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A SELF-HEATED THERMISTOR TECHNIQUE TO MEASURE

BLOOD FLOW FROM THE TISSUE SURFACE

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ABSTRACT

A microcomputer based instrument to measure thermal conductivity, thermal diffusivity and perfusion at the surface of a tissue has been developed. Self-heated spherical thermistors, partially embedded in an insulator, are used to simultaneously deliver thermal energy to the biological tissue and to measure the resulting temperature rise. The temperature increase of the thermistor for a given applied power is a function of the combined thermal properties of the insulator, the thermistor and the tissue. Once the probe is calibrated, the instrument accurately measures the thermal properties of tissue. Conductivity measurements are accurate to better than 2% and diffusivity measurements are accurate to better than 4%. The surface thermistor probe is quite sensitive to perfusion.

NOMENCLATURE

a,b	conductivity calibration coefficients
c,d	diffusivity calibration coefficients
e,f	perfusion calibration coefficients
I	steady state power/ ΔT (mW/ $^{\circ}C$)
K	thermal conductivity (mW/cm- $^{\circ}C$)
p	mass fraction of glycerol/agar-gelled water mixture
P	power (mW)
S	slope of power/ ΔT (mW/ $^{\circ}C$ -sec $^{-1/2}$)
t	time (sec)
T	temperature ($^{\circ}C$)
w	tissue perfusion (ml/100g-min)
α	thermal diffusivity (cm 2 /sec)
ΔT	volume average temperature rise ($^{\circ}C$)

Subscripts

0	initial time, baseline
1	glycerol
2	agar-gelled water
eff	effective (with perfusion)
h	heated
m	intrinsic (without perfusion)
mix	glycerol/agar-gelled water mixture

INTRODUCTION

This paper presents an empirical technique to measure the thermal properties and perfusion of tissue using surface thermistor probes. The accuracy of the surface probe for measuring thermal conductivity and diffusivity was evaluated using liquid standards. Experiments to determine the effective depth of measurement were conducted. The effect of poor thermal contact between the probe and the medium surface was evaluated by inserting thin layers of plastic wrap between the probe and the medium. Measurements of thermal conductivity were made under temperature drifts varying from 0 $^{\circ}C$ /min to 0.2 $^{\circ}C$ /min. A baseline temperature drift larger than 0.015 $^{\circ}C$ /min causes a significant error in the thermal conductivity measurement.

A thermal model has been solved numerically and the parametric relations for measuring thermal conductivity, thermal diffusivity and perfusion are presented (Patel, 1986). The perfusion measurements were evaluated using an isolated rat liver apparatus. The apparatus is presented and various design considerations are discussed. The surface thermistor probe was quite sensitive to perfusion. The accuracy of the perfusion measurement could not be determined due to the non-uniform perfusion at the surface of the liver. Perfusion can be quantified only when uniform perfusion extends completely to the tissue surface.

BACKGROUND

Since the eighteenth century, there have been efforts to improve the understanding of the human thermoregulatory system and to develop a means of measuring thermal energy and thermal energy transfer *in vivo* (Jain and Chato, 1983). The rate at which thermal energy is dissipated in biological tissue is a function of the tissue's thermal conductivity, thermal diffusivity and blood flow. Chato (1968), Bowman et al. (1977), Jain (1979), Chen et al. (1981), Valvano et al. (1984a), and Walsh (1984) have shown that self-heated thermistors are capable of measuring thermal properties and perfusion.

Knowledge of the thermal properties of tissue is important for both diagnostic and therapeutic medicine. Thermal properties are required to model thermal transport phenomena in tissue. Such models allow better interpretation of heat transfer processes in thermography, organ preservation, hyperthermia, hypothermia and various peripheral vascular diseases.

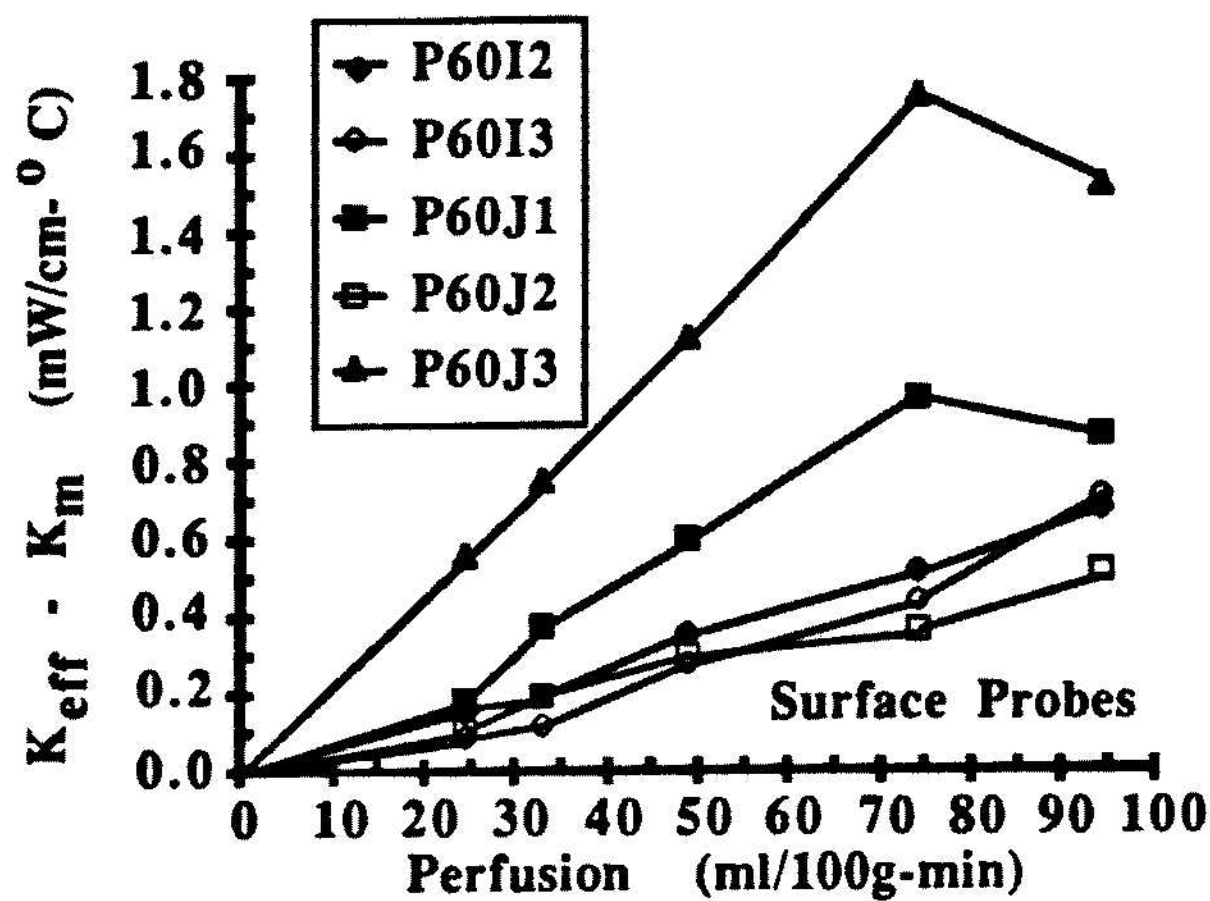


Figure 10. Measured $K_{eff} - K_m$ versus perfusion.

CONCLUSION

The surface measurements of the thermal conductivity and thermal diffusivity were accurate to better than 2% and 4% respectively. *In vitro* experiments to determine the effective depth of measurement showed that the probe was sensitive to the thermal conductivity of a medium located at distances less than 3 mm (6 thermistor radii). The effects of poor contact were found to cause significant errors in the measured thermal properties. The magnitude of the error depended on the conductivity of the material between the probe and the surface. The baseline temperature drift must be less than 0.015 °C/min to avoid the effects of temporal variation during the transient measurement. The isolated rat liver apparatus design is simple and provides adequate control over baseline temperature, total flow rate and pH. Unfortunately, a nonuniform perfusion field in the isolated rat liver prevented quantification of perfusion. Despite this, the surface probes were demonstrated to be sensitive to perfusion.

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Tissue perfusion is a measure of the local blood flow through the capillary network of a tissue. While flow in a single vessel is a vector quantity, the convoluted nature of the capillary bed forces the analysis of blood flow in a macroscopic region to be non-directional. Perfusion is measured as the volume flow rate of blood per unit mass of tissue (ml/100g-min). Blood flow in arteries and veins is directional and is measured in units of volume of blood per time (ml/min). Blood flow and tissue perfusion are clearly related, but there may be significant perfusion abnormalities in the presence of normal blood flow (e.g. a myocardial infarction). Tissue perfusion provides a reliable estimate of the viability of an ischemic or reimplanted tissue.

INSTRUMENTATION

Probe Design

The essence of the surface thermal probe is a thermistor, partially embedded in an insulator, placed on the surface of a tissue (Figure 1). A large 1 mm diameter thermistor is used as the active transducer. An insulator with low thermal conductivity and low thermal diffusivity is used to direct the heat supplied by the thermistor into the tissue. The insulator also shields the thermistor from the ambient air. Although a smaller thermistor would have a faster response, the sensitivity to conductivity and perfusion increases with probe size.

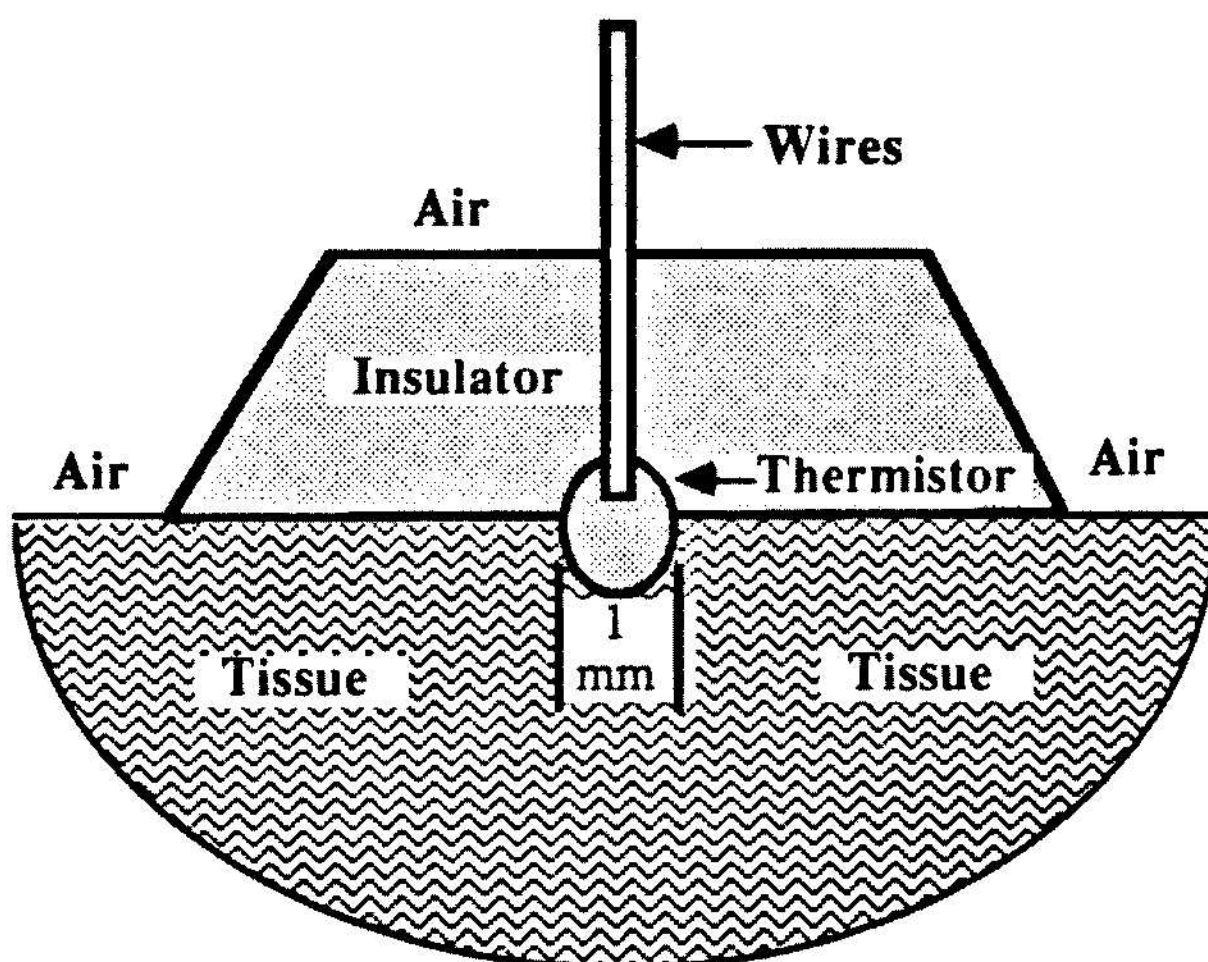


Figure 1. Surface thermistor probe.

General approach

The thermistor is self-heated, and the applied power is dissipated into the tissue medium. Tissue can conduct heat either by intrinsic thermal conduction or perfusion. In a perfused tissue, the intrinsic thermal properties of the tissue (K_m , α_m), the local blood flow rate, and specific heat of the blood are all physical characteristics that affect tissue heat transfer. All these characteristics can be lumped together as effective thermal properties K_{eff} , α_{eff} . The instrument simultaneously measures the applied power $P(t)$, and the resulting heated thermistor temperature $T_h(t)$. The temperature rise is a function of the thermal properties of the thermistor, the insulator and the tissue. Tissue thermal properties and perfusion can be derived from measured thermistor power and temperature if relations between these and the measurands are known.

Measurement protocol

The measurement of thermal properties and perfusion involves the placing of the thermal probe in contact with the perfused tissue, which is initially at a constant baseline temperature. The probe is allowed to equilibrate thermally with the medium. The instrument is first used in a passive mode to sense the baseline temperature T_0 . A constant voltage is then applied to the probe to self-heat the thermistor. When a constant voltage of 5 volts is applied, a total power of about 17 mW is dissipated by the thermistor. This results in an average thermistor temperature rise of about 8 °C, and a surface thermistor temperature rise of about 3 °C. The heated thermistor temperature $T_h(t)$, and applied power $P(t)$, are then recorded during an 88 second heating interval. A linear regression is performed to estimate the steady state response from the transient data. The heating profile was found empirically to follow $t^{-1/2}$.

$$\frac{P(t)}{T_h(t) - T_0} = I + S t^{-1/2} \quad (1)$$

The heated temperature $T_h(t)$ is assumed to be the average temperature in the bead over the entire volume of the bead. The power $P(t)$ is the total power applied to the bead. The steady state response, I , depends on the thermal conductivity of the medium. The transient response, S , depends on both the thermal conductivity and diffusivity of the medium. The presence of perfusion increases I and decreases S .

Asymmetric boundary conditions along the periphery of the thermistor complicate the closed form analytic solution for thermal conductivity, thermal diffusivity, and tissue perfusion. The model has been solved numerically using the finite element method (Patel, 1986). The parametric equations are:

$$\frac{1}{K_{eff}} = \frac{a}{I} + b \quad (2)$$

$$\frac{1}{\sqrt{\alpha_{eff}}} = c \frac{S}{I} + d \quad (3)$$

$$w = e + f \frac{(K_{eff} - K_m)^2}{K_{eff}} \quad (4)$$

It is necessary to calibrate the thermal probe before it can be used. The thermal probe is calibrated for conductivity and diffusivity using glycerol and agar-gelled water media. An isolated rat liver apparatus was designed and used to evaluate the perfusion measurements.

IN VITRO EXPERIMENTS

Experiments were performed to optimize the construction and operation of the surface thermal probe. The parameters studied were, (i) the effective depth of measurement, (ii) the effect of imperfect thermal contact, and (iii) the effect of temporal variations in baseline tissue temperature.

Effective depth of measurement

The effective depth of measurement is defined as the distance between the probe and medium at which the probe becomes insensitive to changes in the thermal properties of the medium. This study used a composite medium of known thermal properties (Figure 2). Since the thermal conductivities of the agar-gelled water and the glycerol are known, they were used to construct the composite medium. The thickness of the glycerol layer was varied from 0 to 0.5 cm. The measured conductivity can be considered as a volume average conductivity of the two liquids. As the thickness of the glycerol increases, the effect of the agar-gelled water on the measurement decreases.

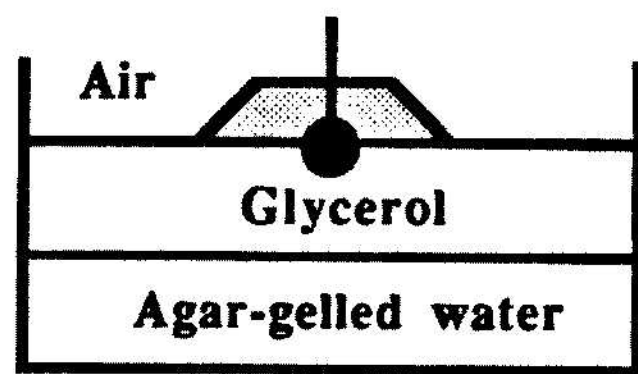


Figure 2. Apparatus to determine effective depth of measurement.

The effective depth of measurement was estimated to be the minimum thickness of glycerol at which the volume average measured conductivity was $3.06 \text{ mW/cm}^\circ\text{C}$. This represents 5% agar-gelled water and 95% glycerol. The thermal conductivities were measured for 20, 40 and 80 second heating intervals to estimate the effect of the heating interval on the effective depth of measurement. The experimental results are presented in Figure 3. From Table 1 it can be seen that the effective depth of measurement increases as the duration of the heating interval increases. Effective depth of measurement also increases with thermistor size.

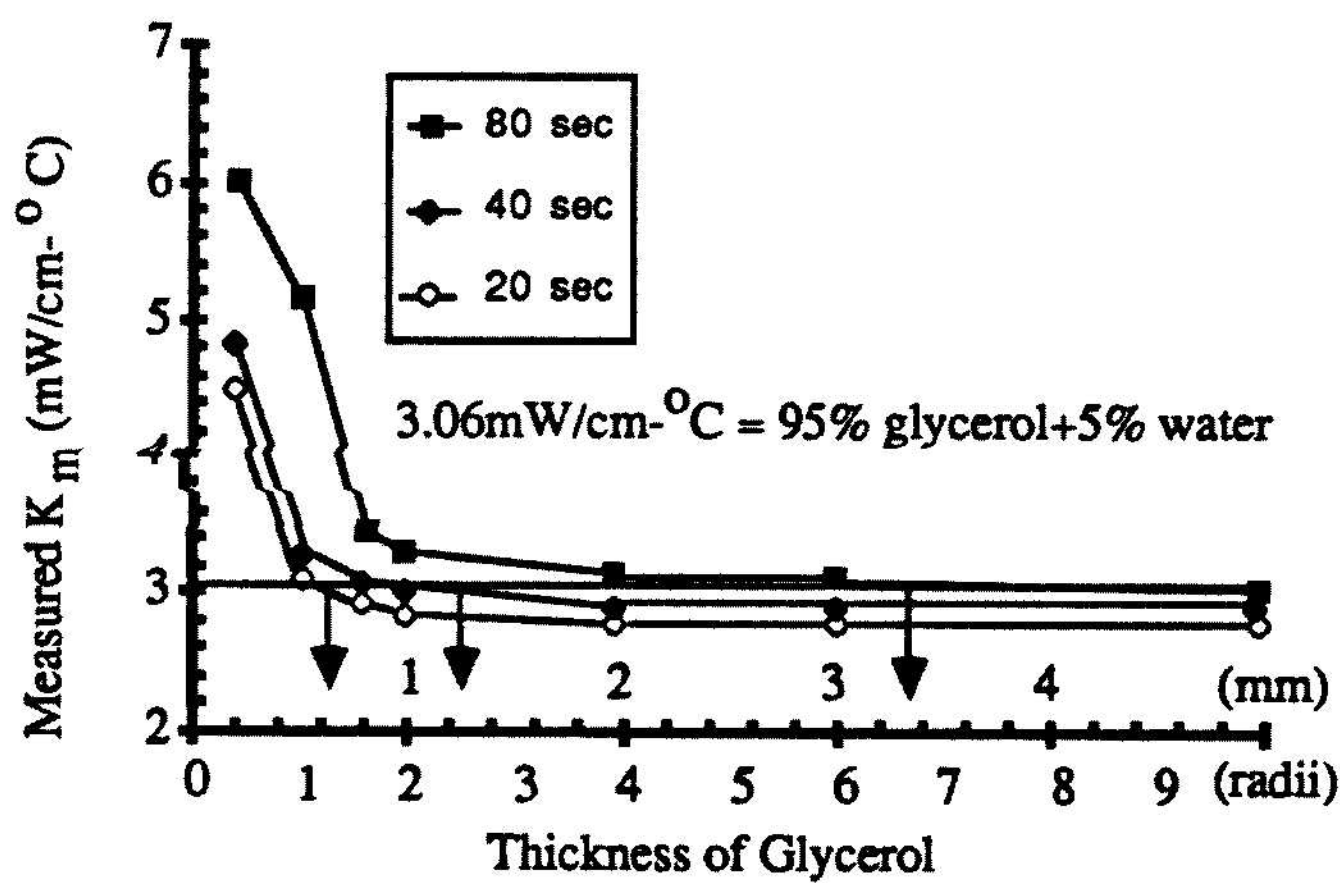


Figure 3. Measured conductivity versus thickness of glycerol.

Heating Interval	Depth of Measurement
20 sec	1.3 radii 0.65 mm
40 sec	2.0 radii 1.00 mm
80 sec	6.8 radii 3.40 mm

Table 1. Effective depth of measurement.

Imperfect thermal/physical contact

This experiment was conducted to estimate the error caused by an imperfect thermal/physical contact between the thermistor and the tissue surface. An imperfect thermal contact could result from a thin air film or a thin liquid film between the probe and tissue. A poor contact could also be caused by the presence of an unperfused layer at the tissue surface.

Figure 4 shows the experimental setup to evaluate errors caused by imperfect contact. This experiment involved glycerol in a flask, a surface probe and some thin plastic wrap layers. The $1.27 \mu\text{m}$ thick plastic wrap layers ($K=1.38 \text{ mW/cm}^\circ\text{C}$) were used to simulate a thin air film. The thermal conductivity of the glycerol was measured first with a perfect contact between the probe and the glycerol. Then, the thermal conductivity was measured with one to four plastic layers between the probe and the glycerol surface. The error due to imperfect contact was then determined by calculating the ratio of the change in measured conductivity due to imperfect contact to the conductivity measured with perfect contact (Table 2). It can be seen that a thin layer of plastic causes a significant error in the thermal conductivity measurement. Of course, the magnitude of the error is a function of the thermal conductivity of the material in the gap.

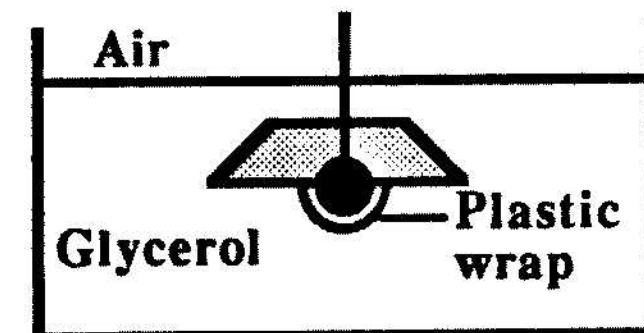


Figure 4. Apparatus to study the effect of imperfect contact.

Thickness(μm)	Measured K_m	% error
0.00	$2.955 \pm .056$	0
1.27	$1.976 \pm .006$	-33
2.54	$1.864 \pm .008$	-37
3.81	$1.734 \pm .010$	-41
5.08	$1.658 \pm .009$	-44

Table 2. Error in Measured K_m due to imperfect contact.

Effects of temporal variations in tissue temperature

An experiment was conducted to evaluate the effect of temporal variation in tissue temperature on the measurement of thermal properties. Two thermal probes were placed on the surface of agar-gelled water in a temperature controlled water bath. The thermal conductivity was first measured at a stable 37°C . Then, the water bath temperature was increased. Using one probe, the temperature drift dT/dt , was measured. Using the other probe, the thermal conductivity was measured. The experiment was repeated for various values of dT/dt . From the results, shown in the Figure 5, it can be seen that there is about a 1% conductivity measurement error for every $0.01^\circ\text{C}/\text{min}$ temperature drift. It is our experience that the baseline temperature drift must be less than $0.015^\circ\text{C}/\text{min}$ to insure accurate thermal conductivity measurements.

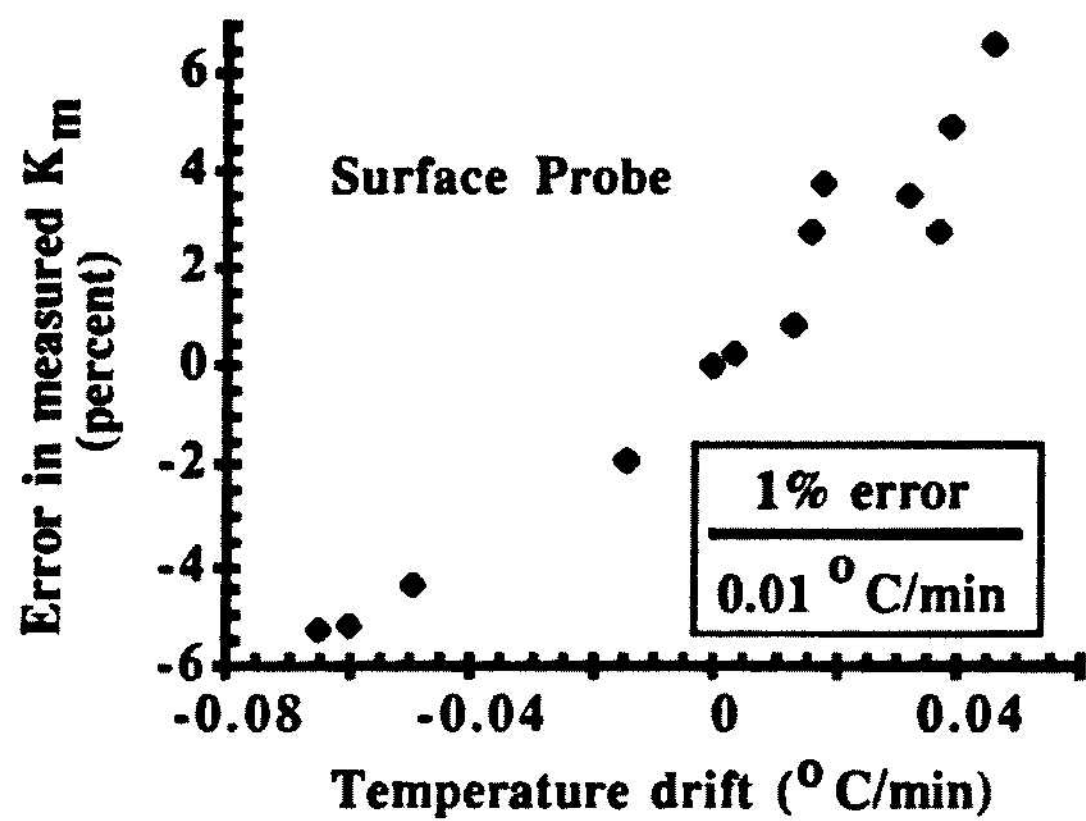


Figure 5. Measurement error versus baseline temperature drift.

Accuracy of the thermal property measurements

The accuracy of the thermal conductivity and thermal diffusivity measurements was tested using seven liquid standards. The seven liquid standards used were glycerol, 1.5% agar-gelled water, and five mixtures of glycerol and agar-gelled water. The agar was added to the water to prevent convection. It was found empirically that the thermal properties of the water are not significantly altered by the presence of agar (Patel 1986.) Thermal conductivity and thermal diffusivity of the mixtures were calculated from the mass fractions p_1 and p_2 (Valvano et al., 1985),

$$K_{mix} = K_1 p_1 + K_2 p_2 - 1.4 p_1 p_2 [K_2 - K_1 - 2] + 0.014 p_1 p_2 (T_0 - 20) \quad (5)$$

$$\alpha_{mix} = \alpha_1 p_1 + \alpha_2 p_2 \quad (6)$$

Twelve experiments were conducted in each of seven media and the measured I and S/I were recorded. After discarding highest and lowest readings, the average I and S/I were calculated. Using average values of I and S/I, the thermal conductivity and diffusivity were calculated for each medium. The experimental results are presented in Figures 6 and 7. The average conductivity and diffusivity errors for the probe were 0.7% and 2.1% respectively and the maximum errors were 1.4% and 3.9% respectively.

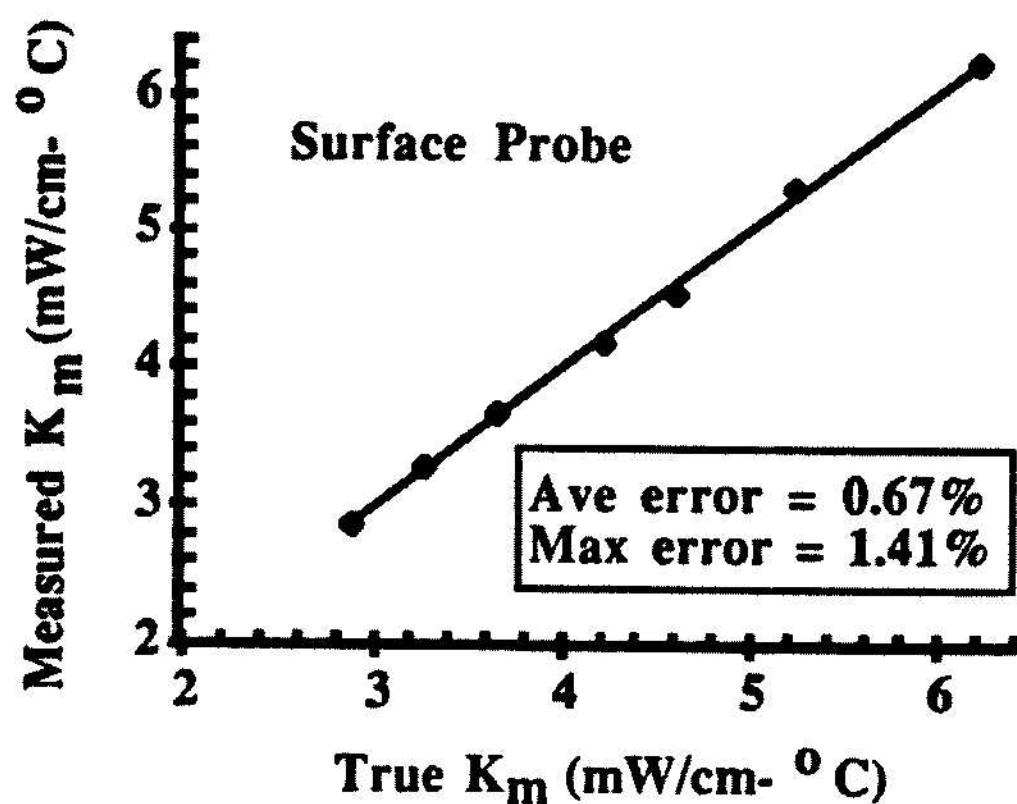


Figure 6. Measured conductivity versus true conductivity.

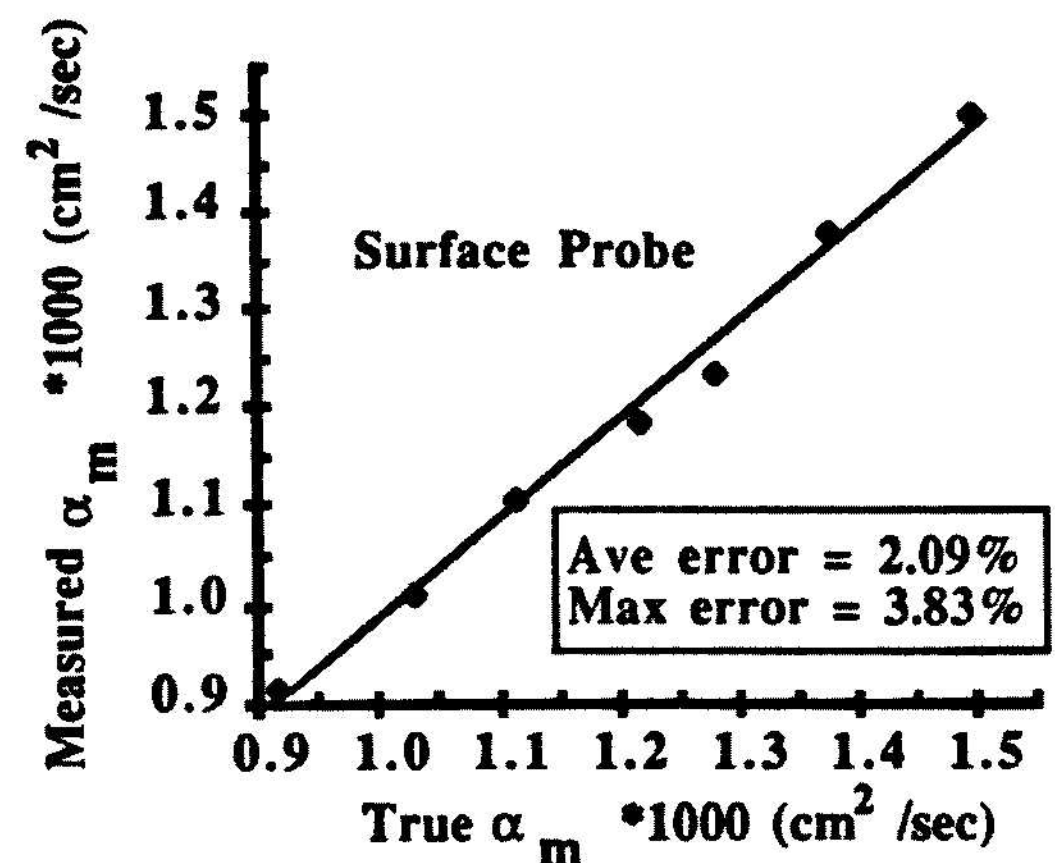


Figure 7. Measured diffusivity versus true diffusivity.

ISOLATED RAT LIVER EXPERIMENTS

To determine the accuracy of the perfusion measurement, it is necessary to know the true perfusion of the tissue on which the probe is placed. It is difficult to control both the perfusion and temperature of a tissue *in vivo*. Hence, an isolated rat liver apparatus was designed to evaluate the perfusion measurements (Brauer et al., 1951), (Bartosek et al., 1973), (Brunengraber et al., 1973), (Valvano et al., 1984b), (Prah, 1986.)

Design considerations for rat liver apparatus

The isolated rat liver apparatus, shown in Figure 8, has been designed considering 1) choice of perfusate, 2) thermal stability, 3) flow control, 4) pH control, and 5) oxygenation. These factors are critical for the viability of the liver. In order to measure effective thermal conductivity at several perfusion rates, it is necessary to keep the liver viable for about three hours.

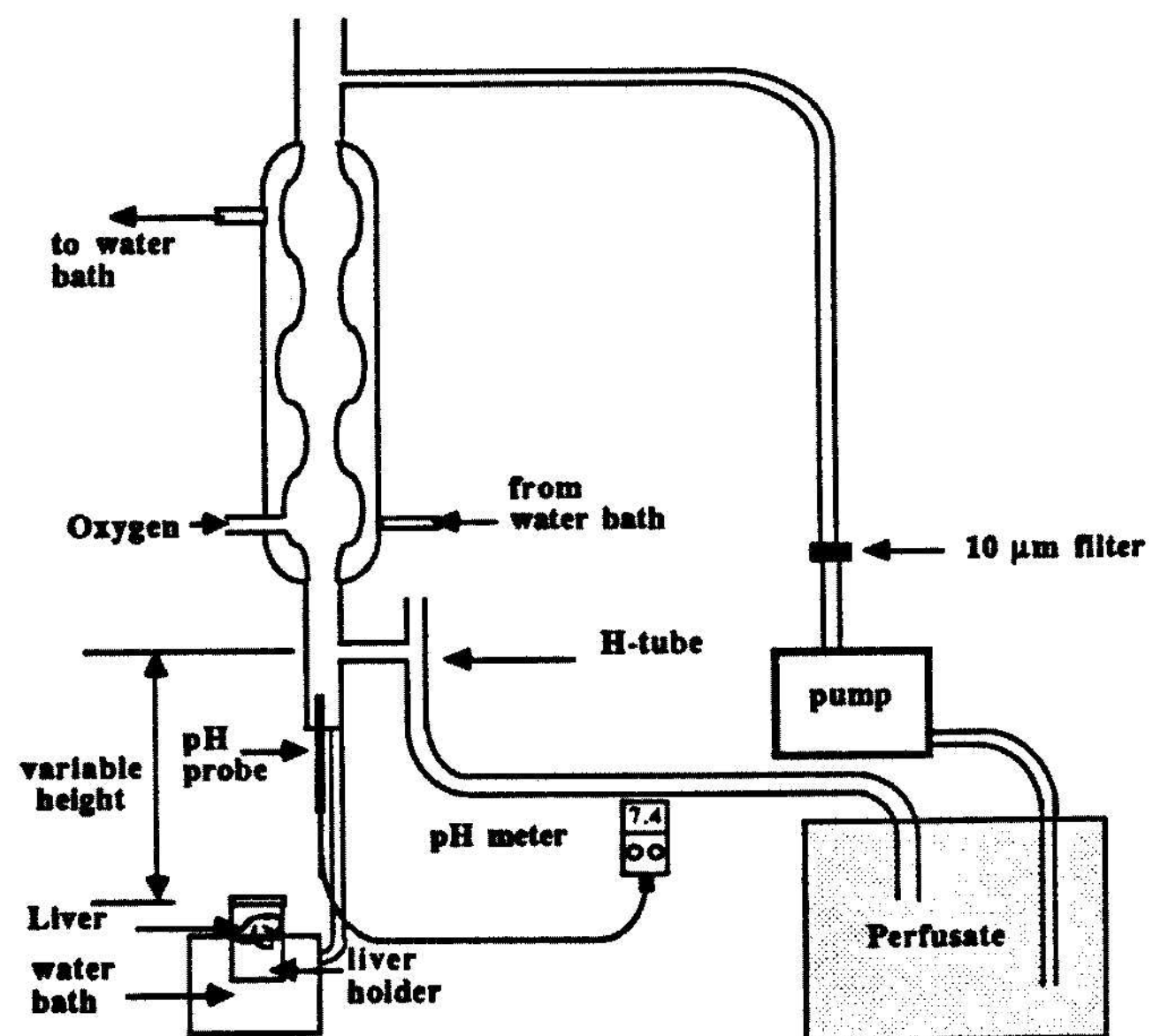


Figure 8. Isolated rat liver apparatus.

The perfusate. Since the constituents needed to keep the liver viable are contained in the fluid passing through the liver, it is necessary to choose a perfusion medium cautiously. The perfusate medium should provide the necessary oxygen in a solution with the correct pH and density. A Krebs-Ringer bicarbonate buffer solution with glucose was used as the perfusate in this research.

Thermal stability. Since the accuracy of the thermal measurements is highly dependent on the baseline temperature stability, the baseline temperature of the tissue must not vary more than 0.015 °C/min. The thermal stability in the perfusion system was obtained by heating the perfusate to 37 °C before it entered the liver. The thermal stability of the environment in the liver holder was maintained by designing a water-jacketed rat liver holder through which water at 37°C continuously circulated.

Flow control. The thermal probe was operated in the transient mode and consequently the flow must be constant during the 88 second measurement. The total flow rate through the liver was controllable and could be varied by changing the height of the oxygenator.

pH control. The normal pH of the rat blood is 7.4. If the blood pH drops to less than 7.0 or increases to more than 8.0, the tissue will die. Small changes in perfusate pH from the normal value lead to qualitative and quantitative changes in the liver's metabolism. During the isolated rat liver experiments it was found that a decrease in pH reduces flow and an increase in pH increases the flow. This is probably due to changes in vascular resistance, hence it was necessary to precisely control the pH in order to maintain a constant flow rate. The pH was monitored constantly and maintained within the range of 7.35 to 7.45. Any increase in pH from the normal was balanced by titrating with CO₂.

Oxygenation. Oxygenation of the perfusate is important for the viability of the isolated rat liver. Solubility of the oxygen in the perfusate is a function of the temperature of the perfusate. Empirically, oxygenation of the perfusate was found to generate bubbles if the temperature of the perfusate was lower than 32 °C and so the perfusate was preheated to 33 °C before it was oxygenated.

With the discussed factors taken into consideration, the rat liver apparatus was designed. The thermal stability of the liver was better than ± 0.01 °C/min. The perfusate flow stability was better than 0.025 ml/min per minute. The pH of the perfusate was controllable to better than 7.40 ± 0.05.

Evaluation of perfusion measurements

Thirty-six laboratory rats were used to develop and test the rat liver apparatus, and to evaluate the thermal probe. Figure 9 shows plots of measured effective thermal conductivity versus perfusion during a typical isolated rat liver experiment. The rat liver experiment protocol was as follows.

1. Circulate four liters of the perfusate through the oxygenator, cannula and back to the reservoir.
2. Anesthetize the rat with sodium pentobarbital IP.
3. Make an incision in the abdomen to expose the liver.
4. Cannulate the portal vein distal to the liver.
5. Cut the inferior vena cava and isolate the liver maintaining the diaphragm.
6. Place the liver in the water jacketed holder, and place the probes on the liver surface.
7. Close the top lid of the holder.
8. Monitor and correct the pH of the perfusate constantly.
9. Measure total flow by venous collection.
10. When flow rate and temperature are stabilized, measure K_{eff} .
11. Repeat steps 8-10 for four or five flow rates.
12. Stop the flow and measure the intrinsic thermal properties.
13. Measure the mass and volume of the liver.
14. Convert the flow rate (ml/min) to perfusion (ml/100g-min), assuming uniform flow.

Problems of isolated rat liver experiments.

During the isolated rat liver experiments, a few problems with the isolated rat liver preparation arose. The measurement of thermal properties using the surface probes was found to be sensitive and sometimes insensitive to perfusion.

The position of the isolated liver was one of the affecting factors. Free suspension of the liver by the diaphragm created problems with the placement of the probes. Because the lobes were hanging in air, it was difficult to obtain good contact between the probe and the tissue surface. When the liver was rested on a screen, lobular vessels sometimes kinked causing non-uniform flow through the lobes. A reasonable compromise was reached by hanging the liver in air and letting it partially rest on an egg-shaped support. The holder gave support which improved probe contact. However, the cannula still sometimes kinked causing irregular flow patterns.

Hysteresis was sometimes noticed in the effective conductivity measurements. K_{eff} would increase as flow increased, but K_{eff} did not decrease when flow was decreased. When the flow was increased again, K_{eff} increased but by a different amount. We believe this hysteresis might be caused by vascular degradation.

The baseline temperature stability was found to be a significant disturbing factor. When the baseline temperature varied during the measurement, the thermal properties measurements were scattered. The results followed a pattern similar to Figure 5.

Probe placement was a critical factor. Poor or imperfect contact between the probe and the tissue surface caused widely scattered measurements even when the baseline temperature was stable. When the contact was very poor, the measurements were insensitive to perfusion.

Results of the rat liver experiments. It was possible to obtain consistent data when the above mentioned disturbing factors were minimized. Figure 9 shows that the measured K_{eff} is sensitive to perfusion. Repeated measurements with the same flow demonstrated the reproducibility of the measurement. Figure 10 shows plots of the difference between effective and intrinsic conductivity ($K_{eff} - K_m$) versus perfusion measured with five surface probes on one rat liver. This data demonstrates that all 5 probes are sensitive, but there is a nonuniform perfusion field in the isolated rat liver. These results also suggest that a simpler linear equation between K_{eff} and perfusion exists.

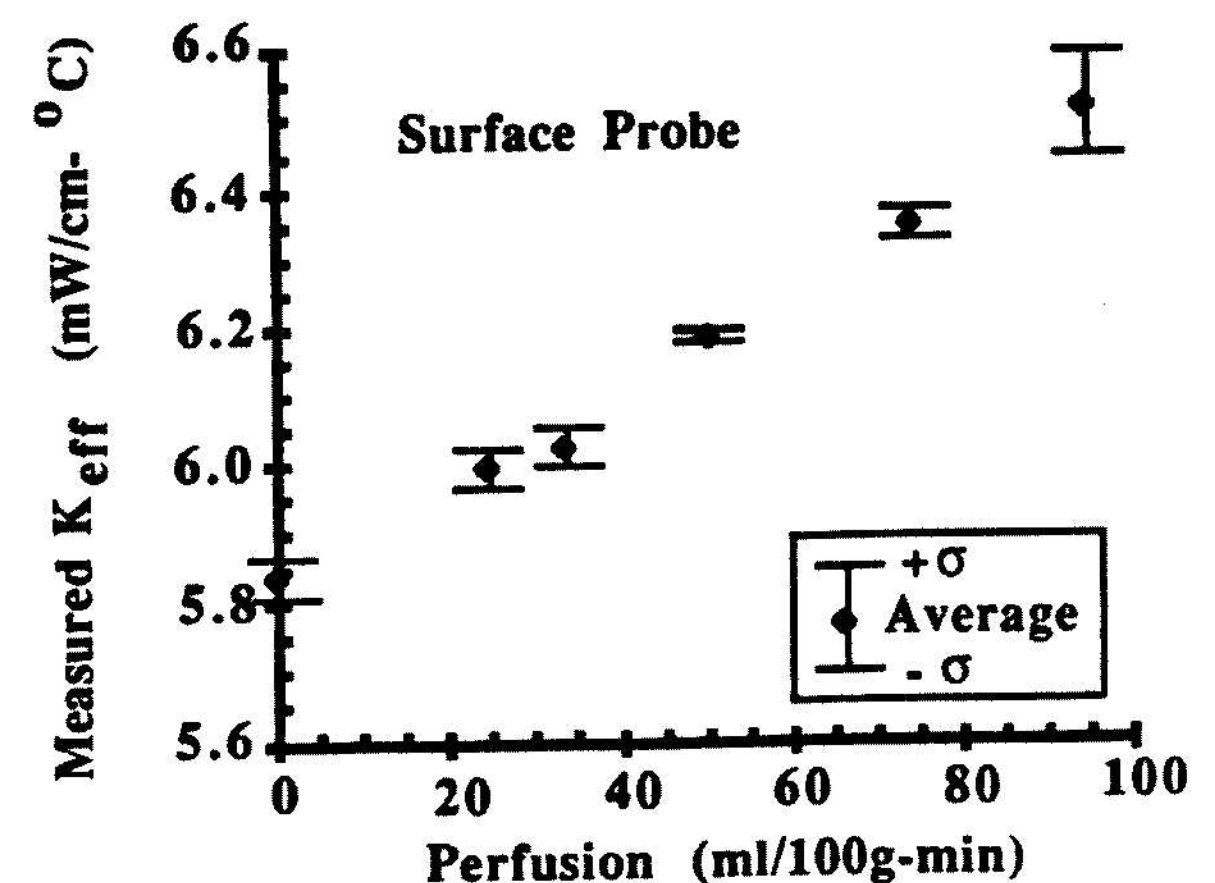


Figure 9. Measured effective conductivity versus perfusion.