THERMAL METHODS FOR
BLOOD PERFUSION MEASUREMENT:
APPLICATION FOR DIFFERENTIAL
DIAGNOSIS OF BREAST CANCER

by

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ABSTRACT

Thermal methods for the evaluation of blood perfusion in (human) tissue are analyzed in Part I. One-dimensional and two-dimensional (axi-symmetric) steady-state solutions to the energy equation in tissue are presented; these solutions are applied for the qualitative and quantitative measurement of tissue perfusion. Limiting expressions for thermally thick and thermally thin tissue are derived. Also considered is the one-dimensional transient solution for thermally thin tissue. Techniques for detecting abnormalities in cerebral blood flow via asymmetries in scalp perfusion are discussed, and a transient local cooling test is proposed. A successful application of (steady-state) local cooling for the daily assessment of tumor perfusion during radiation therapy is presented.

In Part II the analysis from the first part is applied for the development of thermal methods for the differential diagnosis of breast cancer. Infra-red thermography is analyzed, and it is concluded that for medical applications it is not being used in an optimum thermal manner. By optimizing surface thermal conditions thermographic sensitivity (i.e., skin temperature difference between tissue regions of different morphology) can be increased as much as three-fold. A local cooling technique, which theoretically promises several times the sensitivity of thermography, was developed and tested clinically. The local cooling device utilizes a 0 °C heat sink to cool the skin through a copper disk and optimized thermal resistance. Two devices are used in tandem, contralaterally, and skin temperature is measured as a function of time. Local cooling tests have been made on 130 women who were also examined xeroradiographically and thermographically. Diagnostic criteria, developed from the results, would have correctly diagnosed 23 of 31 (74%) of the carcinomas as malignant. A false positive rate of 20% overall was obtained. Computer studies show a transient test to be as sensitive as the local cooling method (as it was practiced). However, a technique which explicitly controls the cooling rate offers, theoretically, nearly twice the sensitivity.

Thesis supervisor: Borivoje B. Mikic
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BIOGRAPHICAL NOTE

John D. Cary was born and grew up in the state of Maine. He is a Capricorn; his moon is in Aquarius and he has Scorpio rising. After graduating from Morse High School in Bath, he attended Bowdoin College for three years before entering MIT in 1967 as a junior.


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Future plans include employment in the bio-engineering field, hopefully in furtherance of his doctoral research.
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NOMENCLATURE

a  radius of local cooling disk
B  variable defined in Appendix VII
BT benign tumor
C  cyst
C_b specific heat of blood
C_p specific heat
CA cancer
D  penetration depth of local cooling device
DD diffuse breast disease
e  electric potential difference or voltage
F  \( \{ V_g/V_w \} \) volume fraction
h heat transfer coefficient
i  electrical current
I  integral derived in Appendix I
k thermal conductivity
L thickness of bone
m mass per unit area of copper
M diagnostic criterion related to slopes of cooling curves
N  normal
q'' \(_S\) heat flux from skin
(q'' \(_S\)) \(_o\) heat flux from skin for h = 0
(q'' \(_S\)) \(_{opt}\) heat flux from skin when h = h \(_{opt}\)
Q_c volumetric heat conduction interaction of tissue
Q_m metabolic heat generation
\( \bar{Q} \) \[= \frac{Q_m}{w_b c_b (T_a - T_o)} \]

- \( r \) radial coordinate
- \( R \) thermal resistance
- \( t \) time
- \( T \) temperature
- \( T_a \) arterial blood temperature, nominally 37 °C
- \( T_e \) environmental temperature
- \( T_s \) skin temperature
- \( T_o \) heat sink temperature
- \( U_A \) overall heat transfer conductance
- \( w_b \) blood perfusion
- \( V \) volume
- \( x \) one-dimensional coordinate
- \( X \) variable defined in Appendix VII
- \( z \) axial coordinate
- \( \alpha \) thermal diffusivity, also dummy variable used in Appendix I
- \( \delta \) tissue thickness
- \( \delta_{Cu} \) copper thickness
- \( \Delta T_c \) control temperature difference
- \( \Delta T_s \) skin temperature difference
- \( \lambda \) \[= (w_b c_b / k)^{0.5} \] commonly called perfusion
- \( \lambda_o \) basal value of \( \lambda \) (at \( T = T_a \))
- \( \phi \) variable defined in Appendix VII
- \( \rho \) density
- \( \theta \) \[= T - T_a \]
- \( \zeta \) \[= \alpha a \]
Subscripts:

a  arterial
B  bone
Cu  copper
eff  effective
g  glass
i  initial
N  normal tissue
opt  optimum
s  skin
T  tumor tissue, also thermistor
v  venous
w  water
Knowledge of the spatial temperature field in human tissues can be of considerable value to the medical diagnostician. Various human afflictions, such as broken and knitting bones, blocked or constricted blood vessels, contusions, infections, frostbite, burns, rhematoid arthritis, and especially malignant cancer growths are characterized by abnormal local (and non-local) body temperatures [1-7]. An inexpensive, non-invasive, non-toxic, and comfortable (for the patient) clinical method for measuring and interpreting tissue temperatures would be of great value.

At present infra-red thermography is the only technique in clinical use, albeit limited, for the diagnosis and evaluation of the above-mentioned afflictions using quick, non-invasive temperature measurements. Electro-magnetic emissions in the infra-red band (8000 A° to 1 mm) from the skin are measured. For those wavelengths, the skin behaves essentially as a black body [8]. Thermography is basically a passive technique; it is used to measure the skin temperature without interacting with it. The skin temperature is determined by physiological conditions in the tissue and environmental conditions to which the body (i.e., skin) is exposed. Thermography cannot be used for measuring heat flux from the skin. Usually, the medical thermographer must rely upon comparative temperature measurements for his diagnosis; asymmetries in skin temperature levels and patterns provide the diagnostic basis. There is no guarantee that infra-red thermography is performed optimally; (i.e., that the observed skin temperatures most accurately and sensitively reflect morphological conditions that one wishes to detect); its medical
application was secondary to its development for military purposes.

Other thermal techniques include liquid crystal thermography [9] and radiometric thermometry[10 - 12]. Liquid crystals change color with temperature. Their application is similar to infra-red thermography. The microwave radiometer has the potential of measuring temperatures at a depth within tissue [13]. It measures microwave radiation (1 mm to 20 cm) emitted from body tissues at a depth. Thus its signal is proportional to an average temperature at a depth within the tissue. The technique is in early stages of development.

Successful treatment of malignant neoplasms requires early diagnosis so that surgical removal has a higher probability of removing all malignant cells. Screening for breast cancer of clinically occult women, i.e., the identification of that part of the population which has a high probability either of having or of contracting the disease, but which exhibits no symptoms, can result in lower mortality rates; axillary node involvement for these screened women has been significantly lower than for the whole population [14]. Infra-red thermography can be and is used both for screening high risk women and differential diagnosis of clinically occult masses. It suffers as a diagnostic method because of high false positive and false negative rates [15].

To be effective, a screening technique, because it by necessity involves a significant portion of the population, must be quick, non-invasive, convenient, comfortable, and non-toxic. Thermal methods for cancer detection fill this prescription; they only need more accuracy to become accepted. Xerography offers the skilled radiologist a high degree of accuracy [16], and it can be used for screening [14]. However, it is
not as convenient as thermography for the person being examined; moreover, the hazards of excess radiation exposure discourage the use of radiographic methods for screening. Obviously, biopsy, a nearly foolproof diagnostic test for symptomatic cancer, cannot be used for screening.

Infra-red thermography was first used by Lawson in 1956 [4] for the diagnosis of breast cancer. Despite the period of time since its discovery and application, there is still controversy surrounding the tissue mechanism of the thermographically observed elevated skin temperatures found over malignant tumors. Lawson [17] maintains that they are due to elevated metabolic rates in tumors. From the work of Cooper [18] one must conclude that, for tumors which are covered by normal tissue, venous convection causes the elevated skin temperatures. Smaller tumors are rapidly growing and have higher perfusion rates [19]. Larger tumors, although their average blood perfusion may be lower, are highly perfused in their peripheries [19]. It is not unreasonable for this to be reflected in a larger superficial venous flow. Thermal measurements by the author indicate that the Cooper interpretation (that elevated skin temperatures are principally due to heat convected to the skin by blood) is qualitatively correct; furthermore, by increasing the thermal interaction of the environment with the tissue, the effect of metabolism on skin temperature can be made small. If the physiological mechanisms underlying the thermal processes in tissue are understood, thermal diagnostic tests can be designed which are more sensitive and more accurate.

The heat transfer through human tissue, in general, is affected by 1) tissue conduction, 2) time perfusion with capillary blood, 3) arterial and venous blood thermal interaction with tissue and 4) metabolic heat generation in tissue. Neglecting anisotropy, and assuming that the sub-
region of interest is homogeneous, the energy equation in tissue may be written [20]:

\[ \rho c_p \frac{\partial T}{\partial t} = k \nabla^2 T - \omega_b c_b (T - T_a) \]

\[ + Q_m - (UA)_a (T - T_a) - (UA)_v (T - T_v) \]

The term on the left-hand side of the equation and the first term on the right-hand side are the transient and conduction terms respectively, for the tissue. The second term, right-hand side, is the heat delivered to the tissue in capillaries. The third term right-hand side, is the heat generated by metabolism. The fourth and fifth terms, right-hand side, represent the tissue interaction with arterial and venous blood, respectively.

If \((UA)_a\) and \((UA)_v\) are finite then \(T_a\) and \(T_v\) are a function of position. For this case, energy balances must be written for both the arterial and venous blood; the directionality of the blood flow must be accounted for in these equations. A host of geometrical assumptions must be made to solve the tissue energy equation for this case.

If \((UA)_a = (UA)_v = 0\), then the energy equation in tissue becomes

\[ \frac{1}{\kappa} \frac{\partial \Theta}{\partial t} = \nabla^2 \Theta - \lambda^2 \Theta + \frac{Q_m}{\kappa} \]

where \( \Theta = T - T_a \) and \( \lambda^2 = \omega_b c_b / \kappa \).

In this formulation it is assumed that the interaction between large blood vessels and the tissue may be neglected. The second term in the right-hand side of the equation approximates the effect of the tissue perfusion.
by blood in capillaries. The derivation of this term, \( \lambda^2 (T - T_a) \), is based on the following assumed conditions [21]: all capillaries within a differential element originate within that element; the blood entering a capillary is at a constant arterial temperature, \( T_a \); and the flowing blood leaving a differential element has reached thermal equilibrium with the element. The first and third assumptions are based on the geometry and hemodynamics of capillaries (average length and diameter of 750 and 6 \( \mu \), respectively, and average blood velocity of 0.3 mm/sec.). Because capillaries are relatively short, the probability of originating within an element is high. It can be shown that due to the low blood velocity in capillaries, the time required for thermal equilibrium with the tissue is several orders of magnitude less than the average residence time for blood in capillaries. The condition that capillary inlet temperature is constant at \( T_a \) is a consequence of the previous assumption of negligible interaction between large blood vessels (i.e., larger than capillaries) and the tissue, and it cannot, in general, be justified. Nevertheless, the neglect of large vessel interaction with the tissue, in most cases, does not distort the qualitative picture obtained, and moreover, these effects can be incorporated into an effective perfusion in the second term of the above equation to yield reliable quantitative results.

Part I presents several solutions to the above (simplified) energy equation in tissue for practical situations of interest. These solutions are applied to the measurement of tissue blood perfusion. Two practical methods for blood perfusion measurement, based on these solutions, are described.
Part II applies the analytical results of Part I to a specific problem: the differential diagnosis of breast cancer. An analysis of thermography describes optimum operating conditions. The conclusions of the analysis lead to the design and application of a new local cooling method. Experimental results for the local cooling device are reported, followed by a numerical simulation of the method's performance. Finally, possible modifications and improvements for the local cooling method are described.
PART I

BLOOD PERFUSION MEASUREMENT

1.1 Introduction

The human body is a complex, self-regulating system which maintains a thermal balance between heat generated internally by metabolism and net heat loss to the environment. When the body is healthy and the interaction with the environment is not too severe, it is capable of maintaining its internal regions (commonly called the 'core') at or about 37°C. Besides supplying tissues with life-sustaining nutrients, circulating blood distributes the heat of the body. Blood perfusing in the superficial tissues exerts a profound influence on the thermal processes at and near the skin.

Qualitatively, it is obvious that under normal conditions (i.e., environmental temperature less than 37°C), increased blood perfusion in the skin will result in an elevated skin temperature, other things being equal. Yet other factors also bear on the temperature of a given element of tissue. Consider the following simple arguments regarding an imaginary one-dimensional tissue element. For such an element, which interacts directly with other adjacent elements of tissue (and with the environment if the element is at the surface), the temperature of the element is determined by:

a) the temperature of the perfusing blood, $T_a$

b) the blood perfusion rate, $w_b$

c) the metabolic rate, $Q_m$

d) the conduction interaction with the surrounding tissue and the environment, $Q_c$
In Figure 1.1 the conservation of energy for a tissue element in the steady-state is illustrated. The tissue temperature contains substantial information on the parameters $w_b$ and $Q_m$. For example, under adiabatic conditions ($Q_c = 0$) the tissue temperature is elevated above the arterial blood temperature by the amount of $Q_m/w_c c_b$, where $c_b$ is the specific heat of blood. From Figures 1.2 a-d it is seen that the temperature difference between two elements of tissue with different values of $w_b$ and $Q_m$, except when perfusion does not change, is very much a function of the heat conduction interaction, $Q_c$. The pattern of temperature differences as a function of $Q_c$ clearly indicates the difference in perfusion and metabolic rates which exist between the two elements of tissue. Also, it is evident that if one wishes to interpret temperature measurements (e.g., as an indication of tissue blood flow differences) under a single heat load condition (i.e., under only one value of $Q_c$), this condition must be carefully selected to ensure that the temperature differences observed is meaningful. For example, if $Q_c$ has a moderate value, from Figures 1.2a and 1.2b a small temperature difference is expected, but from Figure 1.2d the temperature difference might be zero, while from Figure 1.2c one would expect a large temperature difference.

The above simple examples of temperature measurements which detect changes in the physiological variables $w_b$ and $Q_m$, are used only to illustrate the significance of conditions which can be controlled. It is not practical, of course, to a) impose arbitrary $Q_c$ distributions within the examined tissue, and b) measure the temperature of the tissue at some depth below the skin. What one can do, however, is impose controlled conditions over the skin area and observe the temperature response
Figure 1.1. Energy balance for an element of tissue

\[ \omega_b C_b (T_a - T) + Q_m = Q_c \]

\[ T = T_a + \frac{1}{\omega_b C_b} (Q_m - Q_c) \]
Figure 1.2. Temperatures of pairs of elements with different $w_b$ and $Q_m$.
at the skin as a function of the physical properties and the perfusion and metabolic rates of the tissue below.

There are two basic approaches to blood perfusion measurement. In certain situations one is desirous of measuring absolute perfusion levels; this requires measurement of both temperature and heat flux from the skin, along with detailed knowledge of tissue property values and their variation beneath the skin. In other situations a comparison of perfusion rates is adequate; for qualitative measurements, the use of body symmetry can effectively negate the influence of tissue inhomogeneity. In either situation, it is important to make intelligent choices of the thermal conditions under which the variables of interest are to be observed, as the preceding simple arguments illustrated. In particular, if one is distinguishing differences in perfusion by differences in skin temperature, optimum thermal conditions for such a measurement would induce the maximum skin temperature difference for a given difference in perfusions. In a similar manner, one can design experiments for absolute perfusion measurement which will result in a minimum of experimental error.

In the next chapter, various solutions to the energy equation in tissue—one and two-dimensional, closed-form and computer, steady-state and transient—are presented. The solutions may be used for either relative or absolute measurements of perfusion. Comments will be offered on the optimization of conditions for relative measurements; these suggestions may be also applied to absolute measurement since tissue property values are the primary hindrance to their determination.

It is, of course, well known that skin blood perfusion is a function of the skin tissue temperature. Temperature depression results in vasoconstriction; elevation causes vasodilation. Thermal perfusion measure-
ments can be made by either heating or cooling the skin and watching the skin temperature response. If two otherwise identical regions of tissue have different perfusion rates in the basal state, identical cooling amplifies the temperature difference because the region of less perfusion experiences greater vasoconstriction. Cooling, therefore, leads to greater sensitivity in perfusion measurements. Heating, on the other hand, lessens basal perfusion differences since the region of less perfusion experiences greater vasodilation. Determination of the basal perfusion rate from the vasoconstricted measurement requires knowledge of the vasoconstriction mechanism. Some simplified attempts to deliniate this mechanism are illustrated in Chapter 1.3. The results show the plausibility of the proposed mechanism; they also justify the use of an effective perfusion which is uniform throughout the tissue.

In the last two chapters two practical methods for blood perfusion measurement are discussed. One is a transient method proposed for the evaluation of head blood flow asymmetry; for this application a ratio of the relative blood flows is entirely adequate. The other method is successfully applied to the daily evaluation of tumor blood perfusion during a course of radiation therapy; in this case relative changes at one location over a period of time are required. For this second application, then, basically absolute measurements are required since temporal variations in the measurement conditions preclude a strictly comparative approach.
1.2 Some Solutions to the Energy Equation in Tissue

1.2.1 Introduction

The assumptions and modeling leading to the energy equation are detailed in the Introduction. For the purposes of the analysis in the work, it was shown to be

\[ \frac{1}{\kappa} \frac{\partial \theta}{\partial t} = \nabla^2 \theta - \lambda^2 \theta + \frac{Q_m}{K} \]  

(1.1)

where \( \theta = T - T_a \) and \( \lambda^2 = \frac{w_c c_b}{k} \). All symbols are explained fully in the Nomenclature. The term involving metabolism \( Q_m \), under conditions of moderate-to-strong cooling, can be justifiably neglected with respect to blood flow. The complete derivation of solutions to equation (1.1) for one and two-dimensional steady-state and one-dimensional transient situations of interest are detailed in Appendix I. The results, listed in this chapter, are applied to practical methods for deducing tissue blood perfusion.

1.2.2 One-Dimensional Steady-State Analysis

The model for the solution domain is shown in Figure 1.3. Tissue of thickness \( \delta \), perfusion \( w_b \), and conductivity \( k \) lies over bone of thickness \( L \) and conductivity \( k_b \). The temperature at \( x = \delta + L \) is fixed at \( T_a \). The skin temperature \( T_s \) (at \( x = 0 \)) is found for \( q_s^\prime \) specified (i.e., skin heat flux) or for specified \( h \) and \( T_o \) at the skin (i.e., specified surface heat transfer coefficient and environmental temperature). Since flux and temperature can only be measured at the skin (i.e., \( x = 0 \)), derived expressions will utilize parameters evaluated at \( x = 0 \).
Figure 1.3. General model for one-dimensional heat transfer in tissue
If the heat flux \( q''_s \) is specified at \( x = 0 \), in Appendix I, it is shown that:

\[
T_s - T_a = -\frac{q''\delta}{k} \frac{1}{\lambda \delta} \left( 1 + \frac{k_B \delta}{kL} \frac{1}{\lambda \delta} \tan h \lambda \delta \right)
\]

(1.2)

where \( q''_s \) is defined as positive in the negative \( x \) direction.

If \( h \) and \( T_0 \)—surface heat transfer coefficient and environmental temperature—are specified at the surface,

\[
T_s - T_a = \frac{-\left(T_a - T_0\right)}{1 + \frac{\lambda \delta}{h \delta/k} \left( \tanh \lambda \delta + \frac{k_B \delta}{kL} \frac{1}{\lambda \delta} \tan h \lambda \delta \right)}
\]

(1.3)

It is readily evident from equations (1.2) and (1.3) that perfusion cannot be found explicitly in terms of measured state variables and (assumed) tissue properties and dimensions. However, for equation (1.2) evaluation of dimensionless parameters \( q''\delta/k(T_a - T_s) \) and \( k_B \delta/kL \) allows determination of \( \lambda \delta \) and hence perfusion; similarly, for equation (1.3), with \( (T_a - T_s)/(T_a - T_0) \), \( h \delta/k \), and \( k_B \delta/kL \) one can find \( \lambda \delta \).

There are two special cases of interest whose solution has value for applications. They are when \( \lambda \delta \gg 1 \) and when \( \lambda \delta \ll 1 \). They are called the thick and thin tissue approximations, respectively.
1.2.2 a (1) Thick Tissue Approximation

For $\lambda \delta >> 1$, $\tanh \lambda \delta \approx 1$. Using this approximation in equations (1.2) and (1.3), it is seen that for prescribed heat flux $q''_s$ from the skin

$$T_s - T_a = \frac{q''_s}{k \lambda} \quad (1.4)$$

or

$$\omega_b = \frac{k \lambda^2}{c_b} = \frac{k}{c_b} \left[ \frac{q''_s}{k(T_a - T_s)} \right]^2 \quad (1.5)$$

and for prescribed heat transfer coefficient and environmental temperature $q''_s = h(T_s - T_o)$

$$\omega_b = \frac{k}{c_b} \left[ \frac{h(T_s - T_o)}{k(T_a - T_s)} \right]^2 \quad (1.7)$$

This one-dimensional result for perfusion in thermally "thick" tissue could be of value for deducing perfusion from infra-red thermographic measurements of breast skin temperature.
1.2.2 a (2) Thick Tissue with two Layers of Different Perfusion

The model is similar but now $\lambda = \lambda_1$, or $0 < x < \delta$ and $\lambda = \lambda_2$ for $x > \delta$. For this situation

$$T - T_a = (T_s - T_a) \left\{ \cosh \lambda_1 x - \frac{\lambda_1}{\lambda_2} \frac{\tanh \lambda_1 x + 1}{\tanh \lambda_2 + \frac{\lambda_1}{\lambda_2}} \sinh \lambda_1 x \right\} \quad (1.8)$$

Heat flux at $x = 0$ may be prescribed, or it may be specified by $h$ and $T_o$.

Since we may define an effective perfusion

$$\lambda_{\text{eff}} = \frac{q^w}{k(T_a - T_s)} \quad (1.9)$$

Differentiating (1.8) it is shown in Appendix I

$$\left( W_b \right)_{\text{eff}} = \frac{\lambda_{\text{eff}} k}{C_b} = \frac{k}{C_b} \left[ \lambda_1 \frac{\lambda_1 \tanh \lambda_1 \delta + 1}{\lambda_2 + \tanh \lambda_2 \delta} \right]^2 \quad (1.10)$$
1.2.2 b Thin Tissue Approximation

For this situation $\lambda \delta \ll 1$ and $\tanh \lambda \delta$ is approximately equal to $\lambda \delta$. Using this approximation in equation (1.2), the reduced expression for perfusion when $q''$ is specified becomes

$$W_b = \frac{k}{C_b \delta^2} \left[ (1 + \frac{k_B \delta}{kL}) \frac{q'' \delta}{k(T_q-T_s)} - \frac{k_B \delta}{kL} \right]$$

(1.11)

When $h$ and $T_0$ are specified as the surface thermal conditions

$$W_b = \frac{k}{C_b \delta^2} \left[ \frac{h \delta (T_s-T_0) - k_B \delta (T_a-T_s)}{(T_a - T_s)} \right]$$

(1.12)

These results are of use in the determination of blood perfusion in the scalp.
1.2.3 Disk Cooling; Two-Dimensional (Axi-Symmetric) Steady-State Analysis

Figure 1.4 gives the geometry for this case: cooling of the tissue occurs over a disk of radius $a$. The tissue is assumed to be homogenous and isotropic with constant properties. The flux through the disk is much larger than through the surrounding skin; thus, the surface area outside the cooling disk is assumed to be adiabatic. The tissue extends radially beyond the region affected by the local cooling; but it is of thickness $\delta$. The boundary at $x = 0$ is assumed to be insulated. The boundary condition at $z = \delta$ and $r < a$ is determined by conditions at the disk.

1.2.3 a Conditions which Approximate Constant Temperature over Disk

If the disk is made of high conductivity material, such as copper, it may be assumed to be at constant temperature, and the problem is completely formulated. The solution to the energy equation is found in Appendix I for this situation. The disk temperature is

$$\Theta_s = \frac{Q_m}{k\lambda^2} = -\frac{q_s'}{k\lambda} I_1,$$  \hspace{1cm} (1.13)

where

$$I_1 = \int_0^\infty \sin(\xi) (\xi) \coth \left[ \frac{\xi^2 + (a\lambda)^2}{2} \delta \frac{\xi}{a} \right] d\xi.$$  \hspace{1cm} (1.14)

Alternatively,

$$\frac{q_s'}{k (T_a - T_s)} = \frac{a\lambda}{I_1} \left[ l + \frac{Q_m}{k\lambda^2 (T_a - T_s)} \right].$$  \hspace{1cm} (1.15)

This solution represents only an approximation since one of the boundary conditions is satisfied only in the average; this imposes infinite heat fluxes at the corners of the disk. Possibly, a better approach would be imposing constant flux over the disk area; this case is solved exactly.
Figure 1.4. Thermal model of tissue for local cooling with a disk

\[ \frac{dT}{dz} = 0 \]
1.2.3 b Constant Flux over Disk Area

For this condition an expression similar to (1.15) is derived

\[
\frac{q_s'' a}{k (T_a - T_s)} = \frac{a \lambda}{I_2} \left[ 1 + \frac{Q_m}{k \lambda^2 (T_a - T_s)} \right]
\]  

(1.16)

where \( T_s \) is the average disk temperature and

\[
I_2 = \int_0^\infty J_1^2(z) \coth \left[ \frac{z}{2} + (a \lambda)^2 \frac{z^2 S}{8} \right] \frac{z}{z + (a \lambda)^2} dz
\]

(1.17)

Solutions for \( I_1 \) and \( I_2 \) were found on an IBM 1130 computer.

For \( \frac{\delta}{a} \to \infty \), \( \lim_{a \lambda \to 0} \frac{a \lambda}{I_1} = \frac{4}{\pi} \) and \( \lim_{a \lambda \to 0} \frac{a \lambda}{I_2} = \frac{3\pi}{8} \)

For \( \frac{\delta}{a} \to 0 \), \( \frac{a \lambda}{I_1} = \frac{a \lambda}{I_2} = a \lambda \tanh \lambda \delta \). \( \frac{a \lambda}{I_1} \) and \( \frac{a \lambda}{I_2} \)

are plotted vs. \( a \lambda \) in Figure 1.5. It is seen that there is not much difference between constant temperature and constant flux solutions.

Using the same arguments advanced in Appendix I for the one-dimensional case, it is possible to neglect the term \( \frac{Q_m}{k \lambda^2 (T_a - T_s)} \) in equations (1.15) and (1.16). Therefore, it is possible to use equations (1.15), (1.16) and Figure 1.5 to determine the perfusion from \( q_s'' a/k(T_a - T_s) \) and \( \delta/a \). It would not be a practical method for small values of \( a \lambda \), especially so if \( \delta/a \gg 1 \).
Figure 1.5. $\frac{a\lambda}{I_1}$ (uniform disk temperature) and $\frac{a\lambda}{I_2}$ (uniform heat flux through the disk) plotted as a function of $\delta/a$ (tissue thickness to disk radius) and $a\lambda$; $I_1$ and $I_2$ are integrals derived in Appendix I.
1.2.4 Transient Solution for a Thin Layer of Tissue

A thin layer of tissue ($\lambda \delta \ll 1$), assumed one-dimensional, is mathematically tractable because the layer is essentially at constant temperature and all the tissue may be lumped into one mass. Some other situations may be solved with the use of infinite series, but, in general, finite difference formulations are necessary to derive useful information. During the course of this research, different specific cases were analyzed transiently on the computer. No general solutions are presented; specific cases are presented where warranted.

For the thin layer of tissue in Figure 1.3, consider the skin to be in contact with a mass per unit area of copper $m$. Assuming that $\rho c_p$ of the bone layer is negligibly small (in any event the transient effect of the bone could be lumped with the tissue, if the bone temperature distribution is linear), the following expression for perfusion is developed in Appendix I:

$$\omega_b = \frac{k}{c_b \delta^2} \left[ \frac{d T_s}{d t} \left\{ \frac{(m c_p)_{Cu}}{\kappa} \frac{\delta^2}{\kappa} + \frac{\delta^2}{\alpha} \right\} - \frac{\kappa B \delta}{\kappa L} \right]$$

(1.18)

One application of this result is to compare scalp perfusion asymmetries. For this application, as it will be discussed later, $k_B \delta/kL$ may be assumed to be negligible. If all other quantities are equal due to symmetry, then

$$\frac{\omega_{bz}}{\omega_b} = \frac{d T_{sz}/d t}{d T_{sz}/d t} = \frac{T_a - T_s}{T_a - T_{sz}}$$

(1.19)
These solutions are found with the assumption that the whole tissue layer can be lumped at the skin temperature. In order to verify the validity of this assumption, a transient one-dimensional finite difference computer program was written. The computer program may be found in Appendix II. The response of scalp tissue 0.4 cm thick with perfusion $1 \text{ cm}^{-1}$ was tested for different copper masses in contact with the skin. Since the representation is one-dimensional the thickness of the copper $\delta_{\text{Cu}}$ is proportional to its mass per unit area. It is seen that after 5 minutes the system response is approximately that of the lumped theory, especially for smaller copper masses.
\[
\frac{dT_s}{dt} = \frac{(T_a - T_s)}{0.05 - \frac{0.04}{\text{[min]}^{-1}}} - \frac{0.03 - 0.02}{\text{[cm}^2\text{s}] = 0.4} \]

\[
\lambda = 1 \text{ cm}^{-1}
\]

\[
\delta_{\text{tissue}} = 0.4 \text{ cm}
\]

Figure 1.6. One-dimensional transient of a thin layer of tissue, lumped theory compared to a computer simulation, as a function of the thickness of copper cooling the tissue.
1.2.5 Optimization of Measurement Conditions

It was pointed out earlier that it is important to be able to control the surface thermal conditions, because they exert a strong influence on the surface temperature response to perfusion differences in the tissue below. Therefore, the mechanisms controlling heat transfer in the tissue determine the optimum surface heat transfer conditions. It has been postulated in this work that tissue blood perfusion and arterial blood temperature control the heat transfer in tissue. In the problem formulation it is shown that the effect of metabolism can be made small by increasing the tissue's thermal interaction with the environment. Indeed, if metabolism were the controlling factor, optimum conditions for infra-red thermography [22] and local cooling [23] would be an insulated skin surface. Such is not the case; both of these methods have shown that increased cooling is advantageous.

If, then, increased cooling is preferred, how much is optimum? In the earlier sections of this chapter, two basic types of steady-state perfusion measurement techniques have been described. One involves prescribing the heat flux at the skin; the other involves prescribing a surface heat transfer coefficient and environmental temperature. The latter situation is the most common since it is difficult to specify the flux (such as with infra-red thermography); the former is possible with local cooling through a disk.

If one increases the surface heat transfer coefficient the skin temperature eventually would be controlled by the heat sink (or environmental) temperature; thus it is possible to overcool. Also, if the skin temperature is lower than 10°C, a vasodilation reaction occurs [24].
Conceptually, the problem of heat transfer to the skin can be thought of as heat conducting from a source at temperature $T_a$ to the skin at temperature $T_s$ through a resistance in between the source and skin. This resistance is a function of perfusion. Thus, for the case of controlled $h$ and $T_o$, it is desired to select the optimum combination of these two parameters that will result in the maximum skin temperature difference for a given tissue perfusion difference. The answer to this question is simple. Examination of equation (1.3) shows that $T_s$ is proportional to $T_a - T_o$. Thus the sensitivity of the method (i.e., temperature difference for a given perfusion difference) can be increased by increasing $T_a - T_o$. However, if $h \to \infty$, $T_s \to T_o$ independent of $\lambda$. Thus $h$ should have some intermediate level.

Since

$$h(T_s - T_o) = (T_a - T_s)/R(\lambda) \quad (1.20)$$

and

$$\frac{(T_s - T_a)\, (T_a - T_o)}{R(\lambda)\, h} = \frac{1}{1 + \frac{1}{R(\lambda)\, h}} \quad (1.21)$$

where $R(\lambda)$ is the tissue resistance, if one applies the condition that

$$\frac{d}{dh}(T_{s2} - T_{s1}) = 0 \quad (1.22)$$

and solves for $h$, one can show that $h_{opt} = [R(\lambda_1) \cdot R(\lambda_2)]^{-0.5} \quad (1.23)$

Thus the optimum value of $h$ is the geometric mean of the inverse of the tissue resistances. For the thick tissue case

$$h_{opt} = k(\lambda_1 \lambda_2)^{0.5} \quad (1.24)$$

Other typical values may be calculated in a similar manner.

The constant heat flux method was originally described as a technique for finding absolute perfusion levels. However, it can also be
used as a technique for discriminating between relative perfusion differences; by cooling at the same rate over two sites, a temperature difference is generated if perfusion differences exist. A comparison can be made between the two methods. For tissue regions, site 1 and site 2, with $\lambda_2 > \lambda_1$, the prescribed $h$ and $T_0$ technique with optimum $h$ will have $T_{s2}$ greater than $T_{s1}$, but $q''_{s2}$ is greater than $q''_{s1}$ also. Suppose that $q''_{s2}$ is lowered to equal $q''_{s1}$, as would be the case with a constant heat flux technique. This would result in an elevation in $T_{s2}$. Therefore, the constant heat flux technique has inherently greater sensitivity than prescribed $h$ and $T_0$. 
1.3 Blood Perfusion as a Function of Temperature

1.3.1 Introduction

The analysis in Chapter 1.2 is all predicated on assuming uniform tissue properties throughout the solution domain. The values used for \( \lambda \) (i.e., perfusion) in the cited examples were the effective values measured under conditions of moderate to strong cooling with a technique described in Chapter 1.5. The effective perfusion is that perfusion which gives the same skin temperature and heat flux if it is uniform throughout the tissue. Of course, tissue perfusion (if only for the reason that blood viscosity is a strong function of temperature) is a function of temperature. This chapter demonstrates a possible model for the influence of temperature on blood perfusion; the results for this model are compared with the homogeneous results using the effective perfusion generated by the model.
1.3.2 Physiological Basis

The body reacts to a hostile thermal environment in two different ways: passively, on a local scale; and actively, on command from the central nervous system (CNS). Tissue blood perfusion is regulated by arteriole muscle tone (influenced by nerve signals from the hypothalamus), and pre-capillary sphincters (where the local control is primarily exerted). The CNS control is stronger than the local control, but it is activated by a change in the core temperature. The greatest changes in local perfusion occur when both mechanisms are operating in concert [25].

Tests which provide a measure of blood perfusion—such as infrared thermography and local cooling—do not put a strong stress on the body's thermoregulatory mechanisms. Temperature-related vasoconstriction, as considered in this work, is on a mostly local basis.

There are a number of indications that tissue blood perfusion is intimately related to tissue metabolism. Cell metabolism decreases with temperature, other things being equal. This is a consequence of the fact that chemical reaction rates are an exponential function of absolute temperature [27]. Also, oxygen demand can have antoregulatory control over the local perfusion. Furthermore, there is evidence that cellular oxygen saturation results in adenosine being released interstitially which causes constriction of pre-capillary sphincters [26]. Many biochemical reactions have activation energies such that a $10^\circ$ C drop in temperature results in a halving of the reaction rate [27]. Lastly, Stolwicj [30], in his modeling of the human thermoregulatory system, assumed that heat delivered to the skin by blood falls off by a factor of two for each $10^\circ$ C decrease in the skin temperature.
The above discussion applies to healthy tissue. A malignant growth does not respond in the same way as healthy tissue to vasoconstricting chemical agents [28]. Tumor blood vessels, similarly, do not vasoconstrict with cold as strongly as normal vessels. Tumor arterioles are coarse, irregular, and nonhomogeneous [29]; often they appear to lack the smooth muscle control-capability of the normal vasculature. Tumors are also characterized by fast-growing, highly perfused peripheries and lowly perfused anoxic central regions [19].

The reason for the malignant pathology's relative insensitivity to cold is not known. Perhaps the tumor vasculature does not respond to a vasoconstrictive agent such as intercellular adenosine. Perhaps the anoxic regions of tumors provide a sink for surplus oxygen. In any event, it is a phenomenon whose importance is demonstrated in Part II.
1.3.3 Perfusion - Temperature Model

Tissue perfusion is assumed to behave as an exponential function of temperature:

$$\lambda^2 = \lambda_o^2 \times (0.5) \times \left[ \frac{T_a - T}{\Delta T_c} \right]$$  \hspace{1cm} (1.25)

$\lambda_o^2$ is the basal perfusion rate (at $T_a = 37^\circ$ C), and $\Delta T_c$ is the control temperature difference for a 50% change in perfusion. $\lambda_o^2$ and $\Delta T_c$ are also permitted to be functions of position. Skin undergoes greater vasoconstrictive changes with temperature than muscle tissue [24]; tumor perfusion changes with temperature less than these normal tissues. However, $\lambda_o^2$ for tumors (at least in the periphery) should be greater than for normal tissue.

To test the qualitative effect of equation (1.25) on the solution of the energy equation (1.1), a one-dimensional steady-state, finite difference computer program was written (see Appendix II). Under conditions of strong cooling through a disk, a 16:1 ratio of effective tumor perfusion to effective normal tissue perfusion has been measured ($\lambda_{tumor} = 2.0 \text{ cm}^{-1}$ and $\lambda_{normal} = 0.5 \text{ cm}^{-1}$). Values for $\Delta T_c$ and $\lambda_o^2$ were selected such that approximately this ratio of effective perfusion would be achieved; they are shown in Table 1.1.
<table>
<thead>
<tr>
<th></th>
<th>$\lambda_o$</th>
<th>$\Delta T_c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal tissue</td>
<td>1.0 cm$^{-1}$</td>
<td>5 °C</td>
</tr>
<tr>
<td>Tumor tissue</td>
<td>2.0 cm$^{-1}$</td>
<td>10 °C</td>
</tr>
</tbody>
</table>

Table 1.1. Parameters for temperature-controlled perfusion
Four hypothetical tissue situations are analyzed: normal tissue everywhere in the thermally affected region, tumor tissue everywhere, tumor covered by 1 cm of normal tissue, and tumor covered by 2 cm of normal tissue. These four difference tissue geometries are applied to three surface conditions: \( h = 1.06 \times 10^{-4} \text{cal/cm}^2/\text{sec/}^{\circ} \text{C} \) and \( h = 2.12 \times 10^{-2} \text{cal/cm}^2/\text{sec/}^{\circ} \text{C} \) with environmental temperature of 20\(^{\circ} \text{C} \) (moderate cooling conditions approximating thermography) and \( h = 10^{-3} \text{cal/cm}^3/\text{sec/}^{\circ} \text{C} \) with a heat sink temperature at 0\(^{\circ} \text{C} \) (strong cooling conditions approximating local cooling).
1.3.4 Results

The computer solution for strong cooling allows calculation of the effective perfusion, where

$$\lambda_{\text{eff}} = \frac{q_s}{[k(T_s - T_o)]} \tag{1.26}$$

Using the above defined values for $\Delta T_c$ and $\lambda_o^2$, $(\lambda_{\text{eff}})_{\text{tumor}} = 1.45 \text{cm}^{-1}$ and $(\lambda_{\text{eff}})_{\text{normal}} = 0.37 \text{cm}^{-1}$, a 15.3 ratio in effective blood perfusion. With these effective perfusions, solutions for $T_s$ are found from the equations in Chapter 1.2. These analytical results for skin temperature are compared with the computer-generated values in Table 1.2. The analytical solution using $\lambda_{\text{eff}}$ gives acceptable results for the case of strong cooling. For moderate cooling the skin temperatures are too low and the temperature differences between different tissue configurations (for the same cooling conditions) are too great using the effective perfusion analytical solution. This is a direct result of $\lambda_{\text{eff}}$ being defined for the case of strong cooling. $\lambda_{\text{eff}}$ is a function of the cooling conditions; defining $\lambda_{\text{eff}}$ for moderate cooling would have given better results for those conditions.

A plot of $T$ vs. $x$ (temperature as a function of position in tissue) is shown in Figure 1.7. The skin is at $x = 0$. The upper curve was generated by the computer with $\Delta T_c = 5^\circ \text{C}$ and $\lambda_o = 1.0 \text{ cm}^{-1}$. This resulted in an effective perfusion $\lambda_{\text{eff}} = 0.37 \text{ cm}^{-1}$ which allowed calculation of the lower curve from the analytical solution. Figure 1.7 illustrates that the existence of a perfusion-temperature mechanism permits a warmer average tissue temperature than with uniform perfusion.

Much more accurate information of the behavior of $\lambda$ with temperature is needed before estimates of the basal perfusion rate can be made from the effective, vasoconstricted value.
\[ T_0 = 20 \, ^\circ C \quad \text{or} \quad T_0 = 0 \, ^\circ C \]

\[ h = 10^{-4} \quad \text{or} \quad h = 2 \times 10^{-4} \quad \text{or} \quad h = 10^{-3} \]

\[
\begin{array}{|c|c|c|c|}
\hline
\lambda_{\text{eff}} & \lambda(T) & \lambda_{\text{eff}} & \lambda(T) \\
\hline
\text{Normal} & 33.1 & 35.2 & 30.8 & 33.6 & 10.0 & 10.0 \\
\hline
\text{Tumor} & 35.2 & 36.1 & 34.8 & 35.1 & 21.9 & 21.9 \\
\hline
\text{Tumor} & 34.6 & 35.4 & 32.8 & 34.0 & 16.2 & 15.1 \\
\text{@ 1 cm} & & & & & & \\
\hline
\text{Tumor} & 34.0 & --- & 31.8 & --- & 13.5 & 12.1 \\
\text{@ 2 cm} & & & & & & \\
\hline
\end{array}
\]

Table 1.2. Skin temperature (\(^\circ C\)) from perfusion-temperature model and from analytical model using effective perfusion; the units for \( h \) are cal/cm\(^2\)/sec/\(^\circ C\).
Figure 1.7. Tissue temperature as a function of x (depth) within the tissue for perfusion as a function of temperature and an effective perfusion defined by surface heat transfer.

\[
\lambda^2 = \lambda^2(T) = \left[1 \text{ cm}^{-1}\right]^2 \times \frac{1}{2} \times \frac{T_s - T}{5}
\]

\[
\lambda^2 = \lambda^2_{\text{eff}} = \left[0.37 \text{ cm}^{-1}\right]^2
\]
1.4 A Proposed Method for Measuring Brain Blood Flow Asymmetries

1.4.1 Introduction

Regional blood flow in the brain is an important indication of the state of the cerebral vasculature [31]. Persons with a high potential for stroke exhibit brain flow asymmetries [32]. However, regional blood flow measurements involving Xenon clearance are not a trivial procedure, and they must be interpreted along with the cerebrovascular CO$_2$ reactivity and blood pressure to obtain meaningful results [33].

Infra-red thermography has been used to detect brain blood flow asymmetry. Non-uniform skin temperature patterns on the forehead and around the eyes is the basis of such diagnostic tests [7]. Thermal measurements are simple to use and non-traumatic. However, thermographic equipment is very expensive and is not widely available.

The basis for a thermographic diagnosis does not involve blood perfusing the brain. Blood is supplied to the anterior portion of the brain by the internal carotid artery. Any asymmetry in flow between the two halves of the brain may be reflected in uneven flows in the left and right internal carotid arteries. Just before the internal carotid enters the base of the brain, a branch (opthalmic artery) leaves which perfuses the eye and its appendages and the forehead and nose. Specifically, smaller branches of the opthalmic artery, the supraorbital and the frontal supply the orbit and forehead.[34]. Therefore, uneven blood supply to the two halves of the brain can be manifested by uneven scalp perfusion in and around the eye. Variations in the perfusion (between symmetrical areas of the scalp) of up to 250% are expected [61].

An analysis of thermal measurements of scalp blood flow is presented; important conclusions are drawn regarding the effectiveness of different
thermal methods. A transient local cooling test is proposed, based on the analysis and on practical considerations. A protocol for the testing of patients is given in Appendix IV.
1.4.2 Thermal Model (Steady-State)

The scalp may be modeled as a thin layer of tissue over an insulated surface. The latter assumption is justified by the presence of a thick skull bone and sinus cavities in the regions to be tested. Such a thin layer of tissue may be considered to be at constant temperature. Based on these considerations and restricting ourselves to an area of constant tissue thickness, many but meaningful results may be obtained.

Consider the model illustrated in Figure 1.8. Blood at temperature \( T_a = 37^\circ C \), with specific heat \( c_b \) (1.0 cal/gm/\(^\circ C \)) and perfusion rate \( w_b \) (gm/cm\(^3\)/sec) enters the layer of thickness \( \delta \) (cm) from arteries, and it exits at local tissue temperature \( T \) in veins. An energy balance for this layer may be written:

\[
q'' = w_b c_b \delta (T_a - T) \tag{1.27}
\]

Equation (1.27) states that the heat leaving the scalp \( q'' \) must be equal to the heat loss from the blood under steady-state conditions.
Figure 1.8. Model for one-dimensional heat transfer in scalp tissue
The above result may be applied directly to thermographic measurements. For this case
\[ q''_s = h(T_s - T_e) \]  
(1.28)
where \( h \) is the heat transfer coefficient between skin and environment and \( T_e \) is the environmental temperature. The value of \( h \) is determined by natural convection and radiation.

Combining equations (1.27) and (1.28),
\[ T_s = \frac{h \delta}{k} T_e + \left( \frac{\lambda \delta}{k} \right)^2 T_a \]  
(1.29)
where \( k \) is the thermal conductivity of the tissue and \( \lambda^2 = w_b c_b / k \) with units \( \text{cm}^{-2} \). Equation (1.29) shows that the scalp temperature is a function of two dimensionless parameters, \( \lambda \delta \) and \( h \delta / k \).

Substitution of typical numbers into equation (1.29) yield an estimate of the scalp temperature for different blood perfusion conditions.

Assuming
\[ T_e = 20^\circ \text{C} \]
\[ T_a = 37^\circ \text{C} \]
\[ h = 0.2 \times 10^{-3} \text{ cal/cm}^2/\text{sec/}^\circ \text{C} \]
\[ \delta = 0.5 \text{ cm} \]
\[ k = 0.001 \text{ cal/cm/sec/}^\circ \text{C} \]
we find that \( h \delta / k = 0.1 \). A reasonable range for scalp perfusion is thought to be 8 - 20 ml/100 gm/min. Therefore, if \( w_b = 20 \text{ml/100gm/min} \), then \( (\lambda \delta)^2 = 0.82 \) and scalp temperature \( T_s = 35.1^\circ \text{C} \) if \( w_b = 8 \text{ml/100 gm/min} \), then \( (\lambda \delta)^2 = 0.33 \) and scalp temperature \( T_s = 33.3^\circ \text{C} \).
This tells us that for a 250% change in perfusion, one can expect a 1.8° C change in scalp temperature. With infra-red thermography one can measure very small differences in temperature. However, variations of \( h \) and \( \delta \) between regions which one wishes to compare can adversely affect the above interpretation of the observed temperature differences. Thus, one must be careful to compare regions which are symmetrical in all aspects.
1.4.2b Application to Local Cooling Method

However, if one can increase \( h \) and/or decrease \( T_e \) (i.e., increase the heat loss to the environment) one can increase the observed temperature differences between the regions of different perfusion. It can be shown (see sections 1.2.5 and 1.2.6) that \( \frac{h \delta}{k} = (\lambda_1 \delta) (\lambda_2 \delta) \) will induce the largest observed temperature differences for a given environmental temperature under steady-state conditions. For the above assumed conditions and perfusion rates, \( \left(\frac{h \delta}{k}\right)_{\text{optimum}} = 0.5 \). This could easily be achieved with a local cooling device. Then, for environmental temperature \( T_e = 0^\circ C \) (using equation (1.29)):

\[
\begin{align*}
\text{if } w_b &= 20 \text{ ml/100 gm/min}, \quad T_s = 23^\circ C \\
\text{if } w_b &= 8 \text{ ml/100 gm/min}, \quad T_s = 14.7^\circ C
\end{align*}
\]

By using local cooling to control the thermal conditions at the surface, the observed skin temperature difference is nearly four times as great as that obtained thermographically for the same tissue blood perfusion conditions.
1.4.3 Thermal Model (Transient Method)

The geometry of the head makes it difficult to apply the local cooling method as practiced in Part II; the concave surfaces to be encountered, and (especially) the close proximity of regions which one wishes to compare are the two main problems. Moreover, only a qualitative indication of perfusion differences are obtained. Therefore, a simple transient local cooling method is proposed; this method will provide quantitative estimates of perfusion asymmetries.

Consider the model in Figure 1.9. An insulated copper block, or disk, of thickness $\delta_{Cu}$ sits on the skin. For this case $q''_s$ may be interpreted as follows:

$$ q''_s = \left[ (\rho c_p \delta)_{Cu} + \rho c_p \delta \right] \frac{dT}{dt} \quad (1.30) $$

where $\rho$ and $c_p$ are densities and specific heats, respectively, and the subscript $Cu$ refers to copper. Substituting equation (1.30) into equation (1.27),

$$ \lambda^2 (T_a - T_s) = \left[ \frac{(\rho c_p \delta)_{Cu}}{k S} + \frac{\rho c_p}{k} \right] \frac{dT_s}{dt} \quad (1.31) $$

where $k$ is the thermal conductivity of the tissue and $\lambda^2 = w_b c_b / k$ as before. Equation (1.31) states that heat lost from the blood must go into warming up both the tissue and the copper. The important result is

$$ w_b = \lambda^2 k / c_b = \text{constant} \times \frac{dT}{dt} / (T_a - T) \quad (1.32) $$

Therefore, by recording the time temperature history of two pre-cooled copper blocks placed on symmetrical regions of the scalp, all the information necessary for finding the ratios of perfusions for the two regions is available.
Figure 1.9. Model for transient cooling of scalp tissue with an insulated copper block
1.4.4 Feasibility of Transient Local Cooling Test

One possible drawback to this method is that temperature changes too slowly with time; test periods which consume too much time, or temperature variations too small to measure accurately are to be avoided.

Let us calculate the system response for the assumed conditions as described above.

\[
\frac{k}{k_{p}} = 10^{-3} \text{ cm}^2/\text{sec}
\]

\[
\left(\frac{k}{\rho C_p}\right)_{Cu} = 1.13 \text{ cm}^2/\text{sec}
\]

\[
k_{Cu}/k = 660
\]

\[
\delta_{Cu}/\delta = 2
\]

Thus,

\[
\frac{dT_s}{dt} = 0.00046 \left(\text{cm}^2/\text{sec}\right) \lambda^2 (T_a - T_s)
\]

and for \( w_b = 20 \text{ ml/100gm/min} \) (\( \lambda^2 = 3.3 \text{ cm}^{-2} \)),

\[
\frac{dT_s}{dt} = 0.00152(T_a - T_s) \text{ sec}^{-1}
\]

and for \( w_b = 8 \text{ ml/100gm/min} \) (\( \lambda^2 = 1.32 \text{ cm}^{-2} \)),

\[
\frac{dT_s}{dt} = 0.00061(T_a - T_s) \text{ sec}^{-1}
\]

Now, over a two minute interval, if \( (T_a - T_s)_{\text{mean}} = 20 \text{ °C} \)

for \( w_b = 20 \text{ ml/100gm/min} \), \( \Delta T_s = 3.6 \text{ °C} \)

and for \( w_b = 8 \text{ ml/100gm/min} \), \( \Delta T_s = 1.4 \text{ °C} \)

These temperature differences can be measured accurately and reproducibly with the proper instrumentation. The change in temperature with time could be increased somewhat, if it proves necessary, by decreasing the thickness of the copper.
1.4.5 Test Apparatus

Basically, the equipment will consist of three thermocouples, two operational amplifiers (for the thermocouples), a strip-chart recorder and two identical copper blocks (disks). The amplifiers cost $29.00 each from the Burr-Brown Research Corporation. It is hoped to obtain the loaned use of a strip-chart recorder. The other materials should be obtainable at nominal expense from laboratory supplies. The configuration is outlined in Figure 1.10.

The precise geometry of the copper block has not yet been decided upon. For the initial testing on the forehead, it is expected that it will be in the shape of a disk, 1.5 cm in diameter and 0.5 cm thick. The copper disk will be thermally insulated on its back and sides.
Figure 1.10. Schematic configuration for transient local cooling scalp perfusion measurement
1.5 A Thermal Method for Blood Perfusion Measurements

1.5.1 Introduction

Skin temperature measurements have been used for some time as a qualitative indication of blood flow. The solution of simplified analytical models also enabled quantitative interpretation of this result [35-37]. A detailed analysis is presented by Eberhart, Jackson, and Trezek [38] for a specific case of blood flow in the great toe (which reflected general cardiovascular dynamics). In all the methods mentioned in the foregoing, heat transfer from the skin to the surrounding air was intentionally kept at low values (by avoiding drafts and forced convection over the skin). Under such conditions, surface temperature variations due to perfusion changes are rather modest.

A much more effective method can be built by utilizing local skin cooling and relating the heat flux and skin temperature to the blood perfusion in the tissue. Physically, it is quite obvious that under the same surface conditions, a region with higher blood perfusion would keep the skin warmer when it is cooled. That, of course, was known and was the basis for the use of skin temperature as an indication of the tissue blood flow. Local cooling was not used systematically before, however, nor was it realized that its use can substantially increase the sensitivity of the method. In the following, we present an analysis which provides interpretation of measured thermal parameters in terms of local tissue perfusion.
1.5.2 Thermal Analysis

The analysis for local cooling through a disk is provided in a previous section (1.2.3). The geometry is given in Figure 1.4. A disk with radius, made from high conductivity materials, cools the tissue. The tissue is assumed to be infinite in extent in the radial direction, and it is of thickness $\delta$. All boundaries, except for the disk, are insulated. Physically, blood delivers heat to the tissue; the only mode of heat removal is through the disk. Similar to the arguments of section A1.6, the effect of metabolism may be neglected.

It is found that

$$\frac{q''_a}{k(T_a - T_s)} = \frac{a\lambda}{I} \quad \text{(1.33)}$$

where $I$ is an integral function of $a\lambda$ and $\delta/a$. As before

$$\lambda \equiv \sqrt{\frac{\rho \cdot c_p}{k}}$$

Equation (1.33) is plotted in Figure 1.5 for two different disk conditions: constant disk temperature ($I_1$) and uniform disk heat flux ($I_2$).
1.5.3 Applications

The level of tissue oxygen tension can have a strong influence on the effectiveness of therapeutic radiology. Hyperbaric oxygen can decrease the survival rate of tumor cells by a factor of three after a dose of ionizing radiation. The mechanism of this phenomenon is not completely understood, but it is thought that oxygen promotes the formation of free radicals which are extremely radiosensitive [39]. The implications of the oxygen effect are great, and they pervade all aspects of radiation therapy.

Fractionation, the breaking of a large radiation dose into smaller amounts, applying them over a period of time, is now recognized as one of the most effective methods for treating neoplasms [40]. Since hyperbaric oxygen causes vasoconstriction, its direct application is of questionable benefit [41], but, following a dose of radiation, tumor reoxygenation occurs which results in the oxygenation of previously anoxic cells [42]. It would be desirable, of course, to schedule radiation fractions during the period of maximum tumor reoxygenation.

Tissue oxygen tensions are obviously influenced by local perfusion and metabolic rates; large doses of radiation can lead to increases in tumor perfusion rates [43]. Since the average metabolic activity of a tumor should be reduced following a dose of radiation due to cell kill, it is logical to assume that maximum tumor perfusion corresponds to maximum tumor oxygenation. The use of local cooling with superficial human tumors allows daily assessment of blood perfusion rates; thus, radiation treatment fractions could be scheduled when the tumor is maximally perfused.
A typical system which utilizes local cooling for perfusion measurements should have a heat sink, a flux meter, and a disk of high conductivity material. The heat sink is connected through a flux meter to the disk. From the measured quantities—heat flux through the disk, temperature of the disk, and radius of the disk—and assuming a value for the tissue conductivity, $k$, using equation (1.33) and Figure 1.5, one can calculate $\lambda^2 = \frac{\omega_b c_b}{k}$ from which the blood perfusion rate may be found. With sufficient cooling, the quantity $Q_m/[\left(T_a - T_s\right)\lambda^2 k]$ is much smaller than one and it may be neglected. In practice, if the sink-to-disk thermal resistance is known, one may calculate the skin (i.e., disk) temperature from the heat flux and sink temperature. Such a system has been assembled (shown in Figure 1.11). It is being used in an ongoing program for the measurement of perfusion rates in human tumors during a course of fractionated radiation treatments. Figure 1.12 illustrates the results for the first two patients studied. (It was assumed that $5/a \to \infty$ and $k = 0.7 \times 10^{-3}$ cal/cm/sec/°C for the tumors). A more detailed report of the clinical use of this system will be issued at a later date [44].

Obviously, circulatory disorders readily lend themselves to this technique. Emboli in the circulatory system, for example, can cause strongly asymmetric perfusion patterns.

The sensitivity of these systems is a monotonically increasing function of the disk radius. Any disk of practical size will have a sensitivity substantially lower than that for a disk of infinite radius. A disk of 1 cm radius in only about 50% as sensitive to perfusion changes as a disk of infinite radius. 1 cm represents a practical lower limit on disk size.
Figure 1.11. Schematic drawing of heat sink system for perfusion measurement
Squamous cell carcinoma in lung
(secondary in neck)

Carcinoma of the breast

Figure 1.12. History of tumor perfusion during radiation therapy (↑ indicates day radiation applied)
The use of either $I_1$ or $I_2$ in evaluating the perfusion rates is acceptable as long as one is consistent during data reduction. The behavior of both integrals is the same, and for $a\lambda \geq 1$, they yield similar values for the perfusion.
1.5.4 Conclusions

A new thermal method for blood perfusion measurements based on localized skin cooling was developed. Under conditions of strong cooling, the local perfusion in the superficial tissues is found to be a function of the radius of the skin cooling area, the skin temperature, the heat flux from the skin, and the arterial blood temperature. The method was successfully applied to fractionated radiation therapy.
1.6 Summary

The energy equation in tissue is solved for a number of meaningful one and two-dimensional cooling situations. These solutions are applied to the inference of relative tissue blood perfusion differences (from skin temperature differences) and to the evaluation of absolute perfusion levels (from skin temperature and skin heat flux measurements). It is shown that under conditions of moderate to strong cooling the effect of metabolism upon skin temperature measurements (and, hence, upon perfusion evaluation) may be neglected. A proposed technique for measuring scalp perfusion asymmetries is discussed. Finally, a successful application of local cooling for blood perfusion measurement in superficial tissues during a course of radiation treatment is presented.
PART II

APPLICATION FOR THE DIFFERENTIAL DIAGNOSIS OF BREAST CANCER

2.1 Introduction

The theory and results presented in Chapters 1.2 and 1.3 are applied in Part II for the analysis and development of thermal methods for the differential diagnosis of breast cancer. In Chapter 2.2 a thermal analysis of infra-red thermography is presented; this is based on the one-dimensional thick tissue results of section 1.2.2a. In Chapter 2.3 the development and application of local cooling is discussed; the theoretical basis for this method is developed in section 1.2.3.

The analysis in Part I for the local cooling method is for steady-state conditions with homogeneous tissue properties. However, the local cooling method is principally a transient diagnostic test, since clinical restrictions prevent testing times longer than 10 minutes. Thus Chapter 2.4 is a computer time-simulation of the performance of the local cooling device.

Chapter 2.5 is an appraisal of new directions for the local cooling method. This is followed by a summary and conclusions.
2.2 A Thermal Analysis of Thermography

2.2.1 Introduction

The growth of human tumors is normally accompanied by changes in local blood perfusion and metabolic rates. In general, these changes can effect temperature distributions in the vicinity of tumors. It is logical, therefore, that differential diagnoses of tumors could be made from observations on temperature fields around tumors and in corresponding (usually contra-lateral) healthy tissues. Specifically, for superficial tumors, one could observe temperature variations at the skin. Indeed, Lawson in 1956 reported success in diagnosing breast cancer by observing "abnormal" thermal patterns at the skin.

Infra-red thermography was employed by Lawson to detect skin temperature. Since then thermography has been used with some qualified success, and a number of publications cover details of the method [4, 7, 17, 47, 51]. The primary barriers to its widespread acceptance have been an inability to interpret marginal readings and high system costs. Since the introduction of thermography to medicine was largely a spin-off of infra-red sensing technology and was not due to any optimization of the relevant thermal parameters, it would not be surprising if infra-red thermography as practiced over the years has not been carried out in an optimum manner.

In principle, the thermal patterns within tissue are affected not only by the perfusion and metabolic rates but also by the surface thermal conditions in the proximity of the region of interest. Thus, it is important to state under what surface heat transfer conditions (e.g., cooling, heating, or insulation) the thermal pattern is observed.
Essentially, thermography looks at a surface which is nearly insulated (slight heat transfer occurs between the skin and the basically stationary air [by convection] and the surroundings [by radiation]). This is not necessarily the optimum condition for inducing skin temperature differences which reveal differences in perfusion and metabolic rates between cancerous and (contra-lateral) normal tissue. A more favorable surface thermal condition, which would yield larger skin temperature differences, could exist.

Accordingly, a detailed thermal analysis of human tissue, subject to variable surface heat transfer conditions and with variable perfusion and metabolic rates, has been performed. Parametric results which show optimum conditions for thermography are discussed, and estimates of the heat losses from subjects examined with those conditions are presented.
2.2.2 Thermal Analysis

If one assumes a one-dimensional body of tissue as in Figure 2.1, the expression for the skin temperature \( T_s \), is shown in Appendix A1.1.1 to be:

\[
T_s = T_a - (T_a - T_0) \frac{h/k}{h/k + \lambda} + \frac{Q_m}{w_b c_b} \frac{\lambda}{h/k + \lambda}
\]  \hspace{1cm} (2.1)

where \( \lambda^2 = \frac{w_c b}{k} \) and \( T_0 \) is the environmental temperature. It is assumed that \( \frac{Q_m}{w_b c_b} \) is a constant for a given tissue, independent of the perfusion rate; this assumption is based on the realization that oxygen and fuel for metabolism must ultimately come from the blood stream. However, it will be shown later that the validity of this assumption does not have a strong effect on the conclusions obtained in this paper. Equation (2.1) is plotted in Figure 2.2 for \( T_a = 37^\circ C \) and \( T_0 = 20^\circ C \).

Equation 2.1 and Figure 2.2 illustrate several things which were stated previously in Part I but are repeated here for emphasis:

1. For given changes in \( w_b \) and \( Q_m \) between cancerous and healthy tissue, the skin temperature difference is a strong function of the surface thermal conditions (i.e., the value of \( h \)). Consider the limiting cases; for very large \( h \), regardless of \( w_b \) and \( Q_m \), the skin temperature approaches the environmental temperature, \( T_0 \); for very small \( h \) (i.e., the insulated case), the skin temperature approaches the adiabatic tissue temperature. In the first case the temperature difference goes to zero, and in the second case the difference is on the order of \( 1^\circ C \).

2. It is obvious that an optimum value of \( h \) exists such that the skin temperature difference between cancerous and healthy tissue
Figure 2.1. One-dimensional model for heat transfer from thermally thick tissue to the environment
Figure 2.2. Surface temperatures found in thermography for different surface conditions ($T_a - T_o = 17 \, ^\circ C$)
3. $T_a - T_o$ is normally much greater than $Q_m/\omega_b c_B$. Thus, $T_s$ is primarily a function of $h$ and not $Q_m$.

4. Since measurements are usually carried out for $h = \text{constant}$, the change of $T_s$ with perfusion is proportional to $T_a - T_o$. Therefore, the temperature difference between cancerous and healthy tissues may be increased by lowering the environmental (or heat sink) temperature.

This discussion may be applied directly to thermography.
2.2.3 Implications for Thermography

It was stated in the previous section that the difference in skin temperatures between cancerous and healthy tissue is primarily a function of the surface thermal condition, $h$, and the different perfusion rates, $\lambda_T$ and $\lambda_N$, where $T \equiv$ tumor and $N \equiv$ normal or healthy. For two given but different perfusion rates, the temperature difference can be maximized by selection of the proper value of $h$. This optimum value of $h$ is shown in Appendix A.3 to be:

$$h_{\text{opt}} = k\bar{\lambda}$$  \hspace{1cm} (2.2)

where

$$\bar{\lambda} = (\lambda_T\lambda_N)^{1/2}$$  \hspace{1cm} (2.3)

This relation is exact if $Q_m = 0$ or if $(Q_m/w_b c_b)_T = (Q_m/w_b c_b)_N$, and little error is introduced if this expression is used universally, because the non-linearizing term, $Q_m/w_b c_b [T_a - T_0] \bar{\lambda}$, is normally much smaller than one.

It has been stated that the perfusion rate in cancerous tissue is greater than in normal tissue, when the tissue is being cooled. The following phenomena contribute to this situation.

1. In general, malignant tumor tissue does not show much cold-induced vasoconstriction, while healthy tissue at and near the skin, of course, does.
2. When the body loses heat, the skin adjacent tissues are at a lower temperature than if they were insulated.
3. Due to vasoconstriction in healthy tissue, the cold temperature will propagate further into the tissue, causing more constriction.
4. An elevated metabolic rate in tumor tissue helps resist vasoconstriction, simply by its warming effect.
5. Colder tissue temperatures result in higher blood viscosities, further lowering perfusion. Therefore, a situation exists which leads to different blood perfusion rates when cancerous and healthy tissue are exposed to the same thermal load conditions.

In infra-red thermography usually drafts and air currents are avoided because one would like to retain uniform surface thermal conditions over the examined area. Calculation of the heat transfer coefficient for natural convection and radiation shows that $h/k \approx 0.1\text{cm}^{-1}$. However, perfusion rates during conditions of cooling have been observed such that

$$\lambda_T \approx 2\text{cm}^{-1} \quad \text{and} \quad \lambda_N \approx 0.5\text{cm}^{-1}.$$  

For these perfusion rates, from equations (2.2) and (2.3) $h_{opt}/k = 1\text{cm}$. One can conclude, therefore, that under conditions of natural convection and radiation the surface heat transfer coefficient is about a factor of five less than the optimum value.

From Figure 2.2, for values of $\lambda$ equal to 0.5 and 2.0 cm$^{-1}$, if $h/k = 0.1\text{cm}^{-1}$ it is seen that $\Delta T_S = 2.0^\circ\text{C}$, while if $h/k = 1.0\text{cm}^{-1}$ (the optimum value for these perfusion rates), then $\Delta T_S = 5.8^\circ\text{C}$. Therefore, letting natural convection determine the surface conditions leads to a skin temperature difference between cancerous and healthy tissue which is almost three times less than the maximum which could be obtained for the same air temperature.

For the optimum case, the average surface temperature ($= [ (T_s)_N + (T_s)_T ]/2$) is simply $(T_a - T_o)/2$. This can be seen by inspection of Figure 2.2 or by simply algebraic manipulation of equation (2.1). Thus, by adjusting the cooling conditions (e.g., with a fan) until the surface
temperatures match this criterion, one can find the optimum conditions for a given air temperature.

The skin temperature differences are proportional to $T_a - T_o$. If the difference between the arterial blood temperature and the environmental (or heat sink) temperatures can be increased, the temperature differences observed will be proportionately increased. For the optimum case, if the environmental temperature is lowered to $0^\circ C$ (assuming $T_a = 37^\circ C$), the temperature difference between cancerous and healthy tissue for perfusion differences given above can be increased to $12.3^\circ C$.

Criteria in thermography for malignancy are usually small (1 or $2^\circ C$) temperature rises over a tumor; for this case natural convection and radiation determine the surface conditions. More recently, Feasey [2.2] showed temperature differences of as much as $5^\circ C$ with forced cooling. Draper and Jones [54] and Draper and Boag [47] reported the advisability of increasing the cooling rate. These published results agree well with the model presented above. However, subjects being examined may not be able to tolerate as severe cooling conditions as the present analysis indicates is desirable.

Heat loss during thermographic examination, when the exposed area is large and the examination time is long, is an important factor in deciding under which conditions the examination should be performed. The heat loss is a function mainly of the perfusion rate in healthy tissue (cancerous tissue is normally only a small fraction of the exposed area), the air temperature, and the heat transfer coefficient between the skin and the surrounding air.
The heat loss per unit of exposed area can be written in terms of the above parameters (see Appendix III):

\[ q'_s = \frac{(T_a - T_0)k\lambda_N}{1 + \frac{k\lambda_N}{h}} \]  

(2.4)

Generally, the conditions which lead to an increase in the skin temperature difference between healthy and cancerous tissue would also increase the heat loss. On the other hand, increases in \( \Delta T_s \) could be affected either by changes in the heat transfer coefficient or by lowering the air temperature. For this reason, it would be useful to express the loss in terms of \( \Delta T_s \). This was done in Appendix III (for \( Q_m/[\omega_c b(T_a - T_0)] \) negligible) with the following results:

\[ q''_s = \frac{k\lambda_N(h/k + \lambda_T)}{\lambda_T - \lambda_N} \Delta T_s \]  

(2.5)

Also, the required air temperature for an expected skin temperature difference and given perfusion rates \( \lambda_T \) and \( \lambda_N \) can be expressed as

\[ T_0 = T_a - \frac{(h/k + \lambda_N)(h/k + \lambda_T)}{h/k(h_T - \lambda_N)} \Delta T_s \]  

(2.6)

Figure 2.3 shows \( q''_s/k\lambda_N \Delta T_s \), the dimensionless heat flux, as a function of \( h/k \) for fixed values of \( \lambda_N \) and \( \lambda_T \) (0.5 cm\(^{-1}\) and 2.0 cm\(^{-1}\), respectively). The figure also depicts the air temperatures, \( T_0 \), which will yield specific skin temperature differences, \( \Delta T_s \) (5° C and 10° C), as a function of \( h/k \). Once again, \( \lambda_N = 0.5 \) cm\(^{-1}\) and \( \lambda_T = 2.0 \) cm\(^{-1}\).

If one uses the optimum heat transfer coefficient in order to obtain
Figure 2.3. Heat loss and environmental temperature as a function of surface thermal conditions.
a certain $\Delta T_s$, using (2.3) and (2.5), one obtains

$$
\left( \frac{q_{s}^{'} \text{opt}}{q_{s}^{''}} \right) = 1 + \sqrt{\frac{\lambda_{N}}{\lambda_{T}}} 
$$

(2.7)

where $(q_{s}^{''})_o (= \lambda_T \lambda_N k \Delta T_s / [\lambda_T - \lambda_N])$ represents the absolute minimum flux which can still yield a given $\Delta T_s$ for the hypothetical conditions of zero $h$ and infinite $T_a - T_o$. In general, one would expect $\lambda_N$ to be less than $\lambda_T$ so that at most a factor of two reduction in the heat loss can be obtained by operating at sub-optimum conditions (i.e., low $h$ and low $T_o$).

It is of some importance to note that the minimum heat loss is directly proportional to $\Delta T_s$ for the same $\lambda_T$ and $\lambda_N$. From this follows the estimate that to obtain a $6^\circ$ C temperature difference one would expose the patient to three times higher losses than for a $2^\circ$ C difference. And, this could be higher due to actual losses being greater than the absolute minimum.

It should be pointed out, however, that the above conclusions are based on an idealized model which assumed that perfusion rates remained constant, independent of skin temperature. If one allows for this incorrect assumption in evaluating the heat losses one would find (if $\lambda_N$ decreases with $T_s$) that the heat loss need not increase as fast as $\Delta T_s$. A quantitative estimate of this effect cannot be made without some appropriate experimental evidence.
2.2.4 Discussion and Conclusions

A one-dimensional solution for the heat transfer interaction between superficial human tissues and the environment was applied with metabolic rate, perfusion rate, and surface heat transfer conditions as variables. It is realized that the human body is neither one-dimensional nor homogeneous and isotropic. However, the model is adequate for the purposes of demonstrating the important mechanisms which exist.

Vasoconstriction mechanisms in healthy tissue (and their absence in some tumors) can be the principle reason for the temperature differences seen in thermography. The vasoconstriction phenomena means that tumors at a depth in the tissue will show much greater surface temperatures under conditions of strong cooling than if the effect was due solely to a difference in metabolic rates between healthy and cancerous tissue.

Interpretation of thermographic results are often made difficult by variations in the skin temperature over normal tissue. Stronger cooling, causing severe vasoconstriction, can sharply distinguish between normal variation in perfusion and those due to tumors. Low skin temperatures which cause severe vasoconstriction cannot be obtained without putting a large thermal load on the subject. Thus, it would seem that a more attractive alternative is to cool locally, using small areas and large heat fluxes. In this manner hot spots on a thermogram could be checked to see if the variation in perfusion causing them was due to a tumor or to normal fluctuations. Moreover, suspected tumor masses could be checked with with a local cooling method which, if properly designed, would be more sensitive than thermography (as subject comfort becomes a limiting factor).
During most of the analysis the effect of metabolism was neglected. Although its influence is small under strong cooling conditions, a higher metabolic rate in tumors will in general, increase the $\Delta T_s$ predicted by the simplified theory. Also, the $\Delta T_s$ predicted is relatively insensitive to small changes (less than a factor of two) in the surface heat transfer coefficient for optimum conditions. Thus changes in $h_{opt}$ due to metabolism will not have much effect on predicted observations.
2.2.5 Summary

Several important conclusions may be drawn from the preceding discussion:

a) the skin temperature differences observed in thermography may be enhanced by either forced convection cooling over the examined area or lowering the environmental temperature,

b) for a given air temperature there exists an optimum surface condition such that the observed temperature difference is maximized (for which the average surface temperature is half way between the environmental and blood temperature),

c) the greater the skin temperature difference between healthy and cancerous tissues the greater the heat loss from the examined area, and

d) the heat loss, for a given skin temperature difference may be lessened by operating with a lower heat transfer coefficient and a lower environmental temperature.
Infra-red thermography has been used with some success for the differential diagnosis of a variety of tumor masses which lie near to the skin surface. Dodd et al. [2], Watmough and Oliver [49], Fruendlich [48], Lawson and Chughtai [17], Samuels [50], and Feasey et al. [22] provide a review of the method and its applications. Diagnoses are based on differences in skin temperatures over cancerous and healthy tissues. The problems of interpreting marginal readings and high system costs have prevented more widespread acceptance of thermography as a clinical procedure.

The application of thermography to medicine was not based on any detailed analysis of the relevant thermal parameters. Moreover, thermography has not been practiced in the most effective manner. For a detailed analysis of thermography see Chapter 2.2. It is shown that the skin temperature difference between cancerous and healthy tissue is mainly determined by the perfusion rates in the tissue and, most importantly, that the temperature difference may be enhanced by increasing the thermal interaction with the environment. This may be accomplished either by lowering the environmental temperature or by optimizing the surface heat transfer conditions. The heat loss from the examined area, however, is an increasing function of the skin temperature difference. For enhanced temperature differences between cancerous and healthy tissues, the resulting heat loss may be great enough either to seriously affect patient comfort or to induce physiological responses (shivering, etc.) which are detrimental to the measurement procedure. For these reasons the enhancement in temperature difference which can be practically
achieved by infra-red thermography is somewhat limited by the relatively large heat losses from the examined area. An alternative, then, is a method which employs local cooling. In this case, large temperature differences between cancerous and healthy tissue can be obtained without excessive heat loss from the patient since the cooling area involved is small.

The concept of localized thermal interaction with tissue is not new, but previous analyses were not adequate to explain the observed effects. Baptista [55] correlated perfusion rates with the transient skin temperature response following local cooling. Haberman et al. [56] compared the thermographic patterns caused by local heating with skin temperatures associated with known breast carcinomas. Johnson [44] introduced the use of local cooling for the assessment of tumor vascularity during radiation therapy, and coupled with the analysis of Mikic et al. [21], was able to estimate tumor perfusion rates.

What follows is a thermal analysis which gives the design criteria for a new thermal diagnostic device. The device makes use of an 0°C heat sink and is optimized to give the maximum skin temperature difference between cancerous and healthy tissue within the constraints imposed by geometric and physical limitations.
2.3.2 Thermal Analysis

Consider the situation illustrated in Figure 2.4. A disk of radius, $a$, and uniform temperature, $T_s$, is in contact with the skin. The disk may be assumed to be at a uniform temperature if it is made of high thermal conductivity material. As shown in Appendix IV, the temperature of the disk (and of the skin, also, since the skin and the disk are in intimate contact) is:

$$T_s = T_a - (T_a - T_o) \frac{1}{1 + \frac{R}{a}} + \frac{Q_m}{\omega_b c_b} \frac{\frac{R \kappa}{a}}{1 + \frac{R \kappa}{a}}$$  \hspace{1cm} (2.9)

where $R$ is the thermal resistance between the heat sink (at temperature $T_o$) and the disk (at temperature $T_s$), $T_a$ is the arterial blood temperature, $\kappa$ is the tissue thermal conductivity, $\omega_b$ is the blood perfusion rate, $c_b$ is the specific heat of blood, and $Q_m$ is the metabolic heat generation. $\lambda = (\omega_b c_b / \kappa)^{1/2}$. I, which is a dimensionless function of $a \lambda$ is an integral derived in Appendix I.

Figure 2.5 shows $T_s$ as a function of perfusion rate, assuming $Q_m / \omega_b c_b$ is constant for a given tissue. This is probably a better assumption for healthy tissues, where oxygen demand can have autoregulatory control over local perfusion [57], than for tumors, for which the mechanisms are not as well understood. However, during an ongoing study of the vascular states of tumors undergoing radiation therapy, it was discovered that the adiabatic tumor temperature was never more than 1°C above mouth temperature. From this it directly follows that $Q_m / \omega_b c_b$ is on the order of 1°C or less. Moreover, since $T_a - T_o$ is much greater than one °C, $Q_m / [\omega_b c_b (T_a - T_o)]$ is much less than one. Therefore, the results are not strongly affected by the assumption, and, in fact, under
Figure 2.4. Axi-symmetric model of tissue which is thermally thick for cooling with an isothermal disk.
Figure 2.5. Skin temperature for local cooling to a 0 °C heat sink from thermally thick tissue
moderate to strong cooling conditions one does not introduce significant error by neglecting the effect of metabolism altogether.

With this in mind, let us consider a typical system, utilizing ice water for its heat sink, and examine its response in terms of perfusion rates and thermal resistance. Under conditions of cooling, mainly due to the lack of vasoconstriction mechanisms in tumors, the perfusion rates in healthy tissues can be considerably less than in tumors; perfusion rates, measured with a local cooling method, were found such that in tumors \( \lambda_T = 2 \text{ cm}^{-1} \) and in healthy tissue \( \lambda_N = 0.5 \text{ cm}^{-1} \). (Here, \( T \) = tumor, and \( N \) = normal or healthy). If the radius of the disk for our typical system is 1 cm, it is possible to calculate the response of the device. For example, if the perfusion rates in the cancerous and healthy tissue are as described above, then \( a\lambda_N = 0.5 \) and \( a\lambda_T = 2.0 \). From Figure 2.5 it is seen that the temperature difference which would be observed, when the disk is placed first on cancerous and then on healthy tissue, is very much dependent upon the value of the thermal resistance, \( R \), which controls the heat flow from the skin to the heat sink. For \( Rk/a = 0.44 \), the skin temperature difference, \( \Delta T_s \), is 6° C, while if \( Rk/a = 0.044 \) or 4.4 the temperature difference is only about 2° C. It is evident that there exists an optimum thermal resistance for which one would obtain a maximum temperature difference, \( \Delta T_s \), between cancerous and healthy tissue. This is, of course, completely analogous to thermography, where optimum surface thermal conditions were found.

In Appendix IV, an expression for the optimum value of \( R \), which induces the maximum skin temperature difference between healthy and cancerous tissue is derived
\[ R_{\text{opt}} = \frac{a}{k} \left[ \frac{I(a \lambda_U) I(a \lambda_T)}{(a \lambda_N)(a \lambda_T)} \right]^{0.5} \]  
(2.10)

Equation (2.10) is plotted (in dimensionless form) in Figure 2.6 for differential changes in the perfusion rate. A good approximation is to let \( \lambda = (\lambda_T \lambda_N)^{0.5} \) and evaluate \( R_{\text{opt}} \) from Figure 2.6. If \( R \) is within a factor of two of \( R_{\text{opt}} \) the temperature difference obtained will not be much less than the maximum. It can be shown that \( (Rk/a)_{\text{opt}} = 0.44 \) for the previous example; thus the 6° C temperature difference obtained was the absolute maximum for those assumed perfusion rates and a radius of 1 cm.

In Chapter 2.2 it was shown that for a heat sink temperature of 0° C, the maximum temperature difference which can be induced between cancerous and healthy tissue (with the assumed perfusion rates \( \lambda_T = 2 \text{ cm}^{-1} \) and \( \lambda_N = 0.5 \text{ cm}^{-1} \)) is 12.3° C. Thus, a disk of radius 1 cm is only about 50% as sensitive as the theoretical maximum. The loss in sensitivity is due to the small disk size. Figure 2.7 shows that as the disk radius goes to infinity the sensitivity of the device approaches the theoretical maximum; for small disks (radii less than 1 cm) the sensitivity falls towards zero very rapidly.

The loss of sensitivity (for this particular example) is not very crucial since the 6° C temperature difference which would be obtained is still much greater than that normally obtained in thermography. However, for small differences in the perfusion rate between healthy and cancerous tissue, or for tumors separated from the surface by a layer of norm-
Figure 2.6. Optimal resistance for local cooling for differential differences in perfusion
Figure 2.7. Effect of disk radius on local cooling sensitivity

\[
\Delta T_s \quad [\degree C]
\]

asymptote as \( a \to \infty \)

\[
\lambda_T = 2 \text{ cm}^{-1}
\]
\[
\lambda_N = 0.5 \text{ cm}^{-1}
\]
\[
T_a = 37 \degree C
\]
\[
T_o = 0 \degree C
\]
al tissue, the loss of sensitivity due to the small disk radius would be substantial. This loss is caused by a reduction in the penetration depth (e.g., the depth from where heat energy originates which flows into the disk). The concept of penetration depth is illustrated in Figure 2.8. Furthermore, one sees that, for a small tumor within the region of penetration, the contribution to the overall heat flowing from the tumor through the disk is small; thus the sensitivity of the disk to small tumors will be small.

The concept of penetration depth suggests that one would like to have as large a disk as possible, but the inability to detect small tumors, and the drawback of large heat loss from the patient for large disks, would favor the opposite. However, one sees that (1) the center of the disk in Figure 2.8 has a greater penetration depth which is larger than the average penetration depth, and (2) the heat that flows through this center portion comes from a smaller region. Hence, if one thermally insulates the center part of the disk from the outer annulus, then the center portion of the disk will be more sensitive. Figure 2.9 illustrates this idea. Therefore, the disk was made with an insulated center portion, and the temperature is measured there, independent of the outer annulus.

The analysis to this point has been based on the steady-state. Since any test must have finite length, and especially since the clinical situation dictates as short a test period as possible, much of the test data comes from the transient regime. A computer simulation will illustrate the transient response of the system in Chapter 2.4. Closed form solutions for the transient behavior are not available.
Figure 2.8. Concept of penetration region and penetration depth for local cooling with a one-piece disk.
Figure 2.9. Concept of penetration region and penetration depth for local cooling with a three-piece disk

\[ D \equiv \text{average penetration depth for center part of disk} \]

\[ D_{\infty} \equiv \text{penetration region for an infinitely large disk} \]
However, from the thin layer analysis, it is expected that the quantity \( \frac{dT_s}{dt}/(T_s - T_a) \) is a monotonically increasing function of perfusion rate, other things being equal. Thus, a quantity \( M \), called the slope test, is invoked in the discussion of results, where

\[
M = \frac{dT_{s_2}}{dT_{s_1}} / \frac{T_a - T_{s_2}}{T_a - T_{s_1}}
\]  

(2.11)

\( M \) should be greater than one when the perfusion in region 2 is greater than the perfusion in region 1.
2.3.3 Description of the Diagnostic Local Cooling Device

The analysis in Chapter 2.2 gives the criteria for a new, thermal, diagnostic device which maximizes skin temperature differences between cancerous and healthy tissue. It should have a low heat sink temperature, optimized thermal resistance between the heat sink and the body's surface, and small surface area touching the subject's skin. In the previous section these design parameters are quantified, and it is shown how the device can have increased effectiveness by making the disk, which touches the skin, with an insulated center portion where the temperature is measured. Secondary considerations are simplicity and cheapness of construction, compactness, ease of use, etc. All of these criteria are met.

The device consists of two cylindrical local cooling units, one which is placed over the region of interest and one which is placed over the reference region (i.e., symmetrically located normal tissue). One local cooling unit is schematically depicted in Figure 2.10 and an electrical analog for steady-state heat transfer is shown alongside.

For maximum sensitivity the resistance to heat transfer through the local cooling units should be equal to the geometric mean of the thermal resistance in the tissue (this concept is explained in the previous section). The problem is one of heat sources (body core at 37°C) and heat sinks (ice bath at 0°C) with varying thermal resistances in the tissue (cancerous and normal). By making $R$ (resistance) in the device such that

$$R = (R_{\text{normal}}R_{\text{cancer}})^{0.5}$$

(2.12)

in the steady-state the maximum skin temperature difference between
Figure 2.10. Schematic diagram of local cooling device
the cancerous and normal tissue is induced for this configuration.

The resistance of the device is controlled by the thickness of the water gap between the copper disk and the aluminum fin. A plastic spacer determines the thickness of the water gap; glass wool placed in the gap prevents natural convection in the water. The glass wool has negligible effect on the over-all gap resistance (see Appendix VII). The disk and fin, due to their high thermal conductivities, provide little resistance to heat transfer. Since the area of the fin is about 15 times that of the disk, the average ice particle to fin distance is equal to the gap thickness of the ice bath and fin will contribute only 1/15 of $R$ (the gap resistance). Freshly packing the reservoir with ice will insure that $R$ is the controlling thermal resistance of the system.

By constructing the copper disk which contacts the skin such that the center part (where the temperature is measured) is thermally insulated from the outer part, the device can be made to behave in a more one-dimensional manner. This has the potential to increase both the sensitivity and penetration depth of the system. Both from equation (2.12) (having first experimentally measured perfusion rates under these cooling conditions in cancerous and normal tissue) and trial-and-error, it was found that a water gap of 1 cm between the copper disk and the aluminum fin was adequate for most circumstances.

Temperature is monitored with a UUA 35J3 curved-matched thermistor probe. Two types of read-out meters are employed: a digital thermistor read-out meter manufactured by Omega Engineering and a home-made bridge circuit, described in Appendix VI. These temperature measuring
systems produce reliable and consistent readings which are accurate to \( \pm 0.2^\circ C \). Temperature is measured in the center portion of the copper disk, for reasons discussed above. The temperature of the disk can be approximated to that of the skin because the disk has high thermal conductivity (and is in intimate contact with the skin). Compounds applied to the skin to facilitate thermal contact between the disk and the skin (e.g., ekg jelly) do not appreciably affect the results.

Enough crushed ice may be placed in the reservoir (which is three inches in diameter and four inches high) for one hour's use. Total weight of each device is approximately one half kilogram. The system is only as expensive as the metering system.
2.3.4 Clinical Procedure

Crushed ice is placed in the reservoirs of the cooling units at least one half hour before a test begins. This allows time for the units to sub-cool to a temperature of 10° C or less. Enough water is added to ensure that all of the ice is wetted. No special precautions are taken in terms of thermally equilibrating the patient with the examination room environment. Only the portion of her breasts which are to be cooled need to be exposed.

Tests have been performed at Massachusetts General Hospital and Faulkner Hospital. At Mass General, a suspicious mass is located via xerography and palpation; the patient assumes a supine position before the test. The point where it is closest to the skin is marked with a felt-tipped pen. Once cooling unit is placed on the mark, and the other is placed symmetrically on the other (normal) side. The weight of each unit provides sufficient and uniform pressure; in a vast majority of cases, the patient is able to hold the cooling units herself. This situation is pictured schematically in Figure 2.11. The examinees have not been discomforted by the coolness of the disks touching the skin.

At Faulkner Hospital, the examinees are tested sitting in a chair, following their xeroradiographic and thermographic examinations. Something suspicious from the x-rays, thermograms, or clinical examination is the basis for using the local cooling method. The radiologist locates the spot on the skin nearest to the suspected lesion. The women hold the cooling units themselves, resting their forearms on the arms of the chair.

Data is recorded in the form of disk temperatures (which are the
Figure 2.11. Schematic application of local cooling for breast cancer detection
same as skin temperatures) observed at minute intervals. The temperatures are recorded until:

a) both temperatures reach equilibrium, or
b) both temperatures change little and by the same amount, or
c) ten minutes has elapsed.

Usually ten minutes is sufficient for a test; by this time a steady or quasi-steady situation exists. Once a cooling test has begun, the cooling disk cannot be moved because unrealistically high disk temperatures result.

Since one is interested in comparing both the time-dependent and steady-state temperatures of both sites, it is important that both cooling units be in the same dynamic thermal state when the test begins. This is accomplished by filling both reservoirs with ice at approximately the same time and letting them cool down identically such that when the test begins the units are at (approximately) the same temperature.
2.3.5 Results

A total of 130 women have been treated with the local cooling device (40 at Massachusetts General Hospital and 90 at Faulkner Hospital). The raw data for these cases are tabulated in Appendix X. Xerographic, thermographic (Faulkner Hospital only), clinical, and pathological information (where applicable) is provided. Other tabulated information is $\Delta T_s$, the skin temperature difference after $t$ minutes (usually ten). The polarity of $\Delta T_s$ is referenced to an abnormality — i.e., mass observed or felt, or suspicious area on thermogram (if there is no abnormality, it is listed as positive). $M$, defined in Section 2.3.2, is evaluated at two minutes after the beginning of the test.

Fifty-two of the examined women were "normals"; they exhibited no clinical evidence of a mass, nor did they have any gross diffuse abnormality. Their enclosure is intended to show the normal range of $\Delta T_s$ and $M$ which may be encountered. There were 31 carcinomas, 14 solitary cysts, and 4 benign tumors. 22 women had asymmetric diffuse abnormalities such as cystic disease and sclerosing adenosis. These 123 cases are thus considered as being comprises of five categories [cancer (CA), normal (N), cyst (C), benign tumor (BT), and diffuse disease (DD)]. Other cases listed in Appendix X are five women with assymetrical axillary tail, and two with abscess or inflammation.

For the five categories (CA, DD, N, BT, and C) defined above, the mean and the standard deviation of $\Delta T_s$ and $M$ are listed in Table 2.1. The average diameter of masses tested was 1.7 cm, their average depth was 1.5 cm. Three illustrative cooling curves (for cancer, normal, and cyst) are shown in Figure 2.12; these are the most different categories, judging from the values in Table 2.1.
<table>
<thead>
<tr>
<th>Tissue Morphology</th>
<th>Number in Sample</th>
<th>$\Delta T_s$ (mean ± s.d.)</th>
<th>$M$ (mean ± s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer (CA)</td>
<td>31</td>
<td>1.18 ± 1.01</td>
<td>1.50 ± 0.86</td>
</tr>
<tr>
<td>Diffuse Disease (DD)</td>
<td>22</td>
<td>0.47 ± 1.18</td>
<td>1.29 ± 0.39</td>
</tr>
<tr>
<td>Normal (N)</td>
<td>52</td>
<td>0.44 ± 0.24</td>
<td>1.07 ± 0.14</td>
</tr>
<tr>
<td>Benign Tumor (BT)</td>
<td>4</td>
<td>-0.13 ± 0.74</td>
<td>1.05 ± 0.42</td>
</tr>
<tr>
<td>Cyst (C)</td>
<td>14</td>
<td>-0.73 ± 1.20</td>
<td>1.03 ± 0.32</td>
</tr>
</tbody>
</table>

Table 2.1. Mean and standard deviation of $\Delta T_s$ (skin temperature difference after ten minutes) and $M$ (slope ratio at two minutes) for five different tissue morphologies.
Figure 2.12. Typical local cooling curves for women with normal, cyst, and carcinoma pathologic conditions.
It is, of course, expected that the mean values of $\Delta T_s$ and $M$ should be higher for carcinomas than for normals; they should be lowest for cysts. This is a direct consequence of the expectation that malignant growths, under conditions of cooling, have higher perfusion than non-malignant tissues. The mean values for $\Delta T_s$ and $M$ show the different categories to be well separated, but there is considerable overlap when the range of the standard deviation is included. To determine if the difference between the means of the different categories is significant, a student's $t$ test analysis was performed. The results of this test are shown in Table 2.2; the percentage corresponding to two different categories is the probability that the two different means belong to the same distribution. One sees that, for $\Delta T_s$, the separation between the distributions for cancer and the other four categories is quite good, while the mean $\Delta T_s$ for diffuse disease and normal are similar. The separation between the mean values of $M$ is not so good; there is some statistical difference between cancer, diffuse disease, and the grouping of normal, benign tumor, and cyst.

The student's $t$ test shows that some of the distributions for $\Delta T_s$ and $M$ are mathematically distinct from the others. Hence, the probabilities of $\Delta T_s$ and $M$ for the different categories are plotted in Figure 2.13 and 2.14. These curves are for normal distributions with mean and standard deviation from Table 2.1. False negative (from the overlap of the cancer distribution into the non-malignant groups) probabilities and false positive probabilities (from the overlap of the non-malignant groups into the cancer distribution) can be calculated for diagnostic criteria based on these normal distributions. Using $\Delta T_s$ solely as a diagnostic criterion,
<table>
<thead>
<tr>
<th></th>
<th>CA</th>
<th>DD</th>
<th>N</th>
<th>BT</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer (CA)</td>
<td>--</td>
<td>2-5%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Diffuse Disease (DD)</td>
<td>--</td>
<td>80-90%</td>
<td>30-40%</td>
<td>1-5%</td>
<td></td>
</tr>
<tr>
<td>Normal (N)</td>
<td>--</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Benign Tumor (BT)</td>
<td>--</td>
<td>2-5%</td>
<td>30-40%</td>
<td>1-5%</td>
<td></td>
</tr>
<tr>
<td>Cyst (C)</td>
<td>--</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Table 2.2. Probability that mean values of $\Delta T_s$ and $M$ from Table 2.1 are equivalent
Figure 2.13. Normal distributions of five different tissue conditions (N, CA, BT, DD, and C) for the means and standard deviations of skin temperature difference $\Delta T_s$ given in Table 2.1.
Figure 2.14. Normal distributions for means and standard deviations of M given in Table 2.1
a false negative rate of 24% and a false positive rate of 16% is expected. Using $M$ as the sole diagnostic criterion, 40% negative and 10% false positive rates are expected.

One would expect that $M$ is greater than one when $\Delta T_s$ is greater than zero and vice versa. This is not always the case, the basis of which is not completely understood. Therefore, using $\Delta T_s$ and $M$ together as diagnostic criteria, a decreased false negative rate can be obtained with little increase in the number of false positives.

Since a diagnostic test designed for screening can have elevated false positive rates if the false negative rate is acceptably low, it is instructive to note that the same can be accomplished here. This can be accomplished in two ways. The brute force technique would simply lower the tolerances for cancers; it would be necessary (from the probabilities) to raise the false positive rate to about 50% in order to lower the false negative rate to about 5%. The other method is to consider diffuse disease as a pre-malignant condition, which it often is; it would therefore not be objectionable to have this category "flag out" as cancer, because it is worthy of close attention. In this way, the total false negative rate could be reduced by considering diffuse breast disease to be abnormal.

The actual data was examined to see if diagnostic criteria for it could be established that would yield diagnostic accuracy similar to the probabilities from the normal distributions. Accordingly, criteria were set such that, if either $\Delta T_s > 0.9^\circ C$ or $M > 1.35$, then the test was assumed positive for cancer. Non-malignant criteria were for $\Delta T_s < 0.9^\circ C$ and $M < 1.35$. With these criteria 23 of 31 cancers (74%) and 74 of 92 non-malignancies (80%) are correctly diagnosed. These
results compare acceptably with the probabilities expressed in Figure 2.13 and 2.14.

For the data acquired at Faulkner Hospital there is also thermographic information to compare with local cooling. In Figure 2.15 the local cooling temperature difference is compared with the thermographic temperature elevation for the non-normal categories. One expects temperature elevations due to carcinomas to be positively amplified by local cooling; those due to cysts would be negatively amplified. Also, the normals should be clustered about the origin. This is much the case. However, there are two cancers which have negative $\Delta T_s$ and several other points with a large temperature elevation.

Of the two carcinomas with negative readings, one was clinically occult and it had an insignificant thermographic elevation; the other was a very large "burned-out" neoplasm in an older woman. Diffuse breast disease—sclerosing adenosis, cystic disease, fibroadenomata—can be active inflammatory conditions which result in high temperature readings.

There are six obvious places where error may be introduced in the experimental procedure: uniformity of the ice distribution in the two heat sinks, unequal device resistances, non-calibration of the thermistors, unequal initial disk temperatures, movement of the disks during a test, and improper device location on the skin. All of the errors, except for the last, may be accounted for. Since small temperature differences are being measured, error can have a large effect on results.

If the devices are freshly packed with ice prior to a test, and they are allowed to cool down uniformly, the first and fourth errors should not occur. In Appendix VIII it is shown that a 10% inequality in device resistances can result in as much as 1° C error in the steady-state
Figure 2.15. Local cooling skin temperature difference compared to thermographic skin temperature difference for non-normal categories.
temperature differences. The spacers for the water gap were measured with a micrometer and found to vary less than 2%. Air bubbles trapped in the gap could affect gap resistance, but hot, de-gased water was originally put in the gap, and a groove in the aluminum fin allows air bubbles to escape via buoyancy forces. Thus, errors due to the gap resistance are not considered significant. The thermistors used are curve matched and essentially identical; thus the error due to the thermistors is insignificant. Movement of the disk during a test can be detected due to inequalities in the cooling curve; some tests were discarded because of this.

The human female breast has large variations in perfusion, even for normal people. Poor location for the local cooling device (i.e., either non-symmetrically or not on the region of interest) can adversely affect the results. However, all bad results, i.e. those which do not fit the hypothesis, can not be discarded for intangible "experimental errors". Ideally, one would like to do a follow-up exam for such cases. To date, this had not been possible in a clinical situation.
2.3.7 Conclusions

A new thermal method for the evaluation of breast disease has been introduced. The method uses an ice bath for a cold sink, which cools breast tissue through an optimized thermal resistance and a one inch copper disk which contacts the skin. Local cooling requires a target, but it is a technique which had potentially high accuracy and which is simple to use.

Preliminary indications are that a diagnostic accuracy of greater than 70% might be obtained with the prototype system. Diagnostic criteria were established from the results. Using these criteria, 16 of 18 (89%) benign tumors or cysts and 23 of 31 (74%) malignancies were properly diagnosed. The masses examined were on the average 1.7 cm in diameter and 1.5 cm beneath the skin. Only 6 of 52 (12%) normals would have been incorrectly classified as cancer from the developed diagnostic criteria. However, 10 of 22 (45%) women suffered from asymmetrical diffuse types of breast disease would have been put into the malignant group.

Refinement of the local cooling technique will come with an increased number of cases and with the development of a more sensitive local cooling device.

The local cooling device was used in conjunction with xeroradiography and thermography. It can be used to increase the diagnostic accuracy of those methods.
2.4 Computer Simulation of Local Cooling Device

2.4.1 Introduction

The previous chapter describes the application of a prototype local cooling device for the differential diagnosis of breast cancer. The design of the device was based on the steady-state analysis in Section 1.2.5 (where the response of semi-infinite, homogeneous tissue to a local cooling disk at constant temperature is described). In Chapter 2.3 intuitive arguments are presented for the design and application of a three-piece cooling disk.

This chapter presents a computer analysis of the local cooling device, as described in Chapter 2.3. The transient and steady-state response of the one and three-piece disks are compared. The computer is necessary for any transient analysis and for steady-state solutions when either the disk or tissue is non-homogeneous. Some one-dimensional analysis is also presented; it is acceptable on a qualitative basis. The one-dimensional work is useful for giving an overall picture of the device's behavior.

Unless otherwise stated, the disk is assumed to have 2.5 cm overall diameter and metal parts of the disk are made of copper. The dimensions of the insulating plastic (plexi-glas) in the three-piece disk are inner diameter 1.5 cm and outer diameter 2.0 cm. The disk is 0.5 cm thick, and it is separated from an idealized heat sink at 0°C by 1 cm of water which behaves as an ideal solid heat conductor. The boundary conditions for the problem are similar to the analytical case in Section 1.2.5. The tissue is assumed to have the same conductivity as water; however, perfusion does vary with position (this will be described in detail later).
The computer analysis is accomplished with a finite difference technique. Details are given in Appendix II (one-dimensional heat transfer) and Appendix V (two-dimensional axi-symmetric heat transfer). The technique involves writing the conservation of energy for each nodal element. The cost of each two-dimensional solution was traded off against the total number of nodal points (and their distribution) necessary to obtain an acceptable level of accuracy. A basic 180 point nodal grid is used throughout. One-dimensional problems are programmed on the InterData M70 at the Joint Mechanical-Civil Engineering Computing Facility. Two-dimensional solutions were obtained on the IBM S/370 model 165 at the Information Processing Center.
2.4.2 One-Piece Disk, Uniform Tissue Properties

In order to check the validity of the two-dimensional steady-state program, and also, to determine the nodal grid network fineness required, solutions were generated for a one-piece copper disk cooling a semi-infinite homogeneous mass of tissue. The input and results for several different computer runs are shown in Table 2.3. In Table 2.3, "Resistance" is that assigned to the local cooling device. In Figure 2.16, the generated values of \( \frac{q_s a}{k(T_a - T_s)} \) are plotted along with the analytical curve derived in Section 1.2.5 for constant disk temperature and \( \delta/a \to \infty \) (\( \delta \) is tissue thickness). The agreement between exact theory and the finite difference routine is acceptable.
<table>
<thead>
<tr>
<th>a [cm]</th>
<th>λ [cm^{-1}]</th>
<th>aλ</th>
<th>T_s [°C]</th>
</tr>
</thead>
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<tr>
<td>1.25</td>
<td>2</td>
<td>2.5</td>
<td>27.7</td>
</tr>
<tr>
<td>1.25</td>
<td>1</td>
<td>1.25</td>
<td>24.9</td>
</tr>
<tr>
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<td>0.5</td>
<td>0.625</td>
<td>22.7</td>
</tr>
<tr>
<td>2.5</td>
<td>1</td>
<td>2.5</td>
<td>22.3</td>
</tr>
<tr>
<td>0.3125</td>
<td>2</td>
<td>0.625</td>
<td>31.7</td>
</tr>
</tbody>
</table>

Resistance = $10^3$ °C sec cm$^2$/cal

| 1.25  | 2           | 2.5| 22.2    |
| 1.25  | 0.5         | 0.625| 16.2    |

Resistance = $0.5 \times 10^3$ °C sec cm$^2$/cal

| 0.5   | 0.5         | 0.25| 16.6    |

Resistance = $0.25 \times 10^3$ °C sec cm$^2$/cal

Table 2.3. Different disk diameters and tissue perfusion tested for local cooling of homogeneous tissue; resistance is that between disk and 0 °C heat sink.
Figure 2.16. Computer solutions for isothermal disk cooling of homogeneous thick tissue compared to analytical solution for $a\lambda/I_1$ (from Figure 1.5)
2.4.3 On the Problem of Modeling a Tumor at a Depth

It is established that superficial tumors can have higher effective perfusion rates than normal tissue. Also, in Chapter 1.3, it is shown that it is acceptable to find the steady-state skin temperature of a layered tissue model in terms of the effective perfusion rates of the layers; a tumor covered by a layer of normal (lowly perfused) tissue can then be assigned its effective perfusion rate measured under semi-infinite conditions.

However, local cooling as described in Chapter 2.3 is basically a transient method which may reach the steady-state within the ten minute period. To answer the question of whether ten minutes is long enough for the effect of a tumor covered by a layer of normal tissue to be felt at the skin, a one-dimensional transient cooling simulation has been run.

The geometry is tumor tissue \((\lambda = 2.0 \text{ cm}^{-1})\) covered by 1 cm of normal tissue \((\lambda = 0.5 \text{ cm}^{-1})\). Cooling is by a heat sink at 0° C and a resistance of water 1 cm thick \(= 10^{3} \text{ C cm}^2 \text{ sec/cal}\). The response of the layered model is compared to that of normal tissue everywhere.

Two initial conditions are applied. The first has all the tissue initially at 37° C, arterial blood temperature. The second has the tissue initially in steady-state conditions as approximating infra-red thermography; for this situation the layered tissue is initially 1.4° C warmer at the skin than the normal tissue.

The results are shown in Figures 2.17 and 2.18. For the case where the initial temperature is uniformly at 37° C virtually no difference can be seen between the normal and layered model. For the second case, where initial temperatures in the tissue are determined by thermographic cooling conditions, an initial temperature elevation over the tumor is in-
The initial temperature is 37 °C.

Figure 2.17. One-dimensional cooling to a 0 °C heat sink through a 1 cm water resistance, transient and steady-state values; the initial tissue temperature for the transient cases is 37 °C.
Figure 2.18. One-dimensional cooling to a 0 °C heat sink through a 1 cm water resistance, transient and steady state values; the initial tissue temperature is determined by thermographic examination conditions.
creased only slightly during the ten minute period. However, the steady-state temperature difference for these tissue perfusions in 3.8°C. Therefore, as concerns local cooling, any elevated effective tumor perfusion must exist all the way to the skin.
2.4.4 Comparison of One and Three-Piece Disks

It is stated in Section 2.3.2 that the three-piece disk should be more sensitive than the one-piece disk. The geometry of the one and three-piece disks is described in Section 2.4.1. They are compared in four different situations: 

I, $\lambda = 0.5 \text{ cm}^{-1}$ everywhere (i.e., normal tissue);

II, $\lambda = 0.5 \text{ cm}^{-1}$ for $r \leq 0.5 \text{ cm}$ and $\lambda = 2.0 \text{ cm}^{-1}$ for $r > 1.25 \text{ cm}$;

III, $\lambda = 0.5 \text{ cm}^{-1}$ for $r \leq 1.25 \text{ cm}$ and $\lambda = 2.0 \text{ cm}^{-1}$ for $r > 1.25 \text{ cm}$; and

IV, $\lambda = 2.0 \text{ cm}^{-1}$ everywhere. These four situations are illustrated in Figure 2.19.

The transient (solid lines) and steady-state (broken lines) for the four cases and two disks are shown in Figures 2.20 and 2.21. Basically, one is interested in the temperature difference between I (normal case) and II, III, IV (tumor) configurations. Comparing cases I and IV, the three-piece disk gives only a slightly larger temperature difference. However, after ten minutes, the three-piece disk for cases II and III gives significantly greater sensitivity than the one-piece disk. Examination of the temperature field for the three-piece disk (see Figure 2.22) shows the type of situation qualitatively described in Figures 2.8 and 2.9.
Figure 2.19. Four hypothetical tissue geometries involving normal ($\lambda = 0.5 \text{ cm}^{-1}$) and tumor ($\lambda = 2.0 \text{ cm}^{-1}$) tissue.
Figure 2.20. Transient response of a solid 2.5 cm copper disk to the four tissue geometries illustrated in Figure 2.19.
Figure 2.21. Transient response of a three-piece 2.5 cm diameter copper disk to the four tissue geometries illustrated in Figure 2.19
Figure 2.22. Temperature field and adiabatic lines for steady-state local cooling with a three-piece disk in normal tissue ($\lambda = 0.5 \text{ cm}^{-1}$)
2.4.5 Transient Effects Which Cause a Loss of Sensitivity

In the previous section, a transient effect was seen which increased the temperature difference between two tissue geometries over the steady-state value. More often than not, this probably is not the case. Consider the situation illustrated in Figure 2.23. These are the one-dimensional cooling curves for normal tissue (case I), and tumor tissue (case IV). Of interest is the fact that the normal tissue has overshot its steady-state value by nearly 4° C at ten minutes, while the tumor tissue skin temperature is monotonically approaching the steady-state. Due to this overshoot, only half the steady-state temperature difference is obtained at ten minutes.

2.4.6 Errors Due to Non-Uniform Initial Conditions

The previous analysis assumed initial conditions where the disk is at heat sink temperature 0° C in the beginning. Instead, let us assume that the disk is initially at 10° C. The transient curves for this situation are shown in Figure 2.24. The curve for $T_{S_i} = 0° C$ are also depicted (broken lines). The pre-heated disk causes 2° C more overshoot for the low perfusion case, but only elevates the high perfusion case 1° C.

If the disks are not completely cooled initially, a loss of sensitivity is experienced. Moreover, if they are at different initial temperatures, errors can be associated with interpretation of the results when small temperature differences are observed.
Figure 2.23. One-dimensional transient response for cooling to an 0 °C heat sink through a copper disk and 1 cm water resistance
Figure 2.24. One-dimensional transient response for disks initially at 10 °C (compared to the response for disks initially at 0 °C)
2.4.7 Summary

Tumors at a depth cannot be modeled as being covered with a layer of completely normal tissue for local cooling. An elevated effective perfusion rate must exist all the way to the surface for the local cooling method to show any response after ten minutes.

The three-piece disk is demonstrated to be more sensitive than the one-piece disk, especially for small tumors.

Overshoot of the steady-state disk temperature for low tissue perfusions and unequal initial disk temperatures can cause significant loss of sensitivity and error.
2.5 New Directions for the Local Cooling Method

2.5.1 Introduction

The configuration for the local cooling device described in the prior chapters was arrived at as a logical extension of thermography, where tissue is cooled by the environmental air. The disk geometry, however, was selected in a somewhat arbitrary manner. The overall disk diameter was chosen as a compromise between system sensitivity (large disks have greater sensitivity) and total cooling. The inner disk diameter was chosen for sensitivity to small tumors. Neither the disk design nor the device configuration is necessarily optimum. For this reason, various alternatives are explored in this chapter.

In the previous chapter it was shown that the local cooling method cannot differentiate between normal tissue and the hypothetical geometry of a tumor covered by a layer of normal tissue after only ten minutes of cooling. Instead, the response of the system to regions of high perfusion which extend all the way to the skin surface is considered.

In the next section, modifications to the cooling disk are considered. Next, advantages of a constant heat flux system are outlined. Finally, the merits of a purely transient test are explored.
2.5.2 Modified Disk Geometry

Steady-state computer runs are made for different disk geometries. It is found that assuming zero thermal conductivity for the insulating ring does not appreciably increase the sensitivity of the three-piece disk; thus, the conductivity of the insulating material is assumed to be the same as plexi-glas. The response to different tissue perfusions is tested; the tissue geometry for cases I, II, III, and IV are the same as in Chapter 2.4 (see Figure 2.19).

The steady-state results for different disks are shown in Table 2.4. Of interest is the skin temperature difference between Case I and the others. The larger three-piece and multi-sectioned disks (nos. 3, 4, and 5) yield only small improvement over the present design (no.2). The small 1 cm diameter disk (no. 6) compares favorably with the present design for Case II geometry (where the highly perfused region is only as large as the disk).

The larger and multi-ringed disks (nos. 3, 4, and 5) were tested to see if improvement in the sensitivity of the central part of the disk could be obtained. The small disk (no. 6) was tested for its sensitivity to small tumors. Only marginal improvement in system sensitivity (that is, temperature difference between regions of different perfusion) can be obtained with the illustrated disk modifications. The small disk has much less sensitivity for comparing a large, highly perfused region (case IV) with a lowly perfused (i.e., normal) region. Small disks are fairly sensitive to small regions of high perfusion, but they are not very good in comparison with larger disks when the high perfusion region is of greater extent. Heat short-circuiting through the tissue near the skin and through the device
Tissue Geometry

<table>
<thead>
<tr>
<th>Disk</th>
<th>$\lambda$</th>
<th>$a\lambda$</th>
<th>Resistance</th>
<th>$T_s$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>2.0</td>
<td>2.5</td>
<td>IV</td>
<td>27.7</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>0.625</td>
<td>22.9</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>2.0</td>
<td></td>
<td>IV</td>
<td>27.2</td>
</tr>
<tr>
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<td></td>
<td>I</td>
<td>21.9</td>
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<td>I</td>
<td>19.7</td>
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<tr>
<td>4.</td>
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<td></td>
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<td>I</td>
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<td>IV</td>
<td>25.6</td>
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<tr>
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<td>0.5</td>
<td></td>
<td>I</td>
<td>18.9</td>
</tr>
<tr>
<td>6.</td>
<td>2.0</td>
<td>1.0</td>
<td>IV</td>
<td>18.5</td>
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<tr>
<td></td>
<td>0.5</td>
<td>0.25</td>
<td>I</td>
<td>16.5</td>
</tr>
</tbody>
</table>

Table 2.4. Steady-state response of various disk geometries; resistance is that between heat sink and disk; see Figure 2.19 for tissue geometry.
resistance thwarts the effect of the insulating ring. More improvement in system sensitivity could be obtained by using less resistance between the heat sink and disk (hence, optimizing the system): from Table 2.3 it is seen that halving the device resistance for the one-piece 2.5 cm disk can increase the temperature difference for cases I and IV from 4.8 to 6.0 °C.
2.5.3 Constant Heat Flux Method

In section 1.2.4 the concept of a constant heat flux method was introduced. This method has inherently more sensitivity than the local cooling method, as practiced in Chapter 2.3, where cooling conditions (and not heat fluxes) are controlled.

To quantify the improvement in sensitivity due to the constant heat flux method, consider one-dimensional cooling of thick tissue. Equations (1.5) and (1.6) state that

\[ T_s = T_a - \frac{q''}{k\lambda} \quad (2.13) \]

or

\[ T_s = T_a - \left( T_a - T_0 \right) \frac{1}{\left( 1 + \frac{k\lambda}{h} \right)} \quad (2.14) \]

for the prescribed heat flux and prescribed h and To situations, respectively. Algebraic manipulation of (2.13) and (2.14) when \( h/k = \sqrt{\frac{\lambda_1}{\lambda_2}} \) (optimum condition) and \( T_{s1} \) is the same for both cases, yields

\[ \frac{\left( T_{s1} - T_s \right)}{\left( T_{s1} - T_s \right)} = 1 + \frac{\sqrt{\frac{\lambda_1}{\lambda_2}}}{\sqrt{\frac{\lambda_1}{\lambda_2}}} \quad (2.15) \]

Equation (2.15) is plotted in Figure 2.25 as a function of \( \frac{w_{b2} - w_{b1}}{w_{b2}} \cdot \frac{w_{b1}}{w_{b2}} = (\frac{\lambda_1}{\lambda_2})^2 \). The constant heat flux method offers twice the sensitivity when \( w_{b1} \approx w_{b2} \) and it is 50% better when \( w_{b2} \) is only 30% greater than \( w_{b1} \).
$(T_s^2 - T_s^1)q_s''$

$(T_s^2 - T_s^1)h,T_0$

Figure 2.25. Improvement over local cooling (as analyzed in Chapter 1.1) that may be obtained with the constant heat flux device.
2.5.4 Transient Local Cooling Method

One-dimensional transient computer solutions for an insulated copper block on tissue which is thermally thick are generated in Figures 2.26, 2.27 and 2.28. The copper is 0.5, 1.0, and 2.0 cm thick, respectively. Heat from the tissue warms up the copper (which is assumed to be initially at 0° C). At ten minutes the temperature difference between the high perfusion ($\lambda = 2 \text{ cm}^{-1}$) and low perfusion ($\lambda = 0.5 \text{ cm}^{-1}$) regions is greatest for 1 cm thick copper. This 6.9° C difference compares favorably with the ten minutes temperature difference for the previously plotted (Figure 2.23) one-dimensional cooling through a resistance ($10^3 \degree \text{C sec cm}^2/\text{cal}$) to a heat sink at 0° C.

Two dimensional transient computer solutions for an insulated three-piece disk (similar to the disk used in the prototype device) are shown in Figure 2.29. The temperature differences at ten minutes between the four tissue situations (explained in Figure 2.19) compare favorably with those for the simulated local cooling to a 0° C heat sink (Figure 2.21). Optimization of the disk thickness (as demonstrated for the one-dimensional situation) could improve these results.

The transient method would be simpler to use and easier to control than local cooling as currently practiced. However, it gives good results only at some intermediate time. After a long time, of course, all copper temperatures will approach $T_a = 37° \text{C}$. 
Figure 2.26. One-dimensional transient response of a 0.5 cm thick insulated copper mass (initially at 0 °C) on homogeneous tissue (initially at 37 °C)
Figure 2.27. One-dimensional transient response of a 1.0 cm thick insulated copper mass (initially at 0 °C) on tissue (initially at 37 °C)
Figure 2.28. One-dimensional transient response of a 2.0 cm thick insulated copper mass (initially at 0 °C) on tissue (initially at 37 °C)
Figure 2.29. Transient response of an insulated three-piece copper disk (initially at 0 °C) on tissue (initially at 37 °C)
2.5.5 Summary

Modifications to the disk geometry seem to offer only marginal improvement in system sensitivity over the present design.

The constant heat flux method, where skin temperatures are compared under conditions of the same uniform flux, offers up to twice the sensitivity of local cooling using an optimized resistance and heat sink.

Transient local cooling offers nearly the same sensitivity if skin temperatures are compared at some intermediate time after the beginning of the test. It offers the advantages of being simpler to apply and less error-prone.
2.6 Summary

An analysis of infra-red thermography shows that by increasing the cooling rate up to an optimum level can greatly increase the sensitivity of the method. Since, however, increased cooling may not be tolerated by those being examined, local cooling, which is theoretically much more sensitive than thermography, is applied for the differential diagnosis of breast cancer.

Initial results with the local cooling method from a study of 130 women indicate that diagnostic accuracies of nearly 80% could have been obtained. A computer analysis of the local cooling device shows that the clinical use of local cooling is mostly in a transient regime, and associated errors are isolated. Modifications to the cooling disk are analyzed, but they do not offer significant improvement. However, nearly two-fold improvement in sensitivity could be obtained with a constant heat flux local cooling device.
GENERAL CONCLUSIONS

Thermal methods for blood perfusion measurement have been analyzed. Qualitative methods, where perfusion differences are deduced from skin temperature differences, and quantitative methods, where absolute perfusion levels are calculated from measured thermal parameters, are discussed. In general, one is better off by increasing cooling rates as much as is tolerable. A successful application for monitoring tumor perfusion during radiation therapy is presented.

An analysis of infra-red thermography shows that optimization of surface conditions could substantially increase the sensitivity of that method. However, intolerable cooling loads on those being examined may prevent much enhancement of thermography. Alternatively, local cooling was developed for clinical use in the differential diagnosis of breast cancer. Local cooling permits high heat rates and hence greater sensitivity than infra-red thermography. The initial series of clinical tests on 130 women had promising results. Improvement of the method through a constant heat flux technique offers greater accuracy and reliability. Local cooling was shown to be an asset in the diagnostic procedure when used in conjunction with xeroradiography and thermography.
BIBLIOGRAPHY


44. Johnson, R. J., Lahey Clinic, Boston, Massachusetts, Personal Communication, March 1973


49. Watmough, D.J. and R. Oliver, "The Emission of Infra-red Radiation from the Skin - Implications for Clinical Thermography", *British Journal of Radiology*, 42.6, 1969, p.411


61. Ackerman, R., Massachusetts General Hospital, Personal Communication, April 1974

APPENDIX I

STEADY-STATE CLOSED FORM SOLUTIONS

A1.1 Generalized One-Dimensional Case

Consider a model as pictured in Figure 1.3. Tissue with perfusion $\lambda$, conductivity $k$, metabolic heat generation $Q_m$ and thickness $\delta$ lies over a layer of bone with conductivity $k_B$ and thickness $L$. The boundary conditions are surface temperature $T_s$, and temperature $T_a$ at the inner surface of the bone (at $x = \delta + L$).

The energy equation for steady-state one-dimensional heat transfer in tissue is:

$$\frac{d^2 \Theta}{dx^2} - \lambda^2 \Theta + \frac{Q_m}{k} = 0$$  \hspace{1cm} (A1.1)

for which the solution may be written

$$\Theta = T - T_a = C_1 \sinh \lambda x + C_2 \cosh \lambda x + \frac{Q_m}{k \lambda^2}$$  \hspace{1cm} (A1.2)

where $C_1$ and $C_2$ are constants which are found from the boundary conditions. Thus:

$$C_2 = T_s - T_a - \frac{Q_m}{k \lambda^2}$$  \hspace{1cm} (A1.3)

$$-\frac{k_B}{L} \left[ C_1 \sinh \lambda \delta + C_2 \cosh \lambda \delta \right] = k\lambda \left[ C_1 \cosh \lambda \delta + C_2 \sinh \lambda \delta \right]$$  \hspace{1cm} (A1.4)
and it may be shown that

\[ T - T_a = \left( T_s - T_a - \frac{Q_m}{K \lambda^2} \right) \left\{ - \frac{\tanh \lambda \delta + \frac{K_B \delta}{K L \lambda \delta}}{1 + \frac{K_B \delta}{K L \lambda \delta} \tanh \lambda \delta} \sinh \lambda x \right\} + \frac{Q_m}{k \lambda^2} \]  

(A.5)

Usually, \( T_s \) is not known and is a function of the surface conditions. If the flux is prescribed at the surface,

\[ q_s'' = \left( T_s - T_a - \frac{Q_m}{K \lambda^2} \right) \left\{ - \frac{\tanh \lambda \delta + \frac{K_B \delta}{K L \lambda \delta}}{1 + \frac{K_B \delta}{K L \lambda \delta} \tanh \lambda \delta} \right\} \]  

or

\[ T_s - T_a = \frac{q_s'' \delta}{K (\lambda \delta)} \frac{1 + \frac{K_B \delta}{K L \lambda \delta} \tanh \lambda \delta} {\tanh \lambda \delta + \frac{K_B \delta}{K L \lambda \delta} \tanh \lambda \delta} + \frac{Q_m \delta^2}{K (\lambda \delta)^2} \]  

(A.7)

Alternatively, an environmental temperature \( T_o \) and heat transfer coefficient \( h \) may be assigned to the surface. Since

\[ h (T_s - T_o) = q_s'' \]  

(A.8)

thus,
\[
\frac{T_s - T_a}{T_a - T_0} = \frac{-\frac{h\delta}{K} \frac{1}{\lambda\delta}}{rac{h\delta}{K} \frac{1}{\lambda\delta} + \frac{\tanh \lambda\delta + \frac{K_B \delta}{KL} \frac{1}{\lambda\delta}}{1 + \frac{K_B \delta}{KL} \frac{1}{\lambda\delta} \tanh \lambda\delta} + \frac{\tanh \lambda\delta + \frac{K_B \delta}{KL} \frac{1}{\lambda\delta}}{1 + \frac{K_B \delta}{KL} \frac{1}{\lambda\delta} \tanh \lambda\delta} \quad \text{(A1.9)}
\]

Equation (A1.7) gives the expression for surface temperature as a function of

\[
\frac{K_B \delta}{KL}, \lambda\delta, \frac{q_s \delta}{K}, \text{and} \quad \frac{Q_m \delta^2}{K}
\]

when heat flux is prescribed. When \( h \) and \( T_0 \) are prescribed surface temperature is a function of

\[
\frac{K_B \delta}{KL}, \lambda\delta, \frac{h\delta}{K}, \frac{Q_m \delta^2}{K (T_a - T_0)}
\]

and \( T_a - T_0 \), as expressed in equation (A1.9).
Al.1.1 Deep Tissue Approximation

For this situation $\lambda \delta \gg 1$ and $\tanh \lambda \delta \approx 1$.

Therefore, for prescribed heat flux,

$$T_s - T_a = \frac{q''_s}{k \lambda} + \frac{Q_m}{k \lambda^2}$$  \hspace{1cm} (A1.10)

and for prescribed $h$ and $T_0$,

$$\frac{T_s - T_a}{T_a - T_0} = \frac{- \frac{h}{k \lambda}}{\frac{h}{k \lambda} + 1} + \frac{Q_m}{k \lambda^2 (T_a - T_0)} \frac{1}{\frac{h}{k \lambda} + 1}$$  \hspace{1cm} (A1.11)

Al.1.2 Thin Tissue Approximation

In this case $\lambda \delta \ll 1$ and $\tanh \lambda \delta \approx \lambda \delta$.

Therefore, for prescribed heat flux at the surface, using (A1.7):

$$T_s - T_a = \frac{q''_s \delta}{k} \frac{1 + \frac{k h \delta}{k L}}{(\lambda \delta)^2 + \frac{k h \delta}{k L}} + \frac{Q_m \delta^2}{k (\lambda \delta)^2}$$  \hspace{1cm} (A1.12)

Similarly, when $h$ and $T_0$ are prescribed, using (A1.9):

$$\frac{T_s - T_a}{T_a - T_0} = \frac{- \frac{h \delta}{k}}{\frac{h \delta}{k} + \frac{(\lambda \delta)^2 + \frac{k h \delta}{k L}}{1 + \frac{k h \delta}{k L}}}$$  \hspace{1cm} (A1.13)

\[ + \frac{Q_m \delta^2}{k (\lambda \delta)^2 (T_a - T_0)} \frac{\delta}{k} + \frac{(\lambda \delta)^2 + \frac{k h \delta}{k L}}{1 + \frac{k h \delta}{k L}}\]
Consider a model similar to that pictured in Figure 1.3.

Let \( \lambda = \lambda_1 \) for \( 0 \leq x \leq \delta \), \( \lambda = \lambda_2 \) for \( x > \delta \), and let \( L \to \infty \). If all other properties are uniform, and \( Q_m = 0 \), then for \( 0 < x \leq \delta \)

\[
\Theta = C_1 \sinh \lambda_1 x + C_2 \cosh \lambda_1 x
\]  
(A1.14)

where

\[
C_2 = T_s - T_a
\]  
(A1.15)

Matching the flux and temperature between the layers at \( x = \delta \) gives two relations for \( C_2 \) and \( C_3 \), where for \( x > \delta \)

\[
\Theta = C_3 e^{-\lambda_2 (x-\delta)}
\]  
(A1.16)

Accordingly, \( C_1 \sinh \lambda_1 \delta + C_2 \cosh \lambda_1 \delta = C_3 \)  
(A1.17)

and

\[
- \frac{\lambda_1}{\lambda_2} \left[ C_1 \cosh \lambda_1 \delta + C_2 \sinh \lambda_1 \delta \right] = C_3
\]  
(A1.18)

Combining equations (A1.15), (A1.17), and (A1.18)

\[
C_1 = - \left( T_s - T_a \right) \frac{\lambda_1}{\lambda_2} \frac{\tanh \lambda_1 \delta + 1}{\tanh \lambda_1 \delta + \frac{\lambda_1}{\lambda_2}}
\]  
(A1.19)

and

\[
T_s - T_a = \left( T_s - T_a \right) \left\{ \cosh \lambda_1 x - \frac{\lambda_1}{\lambda_2} \frac{\tanh \lambda_1 \delta + 1}{\tanh \lambda_1 \delta + \frac{\lambda_1}{\lambda_2}} \sinh \lambda_1 x \right\}
\]  
(A1.20)
for $0 \leq x \leq \delta$. Since $q''_s = k \frac{dT}{dx} \bigg|_{x=0}$

$$q''_s = - (T_s - T_a) k \lambda_1 \left( \frac{\lambda_1}{\lambda_2} \tanh \lambda_1 \delta + 1 \right) \left( \frac{\lambda_1}{\lambda_2} + \tanh \lambda_1 \delta \right)$$

(A1.21)

Either $q''_s$, or $T_0$ and $h$, may be prescribed (in which case $q''_s = h (T_s - T_o)$).

An effective perfusion may be defined:

$$\lambda_{\text{eff}} = \frac{q''_s}{k (T_a - T_s)} = \lambda_1 \left( \frac{\lambda_1}{\lambda_2} \tanh \lambda_1 \delta + 1 \right) \left( \frac{\lambda_1}{\lambda_2} + \tanh \lambda_1 \delta \right)$$

(A1.22)
Al.3 Optimization of Surface Thermal Conditions

When the effect of metabolism is neglected (although it need not be so), the tissue heat transfer may be modeled:

\[ q''_s = \frac{T_a - T_s}{R} \]  \hspace{1cm} (Al.23)

where \( R \) is the tissue heat transfer "resistance" and

\[ R = \frac{1}{k \lambda_{\text{eff}}} \]  \hspace{1cm} (Al.24)

If \( R \) is a function of tissue properties and is independent of temperature, the calculation of \( \lambda_{\text{eff}} \) is more accurate as \( q''_s \) increases. Similarly, if identical cooling rates \( q''_s \) are used on two locations, then for different values of \( R \) (i.e. different \( \lambda_{\text{eff}} \)), the skin temperature difference increases as \( q''_s \) increases. However, if \( h \) and \( T_o \) are specified then \( q''_s = h (T_s - T_o) \) and the cooling rates are not equal on both locations. To induce the maximum skin temperature difference between two regions of different resistance (and hence perfusion) one must use an \( h \) such that

\[ \frac{d}{dh} (T_{s_2} - T_{s_1}) = 0 \]  \hspace{1cm} (Al.25)

Since

\[ T_{s_1} - T_{a} = (T_{a} - T_{o}) \frac{-1}{1 + \frac{1}{R h}} \]  \hspace{1cm} (Al.26)
\[ T_{S_2} - T_{S_1} = \left( \frac{1}{R_2} - \frac{1}{R_1} \right) / \left( h + \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{4hR_1R_2} \right) \]  

(A1.27)

and

\[ \frac{d}{dh} (T_{S_2} - T_{S_1}) = \frac{R_2 - R_1}{R_1R_2} \left( 1 - \frac{1}{R_1R_2h^2} \right) / \left( h + \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{4hR_1R_2} \right)^2 \]  

(A1.28)

Condition (A1.25) is satisfied when

\[ h = (R_1R_2)^{-\frac{1}{2}} \]  

(A1.29)

or equivalently, from (A1.24)

\[ h_{opt} = k \left[ (\lambda_{eff}, \lambda_{eff})_z \right]^{\frac{1}{2}} \]  

(A1.30)

When one wishes to compare the perfusion in two different regions, when \( h \) and \( T_0 \) are specified the same for both regions, the comparison is most sensitively made when \( h \) obeys (A1.30).
The transient solution for a thin layer of tissue is tractable because the layer is at constant temperature and everything changes temperature at the same rate. For the model in Figure 1.3, consider the situation where a mass per unit area $m$ of copper rests on the skin surface. If the only heat input into the copper is from the tissue, and if the specific heat of the bone is negligibly small,

$$\left[(mC_p)_{Cu} + \rho C_p \delta \right] \frac{dT}{dt} = W_b C_b (T_a - T) + \frac{k_B \delta}{K_L} (T_a - T)$$  \hspace{1cm} (Al.31)

Since $\Theta = T - T_a$, $\lambda^2 = W_b C_b / k$, and $\alpha = k / \rho C_p$

$$\left[(mC_p)_{Cu} \frac{\delta}{K} + \frac{\delta^2}{\alpha} \right] \frac{d\Theta}{dt} = -\left[ (\lambda \delta)^2 + \frac{k_B \delta}{k L} \right] \Theta$$  \hspace{1cm} (Al.32)

The solution for (Al.30) is simple:

$$\Theta = \Theta_i e^{-\alpha' t}$$  \hspace{1cm} (Al.33)

where

$$\alpha' = \frac{(\lambda \delta)^2 + \frac{k_B \delta}{k L}}{(mC_p)_{Cu} \frac{\delta}{K} + \frac{\delta^2}{\alpha}}$$  \hspace{1cm} (Al.34)

and $\Theta_i$ is the initial temperature when $t = 0$. 
If \( \frac{k_B^s}{kL} = 0 \),

\[
W_b = \frac{\lambda^2 k}{C_b} = K \frac{dT/dt}{T_a - T}
\]  

(A1.35)

where \( K \) is a constant dependent upon the copper and tissue geometries and properties.
Two-Dimensional Steady-State Analysis

Thermal Analysis

Figure 1.4 gives the geometry: cooling of the tissue occurs over a disk of radius \(a\). The tissue is assumed to be homogeneous and isotropic with constant properties. The flux through the disk is much larger than through the surrounding skin; thus, the surface area outside the cooling disk is assumed to be adiabatic. The tissue extends beyond the region affected by the local cooling radially; it has depth \(\delta\) at which boundary it is assumed insulated.

For steady-state conditions, the temperature distribution within the tissue should satisfy the following differential equation:

\[
\frac{i}{r} \frac{\partial}{\partial r} \left( r \frac{\partial \Theta}{\partial r} \right) + \frac{\partial^2 \Theta}{\partial Z^2} - \lambda^2 \Theta + \frac{Q_m}{k} = 0 \tag{Al.36}
\]

where \(\Theta \equiv T - T_a\) and \(\lambda^2 \equiv \omega_c b / k\). Other variables are defined in the Nomenclature.

The homogeneous part of \(\Theta\), \(\Theta = \Theta_h + Q_m / k \lambda^2\) should vanish far from the disk, i.e.

\[
r \to \infty \quad \Theta_h = 0 \tag{Al.37}
\]

Also, at the depth \(\delta\) with the tissue

\[
Z = 0 \quad \frac{\partial \Theta_h}{\partial Z} = 0 \tag{Al.38}
\]

The solution of the homogeneous part of equation (Al.36) which satisfies equation (Al.37) and (Al.38) is
\[ \theta_h = \int_0^\infty f(\alpha) \cosh \left[ (\alpha^2 + \lambda^2)^{\frac{1}{2}} \right] J_0(\alpha r) d\alpha \]  

where \( f(\alpha) \) is to be determined from the boundary conditions at \( z = \delta \).
Al.5.la Conditions Which Approximate Constant Temperature Over the Disk

For constant disk temperature, one has to satisfy the following:

\[
\begin{align*}
Z &= 0 \\
0 &\leq r \leq a \\
a &< r
\end{align*}
\]

\[\Theta_h = (T_s - T_a) - \frac{Q_m}{k \lambda^2} \quad (A1.40)\]

\[\frac{\partial \Theta_h}{\partial z} = 0 \quad (A1.41)\]

Since [45]:

\[
\int_0^\infty \sin(\alpha a) J_0(\alpha r) d\alpha = \begin{cases} (a^2 - r^2)^{-\frac{1}{2}} & 0 \leq r \leq a \\ 0 & a < r \end{cases} \quad (A1.42)
\]

and also from [37]

\[
\left(\frac{\partial \Theta_h}{\partial z}\right) = \int_0^\infty (\alpha^2 + \lambda^2)^{\frac{1}{2}} \sin[(\alpha^2 + \lambda^2)^{\frac{1}{2}} \delta] f(\alpha) J_0(\alpha r) d\alpha \quad (A1.43)
\]

comparing equation (A1.43) with equation (A1.42), one can conclude that if

\[
f(\alpha) = C \frac{\sin(\alpha a)}{(\alpha^2 + \lambda^2)^{\frac{1}{2}} \sinh[(\alpha^2 + \lambda^2)^{\frac{1}{2}} \delta]} \quad (A1.44)
\]

boundary condition (A1.41) will be satisfied. The constant, C, can be expressed in terms of the average flux over the disk (positive in the +z direction).
or, using the first identity in relation (Al.42)

\[ q_s' = \frac{2kC}{\alpha^2} \int_0^a \left( a^2 - r^2 \right)^{1/2} r \, dr = \frac{2kC}{\alpha^2} \quad (Al.45) \]

Therefore, using equations (Al.44), (Al.45), (Al.37), and (Al.38), the solution for \( \Theta_h \) is

\[ \Theta_h = \frac{q_s'' a}{2k} \int_0^\infty \frac{\sin(\alpha x)\cosh\left[\left(\alpha^2 + \lambda^2\right)^{1/2} z\right] J_0(\alpha r)}{(\alpha^2 + \lambda^2)^{1/2} \sinh\left[\left(\alpha^2 + \lambda^2\right)^{1/2} z\right]} \, d\alpha \quad (Al.46) \]

The average surface temperature over the disk area can be obtained by simple integration of equation (Al.46). This yields

\[ \Theta_s - \frac{Q_m}{k\lambda} \left( 1 + \frac{Q_m}{k\lambda^2\Delta T} \right) \frac{a\lambda}{I_1} \]

or

\[ \frac{q_s'' a}{k\Delta T} = \left( 1 + \frac{Q_m}{k\lambda^2\Delta T} \right) \frac{a\lambda}{I_1} \]

where \( \Delta T = T_a - T_s \) and

\[ I_1 = \int_0^\infty \frac{\sin(\xi) J_1(\xi) \coth\left\{ \xi \left[ 1 + \left( \frac{\xi}{a\lambda} \right)^2 \right]^{1/2} \right\}}{\xi \left[ 1 + \left( \frac{\xi}{a\lambda} \right)^2 \right]^{1/2}} \, d\xi \quad (Al.47) \]

The solution obtained in the foregoing represents only an approximation since boundary condition (Al.40) is satisfied only in the average. Relation (Al.46) becomes exact when \( \lambda \to 0 \) and \( \delta/a \to \infty \) since [45]:

\[ \int_0^\infty \frac{\sin(\alpha x)}{\alpha} J_0(\alpha r) \, d\alpha = \frac{\pi}{2} \quad \text{for} \quad 0 \leq r \leq a \]

It is possible that the approximation (which impresses infinite flux at the corners of the disk for \( \lambda = 0 \)) is unrealistic and that a better approach would be imposing constant flux over the disk area. For this reason, the latter case is solved exactly.
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A1.5.1b  Constant Flux Over the Disk Area

For this case, boundary conditions would remain the same as before except for condition (A1.40) which now is changed to

\[ k \frac{\partial \Theta}{\partial z} \bigg|_{z=\delta} = q_s'' = \text{const}. \]  \hspace{1cm} (A1.48)

Here the identity [45] is used:

\[ \int_0^\infty J_0(\alpha r) J_1(\alpha r') \, d\alpha = \begin{cases} \frac{1}{\alpha} & 0 \leq r \leq a \\ 0 & a < r \end{cases} \]

to determine \( f(\alpha) \) in equation (A1.39) as

\[ f(\alpha) = \frac{q_s'' a J_1(\alpha r)}{k (\alpha^2 + \lambda^2)^{\frac{1}{2}} \sinh \left[ (\alpha^2 + \lambda^2)^{\frac{1}{2}} \delta \right]} \]  \hspace{1cm} (A1.49)

and

\[ \Theta_h = -\frac{q_s'' a}{k} \int_0^\infty \frac{\cosh \left[ (\alpha^2 + \lambda^2)^{\frac{1}{2}} \delta \right] J_1(\alpha r) J_1(\alpha a)}{(\alpha^2 + \lambda^2)^{\frac{1}{2}} \sinh \left[ (\alpha^2 + \lambda^2)^{\frac{1}{2}} \delta \right]} \, d\alpha \]  \hspace{1cm} (A1.50)

In terms of the average disk temperature \( T_s \) ave, an expression similar to equation (A1.47) follows from the foregoing:

\[ \frac{q_s'' a}{k \Delta T} = \left( 1 + \frac{Q_m}{k \lambda^2 \Delta T} \right) \frac{a \lambda}{I_2} \]  \hspace{1cm} (A1.51)

where \( \Delta T \equiv T_a - (T_s) \) ave and

\[ I_2 = \int_0^\infty \frac{J_1^2(\xi) \coth \left[ \xi \sqrt{\lambda^2 (\xi^2 + 1) \frac{1}{\alpha^2}} \right]}{\xi \left[ 1 + \left( \frac{\xi}{\alpha \lambda} \right)^2 \right]^{\frac{1}{2}}} \, d\xi \]  \hspace{1cm} (A1.52)
For large values of $a\lambda$ both $I_1$ and $I_2$ approach a value of one, and
\[
q'' \left. a/k \Delta T \right|_s = a\lambda.
\]

Al.5.2 Results

Solutions for the integrals, $I_1$ and $I_2$, were obtained on an IBM 1130 computer. Figure 1.5 gives $a\lambda/I_1$ and $a\lambda/I_2$, respectively, as a function of $a\lambda$, and $\delta/a$. If $\delta/a \to \infty$ for small values of $a\lambda$, $a\lambda/I_1 \to 4/\pi$ and $a\lambda/I_2 \to 3\pi/8$. It can be seen from the figure that the method is not effective for small values of $a\lambda$ (if $\delta/a$ is large), since in this case the measured quantities would be almost independent of $a\lambda$.

Al.6 Importance of Metabolism on Solutions

From equation (Al.11), for different tissue regions site 1 and site 2, where $\lambda_1 \neq \lambda_2$ but
\[
\left[ \frac{Q_m}{k\lambda^2(T_a - T_0)} \right]_1 = \left[ \frac{Q_m}{k\lambda^2(T_a - T_0)} \right]_2 = \bar{Q}
\]
\[
\frac{T_{S_2} - T_{S_1}}{T_a - T_0} = \frac{h}{k} \left( \frac{1}{\lambda_1} - \frac{1}{\lambda_2} \right) \left[ 1 + \bar{Q} \right]
\]
\[
\left( \frac{h}{k\lambda_2} + 1 \right) \left( \frac{h}{k\lambda_1} + 1 \right)
\]

It is obvious that, if $\bar{Q} \ll 1$, the effect of metabolism may be neglected altogether, and the local tissue temperature is a function only of the boundary conditions, and $\lambda$ (i.e., perfusion). It has been found that $\bar{Q}$ is negligible for healthy tissue, and that $Q_m/w_b c_b \leq 1^\circ C$ for malignant pathology [46]. Furthermore, $\lambda$ is on the order of 2 cm$^{-1}$ for tumors. Thus, if $\bar{Q} \leq 0.1$, $(T_a - T_0)$ must be greater than...
2.5° C. It will become evident that this is indeed the case under conditions of moderate to strong cooling. Therefore, for all applications illustrated in this work, metabolism is neglected.
APPENDIX II

COMPUTER SOLUTIONS FOR ONE-DIMENSIONAL CASE

A2.1 Steady-State

Consider the energy balance for the ith node of a one-dimensional finite difference grid:

\[ k_{i-1} \frac{(T_{i-1} - T_i)}{\Delta x_{i-1}} + k_i \frac{(T_{i+1} - T_i)}{\Delta x_i} + (\omega_b c_b)_{i-1} \frac{\Delta T}{2} + (\omega_b c_b)_i \frac{\Delta T}{2} = 0 \]  \( \text{(A2.1)} \)

\( k_i \) and \((\omega_b c_b)_i\) are parameters which are assumed constant in the region between the ith and ith + 1 nodes. The distance between those nodes is \( \Delta x_i \). The region of constant temperature about the ith nodes is \((\Delta x_i + \Delta x_{i+1})/2\) wide. Equation (A2.1) may be re-written:

\[ T_{i+1} + \frac{k_{i-1} \Delta x_i}{k_i \Delta x_{i-1}} T_{i-1} + \frac{(\lambda \Delta x^2)_{i-1} k_{i-1} \Delta x_i}{k_i \Delta x_{i-1}^2} T_{a} \]

\[ \frac{(\lambda \Delta x^2)_i k_{i-1} \Delta x_i}{k_i \Delta x_{i-1}^2} + \frac{(\lambda \Delta x^2)_i}{2} \] \[ T_i = 0 \]  \( \text{(A2.2)} \)

For solutions found in this thesis, the temperatures at the end points of the finite difference network are specified initially. Then, for \( 2 \leq i \leq N - 1 \), with equation (A2.2) \( N-2 \) linear equations may be written for \( N-2 \) unknown temperatures \( T_i \). Appropriate matrix manipulation techniques are used to find the temperature field.
For some solutions of interest perfusion varies with temperature. This may be expressed as in Chapter 1.3,

\[ \lambda^2 = \lambda_0^2 \times \left( \frac{i}{2} \right) \times \left( \frac{T_a - T}{\Delta T_c} \right) \]  \hspace{1cm} (A2.3)

After substitution of (A2.3) into (A2.2), an iterative technique is used to find a new temperature field in terms of the old one. Initially, \( T_i \) is assumed to be uniformly at \( T_a \); thus initially \( \lambda^2 \) is uniformly equal to \( \lambda_0^2 \).

Since \( T_1 \) and \( T_N \) are specified constant, solutions may also be found for an insulated boundary (by specifying \( k/\Delta x \) at the boundary small enough).

For the solutions found in this work, typically fifteen nodes were assigned to the tissue. The nodes were spaced such that (approximately) the same temperature difference between nodes was obtained.

A listing of the computer program which was used to solve the linear system of equations (A2.2) follows this write-up. Subroutine SIMQ, from the IBM Scientific Subroutines Package [62], was used to find the matrix solution of \( T_i \). This routine uses column pivoting with Gaussian elimination. The input variables for the program are:

- \( N \) : total number of nodal points
- \( NS \) : skin node
- \( DX(I) \) : nodal spacing between \( x_i \) and \( x_{i+1} \)
- \( K(I) \) : thermal conductivity between \( x_i \) and \( x_{i+1} \)
- \( LAMN(I) \) : perfusion \( \{ \Xi \sqrt{\left( \omega_b \omega_n / k \right)} \} \) between \( x_i \) and \( x_{i+1} \)
- \( T(I) \) : initial temperature field
- \( TCTRL(I) \) : control temperature \( \{ \Xi \Delta T_c \} \)
Output parameters are:

- **MCNT**: number of iterations
- **EFLMB**: effective perfusion ($\Xi \lambda_{\text{eff}}$) after MCNT iterations
- **T(I)**: temperature field after MCNT iterations

The iteration procedure ceases when the skin temperature changes less than 0.5°C per iteration.
REAL F(20), BF(20), K(20), DX(20), LAMN(20), T(20), TT(17,17), TCTRL(20)

99 CONTINUE
READ(8,100) N, NS
100 FORMAT(2I10)
WRITE(5,101) N, NS
101 FORMAT(//1H ,13' ELEMENTS, SKIN AT NODE'13//)
N1=N-1
X=0
MCNT=0
WRITE(5,104)
104 FORMAT(1H ,8X'CX'9X'K'6X'LAMN'9X'T'5X'TCTRL'9X'T')
DO 1 I=1,N
READ(8,102) DX(I), K(I), LAMN(I), T(I), TCTRL(I)
102 FORMAT(5F10.5)
WRITE(5,103) DX(I), K(I), LAMN(I), T(I), TCTRL(I), X
103 FORMAT(IH ,6F10.5)
X=X+DX(I)
IF(I.EQ.1.OR.I.EQ.N) CC TO 10
F(I)=K(I-1)*DX(I)/K(I)/DX(I-1)
BF(I)=LAMN(I)*LAMN(I)*CX(I)*CX(I)/2.
10 CONTINUE
1 CONTINUE
25 CONTINUE
DO 88 I=1,N
DO 88 J=1,N
88 TT(I,J)=0
TT(1,1)=1
TT(N,N)=1
TS=T(NS)
DO 2 I=2,N1
TT(I,1+1)=1
TT(I,1-I)=F(I)
DELT=T(N)-T(I)
PC=BF(I-1)*F(I)*.5**((DELT/TCTRL(I-1))+BF(I)*.5**((DELT/TCTRL(I))
TT(I,I)=-1.-F(I)-PC
T(I)=-T(N)*PC
CONTINUE
CALL SIMQ(TT,T,N,IER)
IF(IER.EQ.0) GO TO 3
WRITE(5,105) IER
105 FORMAT(1H 'ERROR CODE IS'13'....ABORT'//)
GO TO 99
3 CONTINUE
MCNT=MCNT+1
X=O
WRITE(5,107)
107 FORMAT(//1H ,6X'NODE'6X'TEMP'9X'X'//)
DO 4 I=1,N
WRITE(5,106) I,T(I),X
X=X+CX(I)
4 CONTINUE
106 FORMAT(1H ,I10,2F10.4)
EFLMB=(T(NS)-T(NS-1))*F(NS)/F(NS)/(T(N)-T(NS))/DX(NS)
WRITE(5,108) EFLMB,MCNT
108 FORMAT(1H 'EFFECTIVE PERF. IS'E12.5' AFTER'13' ITER.'//)
IF(TS-T(NS).LT..5 ) GO TO 99
IF(MCNT.GT.4 ) GO TO 99
GO TO 25
CALL EXIT
END
A2.2 Transient

Now, the energy balance for the ith node must be modified to account for specific heat. Accordingly, (A2.1) becomes:

\[ k_{i-1} \frac{T_{i-1} - T_i}{\Delta X_{i-1}} + k_i \frac{T_{i+1} - T_i}{\Delta X_i} + \left[ \left( w_b c_b \right)_{i-1} \frac{\Delta X_{i-1}}{2} + \left( w_b c_b \right)_i \frac{\Delta X_i}{2} \right] \left( T_a - T_i \right) = \]

\[ \left[ \left( \rho c_p \right)_{i-1} \frac{\Delta X_{i-1}}{2} + \left( \rho c_p \right)_i \frac{\Delta X_i}{2} \right] \frac{T_i' - T_i}{\Delta t} \]  

(A2.4)

\((\rho c_p)_i\) is assumed constant in the region between the ith and ith + 1 node. \(\Delta t\) is the time interval. \(T_i'\) is the time at \(t + \Delta t\). All other parameters are the same as defined before in section A2.1. As before, equation (A2.4) may be re-written:

\[ T_{i+1} + \frac{k_i \Delta X_i}{K_i \Delta X_{i-1}} T_{i-1} + \frac{(\lambda \Delta X)_{i-1}^2 K_{i-1} \Delta X_{i-1}}{K_i \Delta X_{i-1}^2 + (\lambda \Delta X)_i^2} T_a \]

\[ + \left[ M_i - 1 - \frac{k_{i-1} \Delta X_{i-1}}{K_i \Delta X_{i-1}^2} \frac{(\lambda \Delta X)_i^2 K_{i-1} \Delta X_{i-1}}{K_i \Delta X_{i-1}^2 + (\lambda \Delta X)_i^2} \right] T_i = M_i T_i' \]  

(A2.5)

where

\[ M_i = \frac{\left( \frac{\Delta X^2}{\Delta t} \right)_{i-1} + \left( \frac{\Delta X^2}{\Delta t} \right)_i \frac{\Delta X_{i-1} K_i}{\Delta X_i \Delta X_{i-1} K_{i-1}}}{2} \]  

(A2.6)
\( a [=k/\rho c_p] \) is the thermal diffusivity. Given property values \((\lambda, k, a)_i\), the nodal spacing \(\Delta x_i\), and the initial temperature distribution \(T_i\), equation (A2.5) may be solved \(N-2\) times for each time interval \(\Delta t\) into order to march out the transient solution.

In order for this marching technique to be stable \(M\) must satisfy the condition

\[
M_i > 1 + \frac{\left(\lambda \Delta x\right)_{i-1}^2 F_i + \left(\lambda \Delta x\right)_i^2}{2} \quad (A2.7)
\]

where

\[
F_i = \frac{K_{i-1} \Delta x_i}{K_i \Delta x_{i-1}} \quad (A2.8)
\]

This requirement rigidly restricts one choice of \(\Delta x\) and \(\Delta t\).

A listing of the computer program used to solve this problem follows this write-up. The listed version of the program permits variation of perfusion with temperature as governed by equation (A2.3). If one lets \(\Delta T_c\) be very large then perfusion is (effectively) invariant with temperature. The input variables for the program are:

- \( DT \) time interval
- \( NTIME \) total number of iterations
- \( NPRNT \) the number of iterations between printing the output
- \( N \) total number of nodes
- \( NS \) number of skin node
- \( DX(I) \) nodal spacing between \(x_i\) and \(x_{i+1}\)
- \( K(I) \) thermal conductivity between the \(i\)th and \(i+1\) nodes
\[ \text{ALPHA(I)} \text{ thermal diffusivity between the } \text{i} \text{th and } \text{i} \text{th}+1 \text{ nodes} \]

\[ \text{LAMN(I)} \{\text{E/(wbcb/k)}\}_i \text{ perfusion between the } \text{i} \text{th and } \text{i} \text{th}+1 \text{ nodes} \]

\[ \text{T(I)} \text{ initial temperature distribution} \]

\[ \text{TCTRL(I)} \{\text{=ATc}_i\} \text{ control temperature for perfusion between } \text{i} \text{th and } \text{i} \text{th}+1 \text{ nodes} \]

The output parameters are:

\begin{align*}
\text{TIME} & \quad \text{time} \\
\text{J} & \quad \text{number of iterations at the above time} \\
\text{X(I)} & \quad \text{position} \\
\text{T(I)} & \quad \text{temperature at the above temperature and time} \\
\text{DTDT} & \quad \{\text{= } \frac{1}{\text{t}} \text{ } \partial \theta / \partial \text{t} \text{} \} \text{ parameter which is a function of } \lambda \text{ and } t
\end{align*}

This information is printed until J > NTIME.
REAL F(20), BF(20), M(20), P(20), MN(20), K(20), DX(20), LAMN(20), ALPHA(20), T(20), TT(20), TCTRL(20), FA(129)

Z=.5**0.0625
FA(1)=1
DO 29 I=2,129
29 FA(I)=FA(I-1)*Z
99 CONTINUE
READ(8,100) DT, NTIME, NPRNT, N, NS
100 FORMAT(F10.5, 4I10)
WRITE(5, 101) N, DT, NTIME, NPRNT, NS
WRITE(6, 101) N, DT, NTIME, NPRNT, NS
101 FORMAT(/1H *I3* ELEMENTS WITH DT'F6.3/'* TOTAL ITERATIONS ARE *I5* PRINTS EVERY *I5* ITERATION SKIN NODE IS *I3//)
N1=N-1
X=0
WRITE(5, 104)
WRITE(6, 104)
104 FORMAT(1H *I10X'CX'11X*K'7X*ALPHA'6X*LAMN'9X'T'8X'TC'9X*X'//)
DO 1 I=1, N
READ(8, 102) DX(I), K(I), ALPHA(I), LAMN(I), T(I), TCTRL(I)
102 FORMAT(2F10.5, F15.1C, 3F10.5)
WRITE(5, 103) DX(I), K(I), ALPHA(I), LAMN(I), T(I), TCTRL(I), X
WRITE(6, 103) DX(I), K(I), ALPHA(I), LAMN(I), T(I), TCTRL(I), X
103 FORMAT(1H *I2F12.5, F12.4, 3F10.5, F1C.3)
X=X+DX(I)
IF(I.EQ.1.OR.I.EQ.N) GC TO 10
F(I)=K(I-1)*DX(I)/K(I)/DX(I-1)
10 CONTINUE
IF(I.EQ.N) GO TO 1
BF(I)=LAMN(I)*LAMN(I)*DX(I)*DX(I)/2.
1 M(I)=DX(I)*DX(I)/2./ALPHA(I)/DT
TM=T(NS)
DO 2 I=2, N1
P(I)=F(I)*BF(I-1)+8F(I)
2 MN(I)=F(I)*M(I-1)+M(I)
TT(I)=T(I)
\[ TT(N) = T(N) \]
\[ \text{TIME} = 0 \]
\[ \text{DO } 4 \text{ J} = 1, \text{NTIME} \]
\[ \text{DO } 3 \text{ I} = 2, \text{NI} \]
\[ \text{DELT} = T(N) - T(I) \]
\[ \text{IY} = \text{IFIX}(16. \times \text{DELT} / \text{TCTRL}(I)) + 1 \]
\[ \text{IYM} = \text{IFIX}(16. \times \text{DELT} / \text{TCTRL}(I - 1)) + 1 \]
\[ \text{IF}((\text{IY} \cdot \text{GT} \cdot 129) \text{IY} = 129 \]
\[ \text{IF}((\text{IYM} \cdot \text{GT} \cdot 129) \text{IYM} = 129 \]
\[ \text{IF}((\text{IY} \cdot \text{LT} \cdot 1) \text{IY} = 1 \]
\[ \text{IF}((\text{IYM} \cdot \text{LT} \cdot 1) \text{IYM} = 1 \]
\[ \text{PC} = \text{BF}(-1) * \text{F}(I) * \text{FA}(\text{IYM}) + \text{BF}(I) * \text{FA}(\text{IY}) \]
\[ \text{TT}(I) = (T(I + 1) + F(I) * T(I) + PC * T(N) + T(I) * (MN(I) - F(I) - PC) * 1.) \] / MN(I) \]
\[ \text{TIME} = \text{TIME} + \text{DT} \]
\[ \text{JPRNT} = (J / \text{NPRNT}) * \text{NPRNT} - J \]
\[ \text{IF}((\text{JPRNT} \cdot \text{NE} \cdot 0) \text{ GO TO } 6 \]
\[ \text{DTCT} = (\text{TT(NS)} - \text{TM}) / (37. - (\text{TT(NS)} + \text{TM}) / 2.) \]
\[ \text{WRITE}(5,105) \text{ TIME}, J, \text{DTCT} \]
\[ \text{WRITE}(6,105) \text{ TIME}, J, \text{DTCT} \]
\[ 105 \text{ FORMAT}(/ / \text{ TIME IS 'F10.2' AFTER 'I7' ITERATIONS'// GRAD/THETA IS 'E} \]
\[ 113.5// ) \]
\[ \text{TM} = \text{TT(NS)} \]
\[ \text{X} = 0 \]
\[ \text{WRITE}(5,107) \]
\[ \text{WRITE}(6,107) \]
\[ 107 \text{ FORMAT}(11X{*}, \text{9X}, '{'}T')// ) \]
\[ \text{DO } 5 \text{ JJ} = 1, \text{N} \]
\[ \text{WRITE}(5,106) \text{ X}, \text{TT(JJ)} \]
\[ \text{WRITE}(6,106) \text{ X}, \text{TT(JJ)} \]
\[ 106 \text{ FORMAT}(1H\; '2F10.5) \]
\[ 5 \text{ X} = \text{X} + \text{DX(JJ)} \]
\[ 6 \text{ DO } 7 \text{ JJ} = 1, \text{N} \]
\[ 7 \text{ T(JJ)} = \text{TT(JJ)} \]
\[ 4 \text{ CONTINUE} \]
\[ \text{GO TO } 99 \]
Evaluating equation (2.2) (for $Q_m = 0$) at $\lambda_T$ (tumor perfusion) and $\lambda_N$ (normal perfusion) and subtracting:

$$\Delta T_S = T_{S_T} - T_{S_N} = (T_a - T_o) \frac{h}{k} \frac{\lambda_T - \lambda_N}{(\frac{h}{k} + \lambda_T)(\frac{h}{k} + \lambda_N)}$$ (A3.1)

one can solve for the environmental temperature $T_o$ which, as a function of $h/k$, $\lambda_T$, and $\lambda_N$, will support a specified tumor-normal tissue temperature difference $\Delta T_S$:

$$T_o = T_a - \Delta T_S \frac{(\frac{h}{k} + \lambda_T)(\frac{h}{k} + \lambda_N)}{\frac{h}{k} (\lambda_T - \lambda_N)}$$ (A3.2)

The heat flux from the skin is given by equation (1.7); assuming that most of the exposed skin is normal:

$$q''_s = k \lambda_N (T_a - T_S) = h (T_S - T_o)$$ (A3.3)

Eliminating $T_S$ from (A3.3):

$$q''_s = (T_a - T_o) \frac{k \lambda_N}{1 + \frac{k \lambda_N}{\lambda}}$$ (A3.4)

Substituting (A3.2) into (A3.4):

$$q''_s = \frac{k \lambda_N (\frac{h}{k} + \lambda_T)}{\lambda_T - \lambda_N}$$ (A3.5)
Non-dimensionalizing the flux

\[
\frac{q''_s}{k \lambda_N \Delta T_s} = \frac{h}{k} + \frac{\lambda_T}{\lambda_T - \lambda_N}
\]  \hspace{1cm} (A3.6)

Equations (A3.2) and (A3.6) are plotted in Figure 2.3. The limiting expressions for the heat loss \( q''_s \) are derived by setting \( h/k = 0 \) and setting \( h/k = (\lambda_T \lambda_N)^{1/2} \). Substituting \( (h/k)_{opt} \) into (A3.6)

\[
\frac{(q''_s)_{opt}}{k \lambda_N \Delta T_s} = \frac{(\lambda_T \lambda_N)^{1/2} + \lambda_T}{\lambda_T - \lambda_N}
\]  \hspace{1cm} (A3.7)

If \( h/k = 0 \),

\[
\frac{(q''_s)_o}{k \lambda_N \Delta T_s} = \frac{\lambda_T}{\lambda_T - \lambda_N}
\]  \hspace{1cm} (A3.8)

The ratio of (A3.7) to (A3.8) is simply:

\[
\frac{(q''_s)_{opt}}{(q''_s)_o} = 1 + \sqrt{\frac{\lambda_N}{\lambda_T}}
\]  \hspace{1cm} (A3.9)
Since the disk of the local cooling device is made of copper, it can be assumed to be at constant temperature. Thus the analysis in Appendix A1.5.1 (a) applies. For the specific case of breast cancer it is assumed that $\delta/a >> 1$ and $\lambda \delta >> 1$; hence, the deep tissue approximation is used.

Therefore:

$$q''_S = \frac{k (T_a - T_S)}{a} \frac{a \lambda}{I} \left[ 1 + \frac{Q_m}{k \lambda^2 (T_a - T_o)} \right] \quad (A4.1)$$

This expression for heat flux from the skin can be equated with heat flux through the device

$$q''_S = \frac{T_S - T_o}{R} \quad (A4.2)$$

where $R$ is the thermal resistance between the local cooling disk (at temperature $T_S$) and the heat sink (at temperature $T_o$). Combining (A4.1) and (A4.2)

$$T_S = T_a - (T_a - T_o) \frac{1}{1 + \frac{R_k}{a} \frac{a \lambda}{I}} + \frac{Q_m}{\omega_b C_b} \frac{R_k}{a} \frac{a \lambda}{I} \quad (A4.3)$$

The tissue resistance is defined in equation (A1.23); thus, for the local cooling device
Using relation (A1.29), the optimum resistance for the device is defined

\[
R_{\text{tissue}} = \frac{a}{k} \frac{I_i}{a\lambda}
\]  

(A4.4)

\[
R_{\text{opt}} = \frac{a}{k} \left[ \frac{I(a\lambda_N)I(a\lambda_T)}{(a\lambda_N)(a\lambda_T)} \right]^{\frac{1}{2}}
\]  

(A4.5)
APPENDIX V

COMPUTER SOLUTION FOR TWO-DIMENSIONAL

(AXI-SYMMETRIC) CASE

A5.1 Steady State

Similar to the one-dimensional case described in Appendix II, an energy balance may be written for an interior nodal element \((i,j)\) of a two-dimensional grid (see Figure A5.1). Properties are assumed constant within the squares partitioned by the dashed lines, and temperature for node \((i,j)\) as assumed constant within the shaded square. Therefore,

\[
\left( T_{i,j+1} - T_{ij} \right) \frac{k_{i,j} \pi r_{i,j}^2}{2} \frac{r_{i+1,j}^2 - r_{i,j}^2}{r_{i,j}} + \frac{k_{i,j} \pi r_{i,j}^2}{2} \frac{r_{i+1,j}^2 - r_{i,j}^2}{r_{i,j}} \frac{z_{j+1} - z_j}{2} \\
\left( T_{i+1,j} - T_{ij} \right) \frac{k_{i,j} \pi r_{i,j}^2}{2} \frac{r_{i+1,j}^2 - r_{i,j}^2}{r_{i,j}} + \frac{k_{i,j} \pi r_{i,j}^2}{2} \frac{r_{i+1,j}^2 - r_{i,j}^2}{r_{i,j}} \frac{z_{j+1} - z_j}{2} \\
\left( T_{i+1,j} - T_{ij} \right) \frac{k_{i,j} \pi r_{i,j}^2}{2} \frac{r_{i+1,j}^2 - r_{i,j}^2}{r_{i,j}} \frac{z_{j+1} - z_j}{2} + \frac{k_{i,j} \pi r_{i,j}^2}{2} \frac{r_{i+1,j}^2 - r_{i,j}^2}{r_{i,j}} \frac{z_{j+1} - z_j}{2} \\
\left( T_{i+1,j+1} - T_{ij} \right) \frac{k_{i,j} \pi r_{i,j}^2}{2} \frac{r_{i+1,j+1}^2 - r_{i,j}^2}{r_{i,j}} \frac{z_{j+1} - z_j}{2} + \frac{k_{i,j} \pi r_{i,j}^2}{2} \frac{r_{i+1,j+1}^2 - r_{i,j}^2}{r_{i,j}} \frac{z_{j+1} - z_j}{2}
\]
Figure A5.1. Interior nodal element of two-dimensional finite difference grid used for analysis of local cooling.
Equation (A5.1) is the basic difference relation for the steady-state axi-symmetric problem. The equation must be modified at the boundaries; at \( z = 0 \) (i.e., \( j = 1 \)) and at \( z = \delta \) (i.e., \( j = j_{\text{max}} \)), the temperature is specified. The other boundaries at \( r = 0 \) (i.e., \( i = 1 \)) and at \( r = r_{\text{max}} \) (i.e., \( i = i_{\text{max}} \)), the boundary is assumed to be insulated. For the insulated conditions, only the relevant portions of (A5.1) are included in the energy balance; that is, terms which correspond to regions outside of the grid are dropped. For example, when \( i = i_{\text{max}} \), terms involving \( T_{i+1,j} \) and \( r_{i+1,j} \), are dropped.

A typical grid is shown in Figure A5.2. Solutions for the system of equations defined by equation (A5.1) are found with a computer program (a listing follows this write-up), which uses the subroutine RSIMQ [63] from the Scientific Math Library file at M.I.T.'s Information Processing Center for the solution of a set of linear simultaneous equations. RSIMQ uses a technique identical to SIMQ [62] described in Appendix II.

Input variables are:

- **IMAX** maximum number of nodes in the radial direction
- **JMAX** maximum number of nodes in the axial direction
- **TA** \( \{= T_a \} \) arterial blood temperature; also temperature at \( z = \delta \) (i.e., \( j = j_{\text{max}} \))
Figure A5.2 Typical finite difference grid used for local cooling analysis
when $\lambda = 0.5 \text{ cm}^{-1}$ and the disk is one-piece
TO

\{ = T_0 \} \text{ heat sink temperature at } t = 0

IEND

\text{ data parameter (\#0 for last set of data) }

R(I)

\text{ radial spacing }

Z(J)

\text{ axial spacing }

COND(I,J)

\text{ thermal conductivity for area between } r(i), r(i+1) 
\text{ and } z(j), z(j+1)

PERF(I,J)

\{ = \lambda \} \text{ perfusion for area between } r(i), r(i+1) \text{ and } 
\text{ z(j), z(j+1) }

Output is:

B(K)

\text{ temperature field } [k = IMAX \times (J - 1) + I ]

Any region, such as the area above the skin and outside of the 
local cooling device, can be made insulated by making the thermal con-
ductivity low.
REAL*4 COND(12,15),PERF(12,15),R(12),Z(15),T(180,180),B(180)

C
30 CONTINUE
READ(5,1000) IMAX,JMAX,TA,TO,IEND
READ(5,1001) (R(I),I=1,IMAX)
READ(5,1001) (Z(J),J=1,JMAX)
IMAX1=IMAX-1
JMAX1=JMAX-1
DO 500 J=1,JMAX1
READ(5,1001)(COND(I,J),I=1,IMAX)
500 READ(5,1001)(PERF(I,J),I=1,IMAX)

C
WRITE(6,1002) IMAX,JMAX,TA,TA
WRITE(6,1003) (R(I),I=1,IMAX)
WRITE(6,1006)
DO 501 J=1,JMAX1
WRITE(6,1004) J,Z(J)
IF(J.EQ.JMAX) GO TO 501
WRITE(6,1005)(COND(I,J),I=1,IMAX1)
WRITE(6,1005)(PERF(I,J),I=1,IMAX1)
501 CONTINUE

C
1000 FORMAT(213,2F10.6,6,110)
1001 FORMAT(15F5.3)
1002 FORMAT(// 'IMAX',I3,'JMAX',I3,'TA',F4.0,'TA',F4.0//)
1003 FORMAT(1H,'RAID...12F7.3)
1004 FORMAT(3X,I3,'TH DEPTH IS',F7.3//)
1005 FORMAT(1H,F9.3,11(1X,F9.3))
1006 FORMAT(1H,'COND, PERF...//)

C
DO 666 I=1,IMAX
DO 666 J=1,JMAX1
666 PERF(I,J)=PERF(I,J)*PERF(I,J)
MN=IMAX*JMAX
DO 1 KC=1,MN
B(KD)=C
DO 1 LC=1,MN
1 T(KC,LC)=0

DO 2 J=1,JMAX
DO 2 I=1,IMAX
K=(J-1)*IMAX+I

IF(J.GT.I.AND.J.LT.JMAX) GO TO 49
IF(J.EQ.I) B(K)=-TC
IF(J.EQ.JMAX) B(K)=-TA
GO TO 2

49 IF(I.EQ.1) GO TC 51
CR=COND(I-1,J-1)/COND(I,J)
DZ=Z(J)-Z(J-1)
DA=R(I)*R(I)-R(I-1)*R(I-1)
T(K,K-1)= DZ/(R(I)-R(I-1))*SQRT((R(I-1)*R(I-1)+R(I)*R(I))/2.)*CA
IIND(I-1,J-1)
KIMAX=K-IMAX
T(K,KIMAX)=COND(I-1,J-1)*DA/DZ/2.*CR
B(K)=-PERF(I-1,J-1)/4.*DZ*DA*TA*COND(I-1,J-1)

C

CR=COND(I-1,J)/COND(I,J)
DZ=Z(J+1)-Z(J)
T(K,K-1)= DZ/(R(I)-R(I-1))*SQRT((R(I)*R(I)+R(I-1)*R(I-1))/2.)*CA
IIND(I-1,J-1)
KIMAX=K-IMAX
T(K,KIMAX)=COND(I-1,J)*DA/DZ/2.*CR
B(K)=B(K)-PERF(I-1,J)/4.*DZ*DA*TA*COND(I-1,J)

C

51 IF(I.EQ.IMAX) GO TO 53
CR=COND(I,J-1)/COND(I,J)
DZ=Z(J)-Z(J-1)
DA=R(I+1)*R(I+1)-R(I)*R(I)
KIMAX=K-IMAX
T(K,KIMAX)=T(K,KIMAX)+1./2.*DA/DZ*CR

C
\[ T(K, K+1) = \frac{DZ}{(R(I+1) - R(I))} \sqrt{(R(I+1)^2 + R(I)^2)/2} \cdot \cot(K, K+1) \]
\[ \text{INC(I, J-1)} \]
\[ B(K) = B(K) - \text{PERF(I, J-1)/4} \cdot DZ \cdot DA \cdot TA \cdot \text{COND(I, J-1)} \]
\[ DZ = Z(J+1) - Z(J) \]
\[ T(K, K+1) = T(K, K+1) + DZ \cdot (R(I+1) - R(I)) \sqrt{(R(I+1)^2 + R(I)^2)/2} \cdot \cot(K, K+1) \]
\[ \text{KMAX} = K + \text{IMAX} \]
\[ T(K, \text{KMAX}) = T(K, \text{KMAX}) + 0.5 \cdot DA \cdot DZ \cdot \text{COND(I, J-1)} \]
\[ B(K) = B(K) - \text{PERF(I, J-1)/4} \cdot DZ \cdot DA \cdot TA \cdot \text{COND(I, J-1)} \]

53 IF(K.EQ.1) GO TO 80
\[ T(K, K) = -T(K, K-1) \]
80 IF(K.LE.IMAX) GO TO 81
\[ \text{KMAX} = K - \text{IMAX} \]
\[ T(K, K) = T(K, K) - T(K, \text{KMAX}) \]
81 IF(K.GT.MN-IMAX) GO TO 82
\[ \text{KMAX} = K + \text{IMAX} \]
\[ T(K, K) = T(K, K) - T(K, \text{KMAX}) \]
82 IF(K.EQ.MN) GO TO 2
\[ T(K, K) = T(K, K) - T(K, K+1) \]
\[ T(K, K) = T(K, K) + B(K)/TA \]
2 IF(J.EQ.1 OR J.EQ.JMAX) T(K, K) = -1

CALL RSIMQ(180, MN, T, B, IER)
IF(IER.NE.0) WRITE(6, 1500) IER
1500 FORMAT(//' ERRCR CODE = ',12//)
IF(IER.NE.0) GO TO 9999
WRITE(6, 1999)
DO 600 J=1, JMAX
KL = (J-1) * IMAX
KL1 = KL + 1
KLIMX = KL + IMAX
600 WRITE(6, 2000)( B(K), K = KL1, KLIMX)
1999 FORMAT(//' TEMPERATURE FIELD'//)
2000 FORMAT(1H ,12F9.3)
C
9999 CONTINUE
IF(IENC.EQ.0) CC TO 30
CALL EXIT
END
A5.2 Transient

For the transient situation, the energy balance equation must be modified. Accordingly, the right hand term of equation (A5.1) becomes

$$\frac{T_{i,j}' - T_{i,j}}{\Delta t} = \left\{ \left( \rho C_p \right)_{i,j} \frac{r_i - r_{i-1}}{2} + \frac{Z_j - Z_{j-1}}{2} \right\} + \left( \rho C_p \right)_{i,j} \frac{r_{i+1}^2 - r_i^2}{2Z} \frac{Z_{j+1} - Z_j}{2} + \left( \rho C_p \right)_{i,j} \frac{r_{i+1}^2 - r_i^2}{2Z} \frac{Z_{j+1} - Z_j}{2}$$

If the properties (i.e., $k$, $\lambda$, $\rho c_p$) and the initial conditions for temperature, the solution for $T_{i,j}'$ at time $t' = t + \Delta t$ (in terms of $T_{i,j}$ at time $t$) is easily found. The computer program for accomplishing this follows this write-up. Stability criteria similar to those discussed in section A2.2 put restrictions on the nodal spacing and time interval. Restrictions on the computer time required to generate a ten minute simulation made it necessary to lump the copper disk as a mass having specific heat but no resistance.

Input variables for the program are:

- **DT** time interval each iteration
- **NTIME** total number of iterations
- **NPRNT** number of iterations between printing of output parameters
- **IMAX** maximum number of nodes of radial direction
- **JMAX** maximum number of nodes in axial direction
- **TA** arterial blood temperature
TO
heat sink temperature

TSLM
initial temperature of inner part of disk

TSM
initial temperature of outer part of disk

IN
defines radius of inner part of disk

ID
defines radius of outer part of disk

JS
defines axial location of skin

IEND
parameter which defines last set of data ($\neq 0$)

R(I)
radial spacing

Z(J)
axial spacing

T(K)
initial temperature distribution

ALPH(I,J) [$\equiv \alpha$] thermal diffusivity

COND(I,J)
thermal conductivity

PERF(I,J) [$\equiv \lambda$] perfusion

Output parameters are:

L
number of iterations this print

TIME
simulated time for L iterations

TT(K)
temperature field after L iterations
REAL*4  COND(12,17),PERF(12,17),R(12),Z(17),A(204,204),B(204),M(204)
1),T(204),TT(204),ALPH(12,17)

333 CONTINUE
READ(5,1008) DT,NTIME,NPRNT
1008 FORMAT(F10.5,2T10)
WRITE(6,1009) DT,NTIME,NPRNT
1009 FORMAT(1H 'DT=',Fl0.5,' TOTAL ITER.' ,1I0,1H ' PRINT ITER.' ,1I0//)
READ(5,1000) IMAX,JMAX,TA,TO,TS1M,TSM,IN,ID,JS,IEND
READ(5,1001) (R(I),I=1,IMAX)
READ(5,1001) (Z(J),J=1,JMAX)
WRITE(6,1025) IMAX,JMAX,TS1M,TSM
1025 FORMAT(//1H 'IN=',13,F6.3,1H 'ID=',13,F6.3,1H 'JS=',13,F6.3,1H ' TS1M=',F10.6,1H ' TSM=',F10.6)//)
DO 502 I=1,IMAX
K=IMAX*(JMAX-1)+I
502 T(K)=TA
IMAX1=IMAX-1
JMAX1=JMAX-1
DO 500 J=1,JMAX1
K1=(J-1)*IMAX+1
KM=J*IMAX
READ(5,1001)(T(K),K=K1,KM)
READ(5,1001)(ALPH(I,J),I=1,IMAX)
READ(5,1001)(COND(I,J),I=1,IMAX)
500 READ(5,1001)(PERF(I,J),I=1,IMAX)
WRITE(6,1002) IMAX,JMAX,TO,TA
WRITE(6,1003) (R(I),I=1,IMAX)
1003 FORMAT(1H 'RACE ...',12F6.3)
WRITE(6,1006)
DO 501 J=1,IMAX
K1=(J-1)*IMAX+1
KM=J*IMAX
WRITE(6,1004) J,Z(J)
IF(J.EQ.JMAX) GO TO 501
WRITE(6,1005) (COND(I,J),I=1,IMAX)
WRITE(6,1005) (PERF(I,J),I=1,IMAX)
WRITE(6,1005)(ALPH(I,J),I=1,IMAX)
WRITE(6,1005)(T(K),K=K1,KM)

501 CONTINUE

1000 FORMAT(2I3,4F10.6,4I5)
1001 FORMAT(16F5.2)
1002 FORMAT(1H* IMAX*,I3*, JMAX*,I3*, TC*,F4.0*, TA*,F4.0//)
1004 FORMAT(/3X,I3*, 'TH DEPTH IS',F6.3//)
1005 FORMAT(6H*,F7.3,23(1X,F7.3))
1006 FORMAT(/'CCNC,PERF,ALPH//' 'INITIAL TEMPERATURE//' )

MN=IMAX*JMAX
DO 25 I=1,IMAX
DO 25 J=1,JMAX

25 PERF(I,J)=PERF(I,J)*PERF(I,J)
DO 1 KC=1,MN
B(KC)=0
M(KC)=0
DO 1 LC=1,MN

1 A(KC,LC)=0
DO 2 J=2,JMAX
DO 2 I=1,IMAX
K=(J-1)*IMAX+I
IF(I.EQ.1) GO TC 51
CR=COND(I-1,J-1)/CCND(IJ)
IF(J.EQ.JS-1) CR=COND(I-1,J-1)/COND(I-1,J+1)
IF(J.EQ.JS) CR=COND(I-1,J-1)/COND(I-1,J)
DZ=Z(J)-Z(J-1)
DA=R(I)*R(1)-R(I-1)*R(I-1)
IF(I.GT.IA.AND.J.LE.JS) GO TO 800
IF(J.EQ.JS) GC TC 797
A(K,K-1)=CR*DZ/(R(I)-R(I-1))*SQRT((R(I-1)*R(I-1)+R(I)*R(I))/2.)

797 CONTINUE

A(K,KMAX)=CR/K-IMAX
A(K,KMAX)=CR/2.*DA/DZ
B(K)=-PERF(I-1,J-1)/4.*CR*DZ*DA*TA

800 CONTINUE
CR=CONC(I-1,J)/CONC(I,J)
IF(J.EQ.JS-1) CR=COND(I-1,J)/COND(I-1,J+1)
IF(J.EQ.JS) CR=1
DZ=Z(J+1)-Z(J)
IF(J.EQ.JS-1) GO TO 799
A(K,K-1)=A(K,K-1)+CR*DZ/(R(I)-R(I-1))*SQRT((R(I)*R(I)+R(I-1)*R(I-1)))/2.)
KIMAX=K+IMAX
A(K,KIMAX)=A(K,KIMAX)+CR/2.*DA/DZ
B(K)=B(K)-PERF(I-1,J)/4.*CR*DZ*DA*TA
799 CONTINUE
M(K)=M(K)+CR*DZ*DA/4./CT/ALPH(I,J)
51 IF(I.EQ.IMAX) GO TO 53
CR=CONC(I,J-1)/CONC(I,J)
IF(JS.EQ.JS-1) CR=COND(I,J-1)/COND(I,J+1)
IF(J.EQ.JS) CR=COND(I,J-1)/COND(I,J)
DZ=Z(J)-Z(J-1)
DA=R(I+1)*R(I+1)-R(I)*R(I)
KIMAX=K-IMAX
IF(I.GE.ID.AND.J.LE.JS) GO TO 801
IF(J.EQ.JS) GO TO 798
IF(J.EQ.JS-1) CR=1
A(K,KIMAX)=A(K,KIMAX)+CR/2.*DA/DZ
A(K+1)=CR*DZ/(R(I+1)-R(I))*SQRT((R(I+1)*R(I+1)+R(I)*R(I)))/2.)
B(K)=B(K)-PERF(I,J-1)/4.*CR*DZ*DA*TA
798 CONTINUE
M(K)=M(K)+CR*DZ*DA/4./CT/ALPH(I,J-1)
801 CONTINUE
CR=1
IF(J.EQ.JS-1) CR=COND(I,J)/COND(I,J+1)
IF(J.EQ.JS) CR=1
DZ=Z(J+1)-Z(J)
IF(I.GE.ID.AND.J.LE.JS-1) GO TO 53
IF(J.EQ.JS-1) GO TO 796
A(K+1)=A(K+1)+DZ/(R(I+1)-R(I))*SQRT((R(I+1)*R(I+1)+R(I)*R(I)))/12.)
KIMAX=K+IMAX
A(K,KIMAX)=A(K,KIMAX)+.5*DA/DZ
B(K)=B(K)-PERF(I,J)/4.*DZ*DA*TA
CONTINUE
M(K)=M(K)+CR*Z/CT/CA/4./ALPH(I,J)
IF(K.EQ.1) GO TO 80
A(K,K)=-A(K,K-1)
53 IF(K.LE.IMAX) GO TO 81
KIMAX=K-IMAX
A(K,K)=A(K,K)-A(K,KIMAX)
80 IF(K.GT.MN-IMAX) GO TO 82
KIMAX=K+IMAX
A(K,K)=A(K,K)-A(K,KIMAX)
81 IF(K.GT.MN-IMAX) GO TO 82
KIMAX=K+IMAX
A(K,K)=A(K,K)-A(K,K-1)
82 IF(K.EQ.MN) GO TO 2
A(K,K)=A(K,K)+B(K)/TA+M(K)
CONTINUE
TIME=0
DO 10 L=1,NTIME
TIME=TIME+DT
IN1=IN+1
TS=0
TS1=0
COEF=0
C1=0
XM=0
XM1=0
A IN=2.*COND(JS-1,IN)/COND(JS,IN)*SQRT((R(IN)*R(IN)+R(IN1)*R(IN1)))/12.*(Z(JS)-Z(JS-1))/(R(IN1)-R(IN))
IF(IN.EQ.ID) A IN=0
DO 47 II=1,ID
KT=(JS-1)*IMAX+II
KTX=KT+IMAX
KR=KT-IMAX
KRX=KR-IMAX
IF(II.GT.IN) GO TO 45
\[
TS1 = TSL + A(KT, KT) + A(KR, KR) + T(KT) - B(KT)
\]
\[
C1 = C1 + A(KT, KT) + A(KR, KR) - E(KT)/TA
\]
\[
XM1 = XM1 + M(KT) + M(KR)
\]

GO TO 47

45 \[
\]
\[
COEF = COEF + A(KT, KT) + A(KR, KR) - B(KT)/TA
\]
\[
XM = XM + M(KT) + M(KR)
\]

GO TO 47

CONTINUE

47 \[
TS1 = (TS1 + A(KT, KT)*T(KT) + A(KR, KR)*T(KR) - B(KT))/TA
\]
\[
COEF = COEF + A(KT, KT) + A(KR, KR) - B(KT)/TA
\]
\[
XM = XM + M(KT) + M(KR)
\]

GO TO 47

CONTINUE

DO 11 J = 1, JMAX

11 I = 1, IMAX

K = (J-1)*IMAX + I

IF (J.GT.1.AND.J.LT.JMAX) GO TO 49

IF (J.EQ.1) TT(K) = T(K)

IF (J.EQ.JMAX) TT(K) = TA

GO TO 11

49 KMX = K - IMAX

KPx = K + IMAX

IF (J.LT.JS.AND.I.GT.ID) TT(K) = 0

IF (J.LT.JS.AND.I.GT.ID) GO TO 11

IF (J.EQ.JS-1) GO TO 43

IF (J.EQ.JS.AND.I.LE.ID) GO TO 43

TT(K) = (T(KMX) + A(KMX) + T(KPx) + A(KPx) + T(K-1) + A(K-1) + T(K+1) + A(K, K+1) - B(K) + T(K)*A(K, K))/M(K)

GO TO 11

43 IF (I.LE.IN) TT(K) = TS1

IF (I.GT.IN) TT(K) = TS

11 CONTINUE

IF ((L/NPRNT) * NPRNT - L.NE.0) GO TO 12

WRITE(6, 1998) L, TIME

1998 FORMAT (/1H ' Iterations , TIME IS ', F10.5//)
DO 600 J=1,JMAX
KL=(J-1)*IMAX
KLI=KL+1
KLIMX=KL+IMAX
600 WRITE(6,2000) (TT(K),K=KLI,KLIMX)
1999 FORMAT(// TEMPERATURE FIELD//)
12 DO 9999 K=1,MN
 T(K)=TT(K)
9999 CONTINUE
 TSM=TS
 TS1M=TS1
2000 FORMAT(1H ,12F9.3)
10 CONTINUE
 IF(IEND.EQ.0) GO TO 333
 CALL EXIT
 END
A6.1 Problem Formulation

The problem is to design a thermistor bridge circuit (see Figure A1.6) to measure the temperature of a copper disk from 10°C to 35°C using a UUA 35J3 curve matched thermistor manufactured by Omega Engineering. From the Omega specifications [59], the thermistor resistance $R_T$ at the end-points and mid-point of the desired range are:

- $R_T$ (10°C) = 9950 Ω
- $R_T$ (22.5°C) = 5585 Ω
- $R_T$ (35°C) = 3265 Ω
Figure A6.1 Circuit diagram of readout meter for a thermistor; the current $i$ is proportional to the temperature of the thermistor.
A6.2 Circuit Design

For a linear output scale, $R_2 = R_3 = 5585 \ \Omega$. For zero current through the meter at $10^\circ C$, $R_1 = 9950 \ \Omega$. A mercury battery ($e = 1.35$ volts) was chosen for its long life and reliability. The value of $R_M + R_S$ is selected to give a full-scale reading (i.e., $i = 25 \mu A$), when the temperature is $35^\circ C$ (i.e., $R_T = 3265 \ \Omega$).

Since

\[ R_M + R_S = \frac{e}{I} \left( R_1 R_3 R_T - R_1 R_T (R_2 + R_3) - R_2 R_3 (R_1 + R_T) \right) \]

(A6.1)

it is found that $R_M + R_S = 9027 \ \Omega$. 

The simulated meter reading as a function of temperature (dashed line) is shown in Figure A6.2. The maximum non-linearity is about 0.2° C. The power dissipated in the various circuit elements is shown in Figure A6.3. The maximum dissipation in the thermistor is about 0.094 milli-watts. Compared to the average heat flux through the disk, this amount of self-heat exerts negligible influence on the meter reading.
Figure A6.2. Output of meter circuit illustrated in Figure A6.1; the broken line is the theoretical performance, and triangles are actual calibration points.
Figure A6.3. Power dissipated in the circuit of Figure A6.1 for the range of thermistor design temperatures
A6.4 Actual Meter Performance

The performance of the read-out circuitry, tested in a water bath with a calibrated thermometer, is shown (triangles) in Figure A6.2. Since we are interested in temperature differences, this amount of non-linearity is not detrimental.
APPENDIX VII

THERMAL CONDUCTIVITY OF A WATER GAP FILLED WITH GLASS WOOL

A7.1 Analysis

Consider the situation where glass wool (conductivity $k_g$) fills a one-dimensional gap. If the space between the wool fibers is occupied with water (conductivity $k_w$), then the effective conductivity of the gap may be defined [60]:

$$\frac{K_{\text{eff}}}{k_w} = \frac{\phi x + 1}{1 - \phi} \quad (A7.1)$$

where $F$ is the volume fraction ratio of the glass and water

$$F = \frac{V_g}{V_w} \quad (A7.2)$$

and $\phi$ and $x$ have the definitions

$$\phi = F \frac{k_g/k_w - 1}{k_g/k_w + x} \quad (A7.3)$$

$$x = \frac{k_g/k_w - 1 - B k_g/k_w}{k_g/k_w - 1 - B} \quad (A7.4)$$

Further, $B$ is defined

$$B = \frac{1}{3} \frac{1}{1 + \frac{M}{2} (k_g/k_w - 1)} + \frac{k_g/k_w - 1}{1 + (1 - M)(k_g/k_w - 1)} \quad (A7.5)$$
where \( M = \frac{(\theta - 0.5 \sin 20^\circ)}{\sin 30^\circ} \) \hspace{1cm} (A7.6)

and \( \theta = \cos^{-1} \frac{a}{b} \) \hspace{1cm} (A7.7)

\( a \) and \( b \) are the short and long dimensions, respectively, of the filler matrix. For this case, glass wool, \( a/b = 0 \). Therefore, \( \theta = \pi/2 \) and \( M = 2.8 \). Equation (A7.1) is plotted as a function of \( V_g/V_w \), the volume fraction and \( k_{g}/k_{w} \) in Figure A7.1.
Figure A7.1. Effective conductivity of a one-dimensional water gap filled with a material (of geometry) similar to glass wool
A7.2 Results

$k_{\text{eff}}/k_w$ is very nearly a linear function of $V_g/k_w$ for the fiber geometry. $V_g/V_w$ may be found in the following manner:

$$\rho_g V_g + \rho_w V_w = \bar{\rho}(V_g + V_w) \quad (A7.5)$$

where $\bar{\rho}$ is the average density of the gap.

However

$$\rho_f (V_g + V_w) = \rho_g V_g \quad (A7.6)$$

where $\rho_f$ is the density of the fluffed wool in air.

Combining (A7.5) and (A7.6)

$$V_g/V_w = \frac{1}{1 + \rho_g/\rho_f} \quad (A7.7)$$

Since $\rho_g \approx 160 \text{ lbm/ft}^3$ and $\rho_f \approx 2 \text{ lbm/ft}^3$

$$V_g/V_w \leq 0.0125$$

From Figure A7.1, the glass wool is seen to have a very small effect on the gap conductivity ($0.987 \leq k_{\text{eff}}/k_w \leq 1$).
APPENDIX VIII

ERROR ANALYSIS FOR UNEQUAL DEVICE RESISTANCE

The following analyzes the error resulting from different device resistances (they are assumed to be equal in prior analysis). Also, consider the devices to be one-dimensional. Since disk cooling is less sensitive than the one-dimensional situation, this analysis finds an upper bound for the real error due to unequal disk resistances.

For $X_6 >> 1$ and $Q_m = 0$, from equation (A1.16),

$$\Delta \theta_s = \frac{T_{s_2} - T_{s_1}}{T_a - T_o} = \frac{1}{1 + \kappa \lambda_1} - \frac{1}{1 + \kappa \lambda_2} \quad (A8.1)$$

where $R_1$ is the thermal resistance in the device cooling tissue with perfusion $\lambda_1$, and $R_2$ is the device resistance cooling tissue with perfusion $\lambda_2$. Let

$$R_1 = \frac{1}{k \sqrt{\lambda_1 \lambda_2}} \quad (A8.2)$$

and

$$R_2 = R_1 \left( 1 + F \right) \quad (A8.3)$$

$R$ is the "optimum" value for these perfusions. $F$ is a fraction (greater than or equal to zero). Substituting (A8.2) and (A8.3) into (A8.1), it can be shown that

$$\Delta T_s = \frac{(1 \pm F) \sqrt{\frac{\lambda_2}{\lambda_1}} - \sqrt{\frac{\lambda_1}{\lambda_2}}}{(1 \pm F)(1 + \sqrt{\frac{\lambda_2}{\lambda_1}}) + 1 + \sqrt{\frac{\lambda_1}{\lambda_2}}} \quad (A8.4)$$

Defining $\Delta T_{s_0}$ as the temperature difference when $F = 0$, i.e., no error,
Figure A8.1. Error (expected minus actual result) for (one-dimensional) local cooling to a 0 °C heat sink as a function of the fractional difference $F$ between two device resistances (which are assumed equal)
\[
(\Delta T_s)_o = \frac{\left\{ \sqrt{\frac{\lambda_2}{\lambda_1}} - \sqrt{\frac{\lambda_1}{\lambda_2}} \right\} (T_a - T_o)}{2 + \sqrt{\lambda_2/\lambda_1} + \sqrt{\lambda_1/\lambda_2}}
\]

(A8.5)

The component of the signal which is error, \(\Delta T_s - (\Delta T_s)_o\), is plotted in Figure A8.1, as a function of \(\lambda_2/\lambda_1\) and \(F\) for \(T_a - T_o = 37^\circ\) C.

From Figure A8.1, it is seen that a 10% error in the device resistance results in (approximately) 1\(^\circ\) C error in the reading \(\Delta T_s\). However, this is the maximum error because \(R_1\) is not always optimum (and the method has, therefore, somewhat less sensitivity).
A9.1 Test Procedure

Before any experiments are run, the gains and offsets of the operational amplifiers for the thermocouples will be adjusted such that the output from the amplifiers is equal (for equal thermocouple temperatures) and such that full scale on the recorder is calibrated with 37°C.

The reference thermocouple junction will be taped to the subject's armpit and covered with cotton wool for thermal insulation; thus the reference will be at or near arterial blood temperature. The two copper blocks will be pre-cooled in icewater until they are at 0°C.

With the subject lying on his back, symmetrical locations on the forehead will be marked with a washable, felt-tipped pen to assist placement of the copper blocks. Just before the blocks are placed, a layer of ekg jelly (or a similar paste), to enhance thermal contact, will be applied to the skin; then the copper blocks will be placed on the marked locations with the strip-chart recorder running.

The weight of the blocks would be enough to ensure equal and uniform pressure. The person running the test must only check to prevent the blocks from slipping. The test should run for five to ten minutes.
A9.2 Interpretation of Results

The ratio of the perfusions can be calculated from the strip-chart tracing in the following manner. At the same time ( = t, greater than two minutes) record \( T_{l} \) and \( T_{r} \) ( \( l \equiv \text{left} \) and \( r \equiv \text{right} \)) and at time \( t' \) (= \( t + \Delta t \)) record \( T'_{l} \) and \( T'_{r} \). Then

\[
\frac{(\text{Blood perfusion})_{\text{left}}}{(\text{Blood perfusion})_{\text{right}}} = \frac{T'_{l} - T_{l}}{T_{r}' - T_{r}} \cdot \frac{T_{r} + T_{r}'}{T_{l} + T_{l}} \quad (A9.1)
\]

where \( T \) is simply the scale reading from the strip-chart recorder. This ratio may be calculated for a number of different time intervals. As \( t \) increases, the ratios calculated should converge to a constant value. However, as time gets large, \( dT/dt \) gets small, so it will become increasingly more difficult to accurately scale off the input numbers into equation (A9.1).

A9.3 Evolution of Experiments

First, normals will be tested on the forehead. Next subjects who are expected to have some head blood flow asymmetry will be tested. From the results of this initial testing, a decision will be made whether or not to design and implement a system for measuring perfusion asymmetries in the corner of the eye depressions. This will involve construction of a "pinching" device which will hold the cooling copper blocks comfortably and securely in place and with equal pressure.
The following tables present the raw data accumulated from tests run at Massachusetts General Hospital (where persons tested are listed by their initials) and at Faulkner Hospital (where identification is by unit number). Table headings, although explained in the text, should be self-explanatory. Three commonly used acronyms are FC (fibrocystic), FCD (fibrocystic disease), and CA (cancer). Irregular, bilateral, and calcifications are sometimes abbreviated to irreg., bilat, and calcif., respectively.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Mass size depth</th>
<th>ΔT</th>
<th>t</th>
<th>M</th>
<th>Diagnosis xerographic</th>
<th>Diagnosis pathologic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[cm] [cm]</td>
<td>[°C]</td>
<td>[min]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A.D.(1)</td>
<td>0.3</td>
<td>10</td>
<td>0.85</td>
<td>bilateral FCD</td>
<td>cystic disease with fibrosis and sclerosing adenosis</td>
<td></td>
</tr>
<tr>
<td>L.K.</td>
<td>3 1</td>
<td>-0.4</td>
<td>10</td>
<td>irreg. non-palpable mass ? of secondary CA</td>
<td>biopsy normal</td>
<td></td>
</tr>
<tr>
<td>L.C.</td>
<td>0.1</td>
<td>10</td>
<td>1.00</td>
<td>FC changes, x-ray occult thickening</td>
<td>biopsy, normal</td>
<td></td>
</tr>
<tr>
<td>G.R.</td>
<td>1.2</td>
<td>10</td>
<td>1.14</td>
<td>FCD, mixed type</td>
<td>clinical follow-up</td>
<td></td>
</tr>
<tr>
<td>B.A.</td>
<td>0.7 0.7</td>
<td>10</td>
<td>1.73</td>
<td>ductal thickening with minimal FCD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E.A.</td>
<td>-0.7</td>
<td>10</td>
<td>irreg. multicystic disease</td>
<td>biopsied, not malignant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M.S.</td>
<td>1 1</td>
<td>-1.8</td>
<td>6</td>
<td>0.95</td>
<td>solitary cyst</td>
<td>clinical follow-up</td>
</tr>
<tr>
<td>B.S.</td>
<td>1.5 2</td>
<td>-4.6</td>
<td>10</td>
<td>0.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S.E.</td>
<td>1 1.5</td>
<td>0</td>
<td>10</td>
<td>irreg.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M.G.</td>
<td>1 0.5</td>
<td>-0.5</td>
<td>8</td>
<td>1.26</td>
<td>benign lesion</td>
<td>foci of sclerosing adenosis</td>
</tr>
<tr>
<td>J.B.</td>
<td>2 1</td>
<td>-0.5</td>
<td>8</td>
<td>1.07</td>
<td>benign cyst or adenoma</td>
<td>fibroadenoma</td>
</tr>
<tr>
<td>V.W.</td>
<td>2 0.2</td>
<td>+2.1</td>
<td>10</td>
<td>5.40</td>
<td>abcess</td>
<td>chronic inflammation</td>
</tr>
<tr>
<td>H.B.</td>
<td>+2.6</td>
<td>9</td>
<td>2.00</td>
<td>axillary tail</td>
<td>clinical follow-up</td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>---------------</td>
<td>----------------</td>
<td>-----------</td>
<td>--------</td>
<td>---</td>
<td>---------------------</td>
</tr>
<tr>
<td>G.S.</td>
<td>2</td>
<td>1</td>
<td>+1.9</td>
<td>10</td>
<td>0.82</td>
<td>probable cancer</td>
</tr>
<tr>
<td>M.R.</td>
<td>2</td>
<td>1</td>
<td>+5.1</td>
<td>10</td>
<td>1.97</td>
<td>obvious cancer</td>
</tr>
<tr>
<td>L.M.</td>
<td>4</td>
<td>2</td>
<td>+2.9</td>
<td>10</td>
<td>1.05</td>
<td>probable cancer</td>
</tr>
<tr>
<td>A.W.</td>
<td>2</td>
<td>3</td>
<td>+0.8</td>
<td>10</td>
<td>irreg.</td>
<td>&quot;</td>
</tr>
<tr>
<td>R.G.(1)</td>
<td>3.5</td>
<td>1.5</td>
<td>+0.5</td>
<td>10</td>
<td>1.84</td>
<td>&quot;</td>
</tr>
<tr>
<td>R.G.(2)</td>
<td>1.5</td>
<td>2</td>
<td>+0.3</td>
<td>10</td>
<td>0.94</td>
<td>&quot;</td>
</tr>
<tr>
<td>A.D.(2)</td>
<td>1</td>
<td>3</td>
<td>+1.4</td>
<td>10</td>
<td>1.55</td>
<td>obvious cancer</td>
</tr>
<tr>
<td>R.P.</td>
<td>1.5</td>
<td>2</td>
<td>+0.7</td>
<td>8</td>
<td>5.95</td>
<td>classical cancer</td>
</tr>
<tr>
<td>C.J.</td>
<td>3</td>
<td>2</td>
<td>+0.9</td>
<td>10</td>
<td>1.35</td>
<td>probable cancer</td>
</tr>
<tr>
<td>C.M.</td>
<td>2</td>
<td>3</td>
<td>+0.5</td>
<td>6</td>
<td>2.45</td>
<td>&quot;</td>
</tr>
<tr>
<td>E.S.</td>
<td>2</td>
<td>2</td>
<td>+0.7</td>
<td>10</td>
<td>1.91</td>
<td>solitary cyst</td>
</tr>
<tr>
<td>A.C.</td>
<td>1.5</td>
<td>2</td>
<td>+0.4</td>
<td>10</td>
<td>1.17</td>
<td>probable cancer</td>
</tr>
<tr>
<td>McQ.</td>
<td>1.5</td>
<td>2</td>
<td>+0.7</td>
<td>10</td>
<td>1.30</td>
<td>&quot;</td>
</tr>
<tr>
<td>C.P.</td>
<td>0.6</td>
<td></td>
<td></td>
<td>10</td>
<td>1.08</td>
<td>&quot;</td>
</tr>
<tr>
<td>Patient</td>
<td>Mass size [cm]</td>
<td>Depth [cm]</td>
<td>$\Delta T$ [°C]</td>
<td>$t$ [min]</td>
<td>Mxerographic</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>---------</td>
<td>---------------</td>
<td>------------</td>
<td>-----------------</td>
<td>----------</td>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>J.S.</td>
<td>2.5</td>
<td>2</td>
<td>2.4</td>
<td>10</td>
<td>1.50</td>
<td>bilateral cysts</td>
</tr>
<tr>
<td>L.T.</td>
<td>1.5</td>
<td>1.5</td>
<td>+0.1</td>
<td>10</td>
<td>irreg. ? of cancer</td>
<td>proven by biopsy</td>
</tr>
<tr>
<td>E.B.</td>
<td>1</td>
<td>1</td>
<td>-0.3</td>
<td>10</td>
<td>1.22</td>
<td>solitary cyst</td>
</tr>
<tr>
<td>L.W.</td>
<td>2</td>
<td>2</td>
<td>+0.8</td>
<td>10</td>
<td>1.40</td>
<td>? of cancer</td>
</tr>
<tr>
<td>K.W.</td>
<td>1.5</td>
<td>2</td>
<td>+1.5</td>
<td>10</td>
<td>1.67</td>
<td>? of cancer</td>
</tr>
<tr>
<td>K.L.</td>
<td>1.5</td>
<td>1.5</td>
<td>+1.2</td>
<td>10</td>
<td>irreg. ? of cancer</td>
<td>&quot;</td>
</tr>
<tr>
<td>R.H.</td>
<td>1</td>
<td>1</td>
<td>-0.2</td>
<td>10</td>
<td>0.75</td>
<td>benign cyst</td>
</tr>
<tr>
<td>R.W.</td>
<td>2</td>
<td>0.5</td>
<td>0</td>
<td>10</td>
<td>1.00</td>
<td>lypoma</td>
</tr>
<tr>
<td>K.D.</td>
<td>3</td>
<td>1</td>
<td>+0.4</td>
<td>10</td>
<td>1.70</td>
<td>? of cancer</td>
</tr>
<tr>
<td>A.D.(3)</td>
<td>2</td>
<td>1</td>
<td>-1.3</td>
<td>10</td>
<td>0.67</td>
<td>solitary cyst</td>
</tr>
<tr>
<td>J.R.</td>
<td>1</td>
<td>1.5</td>
<td>+2.0</td>
<td>10</td>
<td>1.46</td>
<td>probable cancer</td>
</tr>
<tr>
<td>L.U.</td>
<td>1</td>
<td>1</td>
<td>+1.5</td>
<td>10</td>
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clinical follow-up
proven by biopsy

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<td>proven by biopsy</td>
</tr>
<tr>
<td>28-32</td>
<td>2 2</td>
<td>-0.6 1.13</td>
<td>+0.7</td>
<td>obvious cancer</td>
<td>same</td>
<td>proven by biopsy</td>
</tr>
<tr>
<td>28-35</td>
<td>1.5 1</td>
<td>-1.2 0.94</td>
<td>+0.7</td>
<td>? of cancer</td>
<td>same</td>
<td>FCD</td>
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<tr>
<td>28-45</td>
<td>1.5 1</td>
<td>-0.6 1.00</td>
<td>+0.5</td>
<td>mild FC changes</td>
<td>normal</td>
<td>clinical follow-up</td>
</tr>
<tr>
<td>28-52</td>
<td>1.5 1</td>
<td>+0.3 1.18</td>
<td>normal</td>
<td>? of cancer</td>
<td>same</td>
<td>ductal hyperplasia</td>
</tr>
<tr>
<td>28-70</td>
<td>1 1</td>
<td>+2.6 1.34</td>
<td>+1.0</td>
<td>small density</td>
<td>fibroadenoma</td>
<td>abcess</td>
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<tr>
<td>28-78</td>
<td>2.5 1</td>
<td>+0.7 1.53</td>
<td>halo around nipple</td>
<td>large mass</td>
<td>? of cancer</td>
<td>proven by biopsy</td>
</tr>
<tr>
<td>29-47</td>
<td>1.03</td>
<td>+0.6</td>
<td>+1.0</td>
<td>cystic changes</td>
<td>bilat. FCD</td>
<td>6 months follow-up</td>
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<tr>
<td>29-67</td>
<td>0195</td>
<td>-0.6</td>
<td>+0.2</td>
<td>punctate calcif. cancer (no mssss)</td>
<td>cancer</td>
<td>proven by biopsy</td>
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