the TDP method due to its ability to simultaneously determine thermal conductivity and perfusion, ease of implementation, and lack of need for a calibration procedure for the effective probe properties.
The spherical source model is more accurate than the point source model in describing the thermal pulse-decay process. In regions with blood flows of 5 to 10 Kg/m³-s or less the two models are inaccurate and produce errors in perfusion predictions in excess of 10%. For large measurement times and high perfusions, these errors are limited to within 10%. The magnitude of these errors increase as the values of actual perfusion and thermal conductivity decrease. These errors decrease with longer measurement times, shorter pulse lengths, and smaller bead diameters. The effect of tissue trauma within 2 bead diameters of the probe is negligible.

6.3 Suggestions for Future Work

The behavior and accuracy of the TPD and TDP methods at low levels of blood perfusion needs to be determined. If the perfusion is inaccurately predicted in this situation, then the possibility of obtaining accurate thermal conductivity values should be investigated. For instance, when the perfusion is neglected (but still exists), the ability of each of these methods to determine the intrinsic value of thermal conductivity could be determined. Also, a study could be undertaken to determine the sensitivity of each of these methods to constant drifts in the steady state temperature and small perturbations in temperature during the measurement cycle. Alterations in the probe design to minimize the effects of conduction along the probe and to decrease the effective radius could also be undertaken.
APPENDIX A

DERIVATION OF MATHEMATICAL MODELS

This section is a summary of the theoretical derivations of the analytical expressions that describe the thermal pulse decay and thermal diffusion probe methods of determining the local tissue perfusion.

A.1 Models Describing Thermal Pulse-Decay

The thermal pulse-decay technique is described by two analytical models that describe the temperature fields— the point source model (PSM) [4] and the spherical source model (SSM) [16]. Each of these solutions assumes that the thermobead is surrounded by a homogeneous, infinite tissue region composed of a non-directional source of blood perfusion. These assumptions are in agreement with the use of the bioheat transfer equation to describe thermal energy transfer in tissues, as suggested by Pennes [9]. The point source solution to the model assumes that the power source, or thermistor, is infinitesimally small while the spherical source model considers the finite size of the thermistor. That is, the PSM assumes that the power during the pulse is dissipated from a point, while the SSM assumes the power is dissipated from a sphere of defined radius with
a uniform distribution of power. In the SSM, the heated spherical region is still assumed to have the same thermal properties and perfusion as the surrounding tissue medium.

The two thermal models that describe the TPD method are derived from solving the transient bioheat equation which adequately describes the thermal energy transfer in tissue:

$$\rho_t c_t \frac{dT}{dt} = K \nabla^2 T + \dot{W} c_e (T - T_a)$$  \hspace{1cm} \text{(a.1)}

Due to the spherical nature of the problem, the dynamics are best described in spherical coordinates. Equation a.1 is rewritten as:

$$\frac{\partial \theta}{\partial t} - \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial \theta}{\partial r} \right) + c_b \dot{W} \theta = Q$$  \hspace{1cm} \text{(a.2)}

where:

$$\theta = T - T_a$$ and $T_a$ is the arterial blood temperature and is constant throughout the temperature field.

$\rho$ = density

$C$ = specific heat

$K$ = thermal conductivity

$W$ = volumetric blood perfusion rate

$Q$ = power deposition

$b$ = property of blood

t = property of tissue

The above thermal properties are all constant with time and uniform throughout the infinite media.
A.1.1 Point Source Model

The closed form solution used for the point source model is derived from Equation a.2. [4], which is the bioheat transfer equation in spherical coordinates. A Greens function solution for the temperatures at the center of the model \((r=0.)\), the center of the thermistor, is solved for the point source distribution. Assuming that the parameters are constant and uniform in space and time, Equation a.2. can be rewritten as:

\[
\frac{\partial G}{\partial t} = aq^2G - \beta G + \gamma \delta \left(r-r_0\right) \delta \left(t-t_0\right)
\]  

where:

- \(G\) = assumed Greens function solution
- \(a = K/\rho C\) thermal diffusivity
- \(\beta = wC_b/\rho C\)
- \(\gamma = Q/\rho C\)

This is for the temperature at a point source located at a radius \(r_0\) which is instantaneously on at a time \(t_0\). The Greens function solution for an instantaneous source is:

\[
G = \frac{\gamma}{(2\pi)^3} e^{-\beta(t-t_0)} \left[\frac{\pi}{a(t-t_0)}\right]^{3/2} e^{-\frac{(r-r_0)}{4a(t-t_0)}}
\]  

For a point source \((r_0=0; r=0)\) this reduces to:

\[
G = \frac{P(pC)^{1/2}}{8(\pi k)^{3/2}} e^{-\beta(t-t_0)}
\]  

\[
\frac{1}{(2\pi)^3} e^{-\beta(t-t_0)} \left[\frac{\pi}{a(t-t_0)}\right]^{3/2} e^{-\frac{(r-r_0)}{4a(t-t_0)}}
\]  

\[
\frac{P(pC)^{1/2}}{8(\pi k)^{3/2}} e^{-\beta(t-t_0)}
\]
where $P$ is defined as the constant power input. This solution for an instantaneous point source is then superimposed throughout the pulse length to allow for a finite heating source. The instantaneous power is applied from $t_0=0$ to $t_0=t_p$ or over the length of the pulse. Integration of Equation a.5 by these limits yields the point source model solution as derived by M. Chen and K. Holmes:

$$T - T_a = \frac{P(pc)^{1/2}}{8(\pi k)^{3/2}} \int_0^{t_p} \frac{e^{-\beta(t-t_0)}}{(t-t_0)^{3/2}} \, dt_0$$  \hspace{1cm} (a.6)

In the absence of perfusion this reduces to an explicit solution that can be used to compute the thermal conductivity in a non-perfused media.

$$T - T_a = \frac{P(pc)^{1/2}}{4(\pi k)^{3/2}} \left[ (t-t_p)^{-5} - t^{-5} \right]$$  \hspace{1cm} (a.7)

A.1.2 Spherical Source Model

To derive the spherical source solution [16], the temperature field of the power source is assumed to have a spherically heated region of radius $r$. The power deposition is also uniform within this region. The Greens function solution of Equation a.4. for an instantaneous source is integrated in spherical coordinates throughout the media. The integral solution is found from the solution for an instantaneous spherical surface given in Carslaw and Jager [22]. Rearrangement yields:
This solution is integrated as before, to superimpose the instantaneous source solutions to yield a solution for a constant finite source. Solving for the temperature at the center of the sphere, as $r \to 0$, yields:

$$T - T_a = \gamma \frac{1}{\sqrt{4a(t-t_0)}} e^{-\beta(t-t_0)} \left\{ \frac{1}{\sqrt{n\pi}} \left( e^{-\frac{(R-r)}{4a(t-t_0)}} \right) +\frac{1}{\sqrt{4a(t-t_0)}} \left[ \text{erf} \left( \frac{R-r}{\sqrt{4a(t-t_0)}} \right) + \text{erf} \left( \frac{R+r}{\sqrt{4a(t-t_0)}} \right) \right] \right\}$$

This is the solution for the TPD method that describes the temperature at the center of a spherical power source. In implementing the thermal pulse-decay technique, Equations a.6 and a.9 are used to simultaneously optimize the perfusion and thermal conductivity to the temperature decay curves. In a non-perfused medium, the explicit solution of Equation a.7. is used to predict the thermal conductivity or, with perfusion, to calculate the apparent conductivity.

A.2 Model Describing The Thermal Diffusion Probe

The thermal diffusion probe method (TDP) is described by an analytical model that represents the coupled probe/tissue system
The thermistor bead, neglecting the probe assembly, is modeled as a spherical volume with electrical power distributed uniformly throughout the bead. The surrounding tissue region is assumed to be a homogeneous infinite region with a non-directional perfusion. This system model consists of two coupled equations that describe the temperature distribution within the thermobead and the surrounding tissue region, as well as the interactions between them. The temperature field in the tissue is described by the bioheat transfer equation, which due to the symmetrical nature of the problem, is best expressed in spherical coordinates:

\[
\frac{1}{\alpha_m} \frac{\partial \theta_m}{\partial t} = \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial \theta_m}{\partial r} \right) + \frac{\Psi - \rho_b C_b W_b \theta_m}{K_m}
\]

\( T \) = Temperature
\( \theta_m = T_m - T_0 \)
\( \alpha_m \) = thermal diffusivity
\( K_m \) = thermal conductivity
\( q_m \) = metabolic heat generation
\( W_b \) = local blood perfusion
\( \rho_b, C_b \) = density and specific heat of blood, respectively
\( \Psi = q_m + \rho_b W_b C_b (T_a - T_0) \)
\( m \) = denotes property of media
\( b \) = denotes property of blood
The term, $\Psi$, accounts for the base line heat generation due to metabolism and blood flow and allows the transient convective losses due to flow to be written as a function of the surrounding temperature elevation $\theta_m$.

The thermobead is defined as a sphere of radius $a$ with a volumetric heat generation rate, uniform throughout, that is required to maintain a temperature elevation and is described by the following equation:

$$
\frac{1}{\alpha_p} \frac{\partial \theta_p}{\partial t} = \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial \theta_p}{\partial r} \right) + \frac{\Gamma + \rho f(t)}{K_p} \quad a.12
$$

where:

$\theta_p = T_p - T_0$ temperature elevation of probe above steady state
$\Gamma + \rho f(t)$ time dependent volumetric heat generation rate
$p$ denotes probe property

To obtain a complete solution of $\theta_p$ and $\theta_m$ for this system, the set second order of partial differential equations was converted to a similar system of ordinary differential equations using laplace transform methods. The laplace domain solution is expressed as a Frobenius series solution and then inverse transformed. The closed form solutions to the temperature fields are expressed as follows:

$$
\theta_p = \frac{\Gamma a^2}{K_p} + \frac{\beta a^2}{3K_p} \left[ \frac{K_p}{3K (1+K a)} \right] f(t) - \frac{\Gamma a^3 f(t)}{3K_m (a_m)^3} (1-Z) \quad a.13
$$
\[
\theta_m = \frac{\Gamma a^3}{3K_m r(1+\Gamma z)} \left[ \exp\left(\frac{z}{r} (1-r/a)\right) + \frac{(a-r)f(t)}{a_m} \right] - \frac{\Gamma a^4 f(t)}{3K_m r(a_m)^5 (1-z)} + \frac{\beta a^3 f(t)}{3K_m r(1-\Gamma z)}
\]

where:

\[Z = \rho_b C_b W_b a^2 / K_m\]

From the above relations, assuming that the system reaches steady state, an expression for \(f(t)\) in the presence of perfusion can be derived. By setting the transient power component equal to zero, \(\beta f(t) \rightarrow 0\), the following expression can be derived [12]:

\[
f(t) = \frac{e^{-WC_b a_m t}}{K_m} - \frac{WC_b a_m \pi}{K_m} \text{erfc} \left( \frac{WC_b a_m t}{K_m} \right)
\]

To obtain an expression for the volume average temperature within the probe the above equation for the distribution within the thermistor is integrated throughout the volume as follows:

\[
\theta_p = \frac{3}{4\pi a^3} \int_0^a 4\pi r^2 \theta_p (r) dr
\]

In this analysis, it is assumed that this average temperature corresponds to the measured temperature of the thermistor.

Substitution of Equation a.13 into Equation a.16 allows the temperature elevation of the probe to be written as a function of the probe properties and the effective thermal conductivity:
\[ \Delta T_p = \frac{\Gamma a^2}{3K_p} \left( \frac{K_p}{K_{eff}} + 0.2 \right) \]  

The effective thermal conductivity includes the convective heat flux due to the perfusion, if present. From these above equations we get explicit expressions for the parameters of interest:

\[ K_m = \left( \frac{4\pi a \Delta T_p R_p}{V_{ss}^2} - \frac{0.2}{K_p} \right)^{-1} \]  

\[ R_b \text{ - resistance of heated bead} \]
\[ V_{ss}^2 \text{ - square of steady state voltage required to maintain} \]
\[ \text{the bead at a specified temperature increment.} \]

\[ K_{eff} = \left( \frac{3\Delta T_p}{\Gamma a^2} - \frac{0.2}{K_p} \right)^{-1} \]  

\[ a_{eff} = \left[ \frac{a}{(\Gamma \pi \beta / \Gamma) \left( 1 + 0.2K_m/K_p \right)} \right]^2 \]  

The coefficients \( \Gamma \) and \( \beta \) are calculated from a linear regression of the transient power versus time delivered to the bead to maintain the temperature increment. Once these are known, the perfusion can be predicted from either of the following:

\[ W_1 = \left( \frac{K_{eff}}{K_m} - 1 \right)^2 \frac{K_m}{\rho_b C_b a^2} \]
The above equations are used to predict the effective thermal conductivity, the effective thermal diffusivity, and the local tissue perfusion for the TDP method.

\[
W_2 = \left( \frac{a_{\text{eff}} - a_m}{a_m \rho_b C_b a^2} \right) \left( 1 + 0.2 \frac{K_m}{K_p} \right)^2 K_m \quad \text{a.22}
\]
APPENDIX B

TEMPERATURE CALIBRATION OF PROBES

The purpose of this section is to present the experimental protocol used to temperature calibrate the resistance of the thermistor probes. The probes are placed in a temperature controlled water bath and for a series of different temperatures the resistances are determined. The resistance ($R_p$) and temperature ($T$) data are then curve fit to the following expression [17], using the method of least squares:

$$ T = \left[ A_1 + A_2 \log(R_p) + A_3 (\log(R_p))^3 \right]^{-1} - 273.15 \quad \text{b.1} $$

The coefficients $A_1$, $A_2$, and $A_3$ are used to determine the temperature of the probe from any corresponding resistance measurement.

**Protocol**

1) The silica probes are placed within the calibration block in the temperature controlled water bath.

2) The standard thermistor, pre-calibrated from the manufacturer, THERMOMETRICS, is placed within the block and is used to give an accurate measure of temperature.

3) The temperature of the water bath is varied manually from 20°C to 50°C in increments of 5°C. At each temperature the drift within the block is closely monitored, and kept to a minimum.
4) When the block is at equilibrium with the calibration tank, the resistances of the standard thermistor and the probes are recorded and the temperature of the standard is determined.

5) This data are fit to Equation b.1 and the coefficients $A_1$, $A_2$, and $A_3$ are determined.
APPENDIX C

DETERMINATION OF EFFECTIVE PROBE PROPERTIES

The purpose of this section is to summarize and list an experimental protocol used to determine the effective thermal conductivity and effective radius specific to each perfusion probe necessary for the TDP method. These probe properties are also a function of temperature [14], so this dependence within the expected operating range must also be determined. The basis of these calibrations is the following equation that describes the TDP method in a non-perfused media and is derived in Appendix A:

\[
\frac{1}{k_b} = \frac{\Delta T R_f}{\frac{V_{ss}^2}{2} 0.2} - \frac{1}{0.2 k_m}
\]

The calibration procedure involves multiple tests of each probe in two different media of well defined properties including the intrinsic thermal conductivity. After each TDP measurement cycle, the temperature increment (\(\Delta T\)), the steady state voltage squared (\(V_{ss}^2\)), the setpoint resistance (\(R_f\)), and the intrinsic thermal conductivity (\(k_m\)) are recorded. After multiple tests of each probe in each media, the parameters from above are substituted into Equation c.1.
and straight line segments of probe radius (a) as a function of the inverse of the probe thermal conductivity (k_b) are obtained for each test media. These lines intersect at a centroid as shown in Figure 30. This point of intersection leads to a direct computation of k_b and a. This procedure is repeated for a total of three temperatures throughout the expected operating range to account for the temperature dependence.

**Protocol**

1) Solutions of 1.5% agar/water mixture and glycerin are equilibrated in a temperature regulated water bath. Care is taken to insure that the probe is isolated from the container edges and temperature drifts.

2) A total of ten measurements by each probe, using the TDP method, are run for each media.

3) After each measurement, values for the temperature increment, steady state voltage squared, final resistance, and the intrinsic thermal conductivity are recorded.

4) The above data for all tests is entered into a data reduction program (HP 3.0). The point of intersection is then determined by the calculation of the minimum difference between the lines, as a is incremented throughout the expected range, and the final values of k_b and a are displayed.
5) This procedure is repeated for a total of three times for 3 different temperatures; approximately 32°C, 37°C, and 42°C. This determines the calibration coefficients that correspond to a specific temperature. Table 2 shows the results of a similar calibration done on a silica probe. During experimentation a linear interpolation is used to determine the correct coefficients that correspond to the operating temperature.
Figure 30. Traces of Effective Probe Properties for the TDP.

These traces are obtained from two different TDP test results, in two different media, and Equation c.1. Parameters: \( a \) = effective probe radius, \( k_b \) = effective probe thermal conductivity.
TABLE 2. Typical TDP Calibration Coefficients and Temperature Dependence of the Effective Thermal Conductivity and Radius Specific to Silica Probe SP4.

<table>
<thead>
<tr>
<th>Effective Radius (mm)</th>
<th>Effective Conductivity (W/m·°C)</th>
<th>Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.384</td>
<td>0.04085</td>
<td>33.5</td>
</tr>
<tr>
<td>0.369</td>
<td>0.04177</td>
<td>37.0</td>
</tr>
<tr>
<td>0.353</td>
<td>0.04266</td>
<td>41.8</td>
</tr>
</tbody>
</table>
APPENDIX D

PROBE CONSTRUCTION

The purpose of this section is to outline the materials and procedures used to make the thermistor blood flow probes. The final product consisted of a glass encapsulated thermistor fixed to the tip of a small length of fused silica tubing. The lead wires were passed through an attached length of polyethylene tubing and connected to a 4 pin connector to allow for interchangeability.

D.1 Materials

The thermistors used were THERMOMETRICS type BR14 thermobeads with a 0.356 mm outer diameter and a nominal resistance of 2000 ohms +/-5% (@25 C) [16]. The fused silica tubing had an outer diameter of 0.67 mm. The lead wires were 2 mil coated copper wire. The catheter tubing was INTRAMEDIC polyethylene tubing with an inner diameter of 0.58 mm and an outer diameter of 0.965 mm. The connectors used for external attachment were the D series, 4 pin connectors from MICROTECH, Inc. Medical grade silica adhesive and SUPERGLUE epoxy resin were used for fixation.
D.2 Construction Protocol

An 80 cm length of a twisted pair of copper lead wire was inserted through the 60 cm length of polyethylene tubing. This procedure was facilitated by first inserting a fine piece of rigid wire or optical fiber, securing the end to the lead material, and pulling the wires through. Once the copper wires were in place, one end of the lead material was inserted through a 2 cm length of fused silica tubing. At this point the ends of the lead wires were lightly brushed with emory paper to remove the insulation. Next, the wires were cut in a staggered fashion to further isolate the solder joints. The platinum leads of the thermistor were shortened and trimmed in a staggered fashion complementary to the copper lead material. The copper and platinum leads were then secured in a small vice and the corresponding leads were soldered to each other. For this step, the use of solder flux greatly enhanced the connection and decreased the amount of solder needed. Care was taken to limit the amount of solder and also to ensure that the wires were connected in a parallel fashion.

The next step in the process called for a light coat of silica adhesive on the non-insulated lead materials and solder connections. It was important to limit the amount of adhesive used, so as not to block the passage of the lead material into the cavity of the silica tubing. After the adhesive was dry, the epoxy was applied along the lead wires and the lower part of the thermobead, as well as the insertion surface of the silica tubing. After the
epoxy was in place, the thermobead was secured into place against the tip of the fused silica tubing by gently pulling the copper lead wires. The polyethylene tubing was then forced to fit snuggly over the end of silica tubing. After the epoxy was dry, the copper lead wires were trimmed and soldered to the 4 pin connector. This connector was then secured to the polyethylene tubing using silica adhesive and heat shrink tubing.
APPENDIX E

ALCOHOL FIXATION OF DOG KIDNEYS

The purpose of this section is to summarize the alcohol fixation technique, developed by Holmes and associates [15], applied here to the dog kidney. This method allows for a re-usable perfusion phantom with a microvasculature that closely approximates the structure of the original in vivo organ.

E.1 Methods of Fixation

The dogs, previously anesthetized from earlier experimentation, were injected with 500 units of heparin per kilogram of body weight at least 15 minutes prior to sacrificing the animal. This prevents the blood from coagulating within the excised organ and inhibiting the proper fixation. Through an abdominal incision each kidney was cleaned of connective tissue and the renal artery and vein were isolated. Next, the vessels were securely sutured off as far as possible from the organ, thereby allowing a longer extension of the renal artery for later purposes. These vessels were then cut next to the sutures and the kidney was removed and placed in a saline solution.

After each kidney was further cleaned and the artery neatly exposed, a short piece of catheter tubing, with one slightly expanded end, was sutured into place within the lumen. This
expanded end, when secured in the artery, prevents the catheter from being pulled out. The catheter allowed for ease of connection and interchangeability during experimentation. The kidney was then attached to a network of tubing which allowed the fixative solutions to be delivered to the kidney and also the monitoring of the flow and pressure drop across the organ. The necessary equipment included an ultrasonic flowmeter, peristaltic pump, pressure transducer, and various plumbing. The following was the final protocol used in the fixation process.

E.1.1. Fixation Protocol

1) Perfuse the kidney with a de-gassed solution of cool saline and 4% mannitol for approximately 15-30 minutes.

2) Continue perfusing with a solution of 50% ethyl alcohol-water mixture until the vascular resistance across the kidney decreases. For a constant flow to the organ, this resistance drop/rise is noted by a corresponding drop/rise in the pressure across the kidney. Initially the resistance increases but starts to decrease after 10-15 minutes.

3) Allow the kidney to soak in the 50% alcohol solution for 4-6 hours.

4) Perfuse with an 80% alcohol solution for 15-45 minutes. At this point the kidney was considered fixed and was stored in an 80% alcohol solution until ready for future use. Presently, the kidneys can be stored for up to a few months. Before using the kidneys though, they must be re-hydrated according to the following procedures.
5) Remove the fixed kidney from the 80% alcohol solution and place into a 50% solution and allow to soak for 8-10 hours.

6) Place in water for 8-10 hours.

At this stage the re-hydrated fixed kidney was ready to be used as a perfusion phantom. After use, steps 2 and 4 above were repeated, and then the kidney was restored in 80% alcohol solution.
APPENDIX F

TESTS IN KNOWN MEDIA

The TPD and TDP methods were tested in materials of known thermal properties and in the absence of perfusion. The ability of each technique to predict the intrinsic thermal conductivity and a value of zero perfusion was determined. The solutions used for the tests were as follows; silicone oil, ethylene glycol, glycerin, and a 1.5% agar/water mixture.

F.1 Results

The thermal conductivities as predicted by the TPD and TDP methods in different media are listed in Tables 3-4, respectively. The values of conductivity were determined using the non-perfused formulations derived for each technique (Equations 1.1 and 1.5). Also shown are the perfusion and thermal conductivity estimates found using the same transient test data as above but computed from the perfused formulations (Equations 1.2, 1.5 and 1.7).

F.2 Discussion

From these tests in a non-perfused media, the thermal pulse-decay method implemented in our lab has the ability to accurately determine thermal conductivity as calculated from the non-perfused formulation (Table 3). The average percent error was limited to within 1% to 3%, except for the measurements in silicone oil, and
was in good agreement with similar findings reported by Chen and Holmes [4]. For the tests in silicone oil, having an intrinsic thermal conductivity of .159 W/m°C, the prediction error was 15%. This error was most probably due to the low conductivity of the media, which was enhancing the effects of conduction down the length of the probe, causing a high determination of thermal conductivity.

The TPD simultaneous determinations of perfusion and thermal conductivity, when optimizing the same transient temperature decay data as above, yielded larger errors in the determined parameters and often over-estimated the thermal conductivity and produced non-zero values of perfusion. The inaccurate perfusion predictions can be attributed to the small measurement times of the interval of temperature decay used in the solution. For the above tests the parameter estimates were computed by using the same measurement times, 5 to 12 seconds after the pulse, as those used for the perfused cases encountered in the kidney preparations. From the analysis of H. Arkin and associates [7], and the theoretical analysis of Chapter 5, the temperature decay data for non-perfused tests should be analyzed using very large measurement times, 20 seconds or greater. Due to the small temperature signal at these large times, the smaller measurement times were used and these errors were expected. The measurements in silicone oil again produced the largest error in predicting thermal conductivity, this time within 14%. Apart from this error and an error of 6% for probe SP6 in glycerin, the other determinations (TPD simultaneous) of thermal conductivity were still within 2% to 3%.
The Thermal Diffusion Probe method was shown to be able to determine the thermal conductivities but the errors ranged from 0.3% in glycerin to 17% in agar. These large errors were unexpected for two reasons. First, the calibration coefficients (Appendix C) for each probe were calculated from tests in glycerin and agar, so the measurements in these media should be the most accurate. Second, simultaneous determinations of thermal conductivity using the TPD and TDP methods yielded results within 5% of each other for the in vitro case (0.553 and 0.575 W/m·°C respectively) and the in vivo case (0.54 and 0.512 W/m·°C respectively). This illustrates that the TDP method was producing accurate results until this final experiment in standard media.

Chronologically, these tests in the standard media took place after the in vivo and in vitro kidney tests. During these tests in the standard media, the agar solution was used last. This media was a rigid suspension of agar in water. While inserting the probe into the agar, the thermistor tip was moved slightly with respect to the silica tubing causing a consequential change in the previously calibrated effective probe properties. This is evident from the accurate determinations of the thermal conductivity for silicone oil and glycerin prior to those from agar (Table 4). The 9 to 11% error reported for ethylene glycol was probably due to the effects of convection and buoyant forces during the heating sequence, which this method is susceptible to as a result of the long heating times. This was avoided in the other solutions due to their higher
viscosities. Taking these above problems into consideration, the TDP method was shown to be able to determine thermal conductivity to within 3%. However, these results are rather limited since they only account for tests in silicone oil and glycerin. Also, when using the perfused formulation, the TDP method predicted too large of values of thermal conductivity and non-zero values of perfusion, similar to the TPD method.

In summary, the above results indicate that the TPD and TDP techniques of calculating the local tissue perfusion, as implemented in our lab, produce valid results. These tests in known media indicated that each method was able to determine the thermal conductivity to within 3%. The TPD method was able to more accurately predict the zero perfusion and thermal conductivity using the perfused formulation, whereas the TDP method predicted larger values. The above results indicate that in a non-perfused media, each of these methods give a reliable estimate of the thermal conductivity. The TPD method, using either the simultaneous determination or the non-perfused formulation, yields more accurate results than the TDP.
Table 3. Thermal Pulse-Decay Results—Non Perfused Media

<table>
<thead>
<tr>
<th>Media</th>
<th>Probe</th>
<th>Actual k</th>
<th>K-Only</th>
<th>Simultaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>k</td>
<td>k</td>
</tr>
<tr>
<td>Silicone</td>
<td>SP6</td>
<td>.159</td>
<td>.1824</td>
<td>----</td>
</tr>
<tr>
<td>oil</td>
<td>SP12</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Ethylene</td>
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<td>.2558</td>
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<tr>
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<td></td>
<td>SP12</td>
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<td>.2795</td>
<td>3</td>
</tr>
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<td>.5937</td>
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</tr>
<tr>
<td></td>
<td>SP12</td>
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</table>

TPD predictions of thermal conductivity (W/m°C) and perfusion (kg/m³-s) in a non-perfused media using simultaneous and K only solutions (Equations 1.1-1.2). A series of 10 measurements were made in ethylene glycol, glycerin, silicone oil, and 1.5% agar/water mixture.
Table 4. Thermal Diffusion Probe Results-- Non Perfused Media

<table>
<thead>
<tr>
<th>Media</th>
<th>Probe</th>
<th>Actual k</th>
<th>k</th>
<th>% Error</th>
<th>k</th>
<th>% Error</th>
<th>w</th>
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TDP predictions of thermal conductivity (W/m°C) and perfusion (kg/m³-s) in a non-perfused media using the perfused and non-perfused formulated solutions (Equations 1.5 and 1.7). A series of 6 measurements were made in ethylene glycol, glycerin, silicone oil, and 1.5% agar/water mixture.
REFERENCES


