Abstract

The applications of mathematical simulations of tissue temperature distributions in hyperthermia treatments are discussed in terms of four areas, comparative, prospective, concurrent, and retrospective thermal dosimetry. These four aspects of thermal dosimetry cover the range of hyperthermia applications of interest to clinicians, from comparative evaluation of competitive heating modalities to individual treatment planning, through feedback control during a treatment and, finally, to posttreatment therapy evaluation. Mathematical simulations of hyperthermia treatments can play a significant role in each of these areas.

Introduction

Computerized simulations of hyperthermia treatments are beginning to demonstrate their value in clinical situations. This is occurring in all of the traditional manners in which mathematical models are known to be generally useful: (a) invoking mathematical rigor and precision in the formulation and evaluation of problems; (b) providing a theoretical framework which can be used to substantiate, evaluate, and interpret experimental results; (c) allowing extensive parametric studies to be performed quickly and inexpensively so that sensitive (and insensitive) parameters can be identified, systems can be evaluated, and critical experiments can be identified; (d) giving the ability to predict, \textit{a priori}, the outcome of proposed experiments or treatments (in terms of temperature distributions for the hyperthermia applications); and (e) extending the capabilities of available instrumentation by predicting the values of quantities which are difficult or impossible to measure. Examples of these applications are present in the hyperthermia modeling literature, which has been summarized and discussed in several review articles (4, 16, 20, 28–30, 53), most recently by Stroehbuh and Roemer (52).

For hyperthermia, the applications of biothermal simulations can be divided under 4 main headings (8, 9, 46), which can be thought of as progressing in time through a patient treatment: comparative, prospective, concurrent, and retrospective thermal dosimetry. The goal of comparative thermal dosimetry is to compare the abilities of different heating modalities and configurations to properly heat general classes of patients and tumors. Such calculations can be done using standardized patient models which contain only the most significant anatomical and physiological features of "typical" patients and the major characteristics of the power deposition patterns. Conversely, in prospective thermal dosimetry (individual patient treatment planning), detailed information is needed regarding the particular patient's anatomy and expected blood perfusion responses so that detailed power deposition patterns can be calculated and used to determine a complete temperature distribution for that patient. The goal of such simulations is to optimize the proposed thermal treatment by maximizing the therapeutic effects of the tumor temperature distribution while minimizing normal tissue damage and patient stress. Concurrent thermal dosimetry (feedback control during a treatment) involves calculating complete temperature fields during a treatment and adjusting power deposition parameters (and other variable quantities) to optimize the actual treatments. In present applications, measured temperatures at discrete locations are controlled, while the goal of future treatments is to evaluate and control the complete temperature field. Retrospective thermal dosimetry (posttreatment evaluation of a completed therapy) has as its goal the calculation of the complete temperature field (and thermal dose) that was attained during the treatment, based on knowledge of temperatures at the measurement locations. Such data are needed for meaningful clinical evaluations of the equipment’s performance and of the heating protocol utilized during the treatment, as well as for determining the efficacy of the hyperthermia treatment. These 4 thermal dosimetry areas will be discussed in detail after general discussion of the methods used to mathematically predict the tissue temperatures.

Methods

To mathematically predict tissue temperature distributions during hyperthermia treatments, the general procedure followed is as shown in Chart 1. Required knowledge includes: anatomical boundaries of tumor and normal tissues; tissue properties (both thermal properties, such as thermal conductivity ($k$), density ($\rho$), and specific heat ($c$), and properties needed for calculating power deposition patterns, such as permittivity ($\varepsilon$) and conductivity ($\sigma$) for EM problems and the attenuation ($\alpha$) and absorptivity ($\omega$) coefficients for ultrasound problems); environmental boundary conditions for the thermal problem (heat transfer coefficient ($h$) and environmental temperature ($T_e$)); and the physiological response characteristics of the normal and tumor tissues [metabolism ($Q_m$) and blood perfusion ($W$)]. Given this information, the power deposition ($Q_p$) in the tissue can be determined using a mathematical model of the power deposition physics; various models are appropriate, depending on the type of power deposition method (e.g., see Ref. 51). The sum total of this information allows one to calculate the temperature distribution in the tissues. Traditionally, this has been done using the general form of the bioheat transfer equation originally developed by Pennes (44):

$$\nabla \cdot (k \nabla T) + W c_p(T - T_a) + \rho c \frac{dT}{dt} = Q_p + Q_m \tag{A}
$$

in which knowledge of the arterial blood temperature ($T_a$) is required. In situations for which the physiological responses (blood perfusion and metabolism) are temperature dependent (i.e., $W = W(f, T)$ and $Q_m = Q_m(f, T)$), Equation A should be solved using these relationships for blood perfusion and metabolism, if they are known. Similar procedures are required if the tissue properties vary significantly with temperature or if the arterial blood temperature is varying; in the latter case, a whole-body temperature regulatory system model might be appropriate.
The bioheat transfer equation itself is clearly an approximation to the heat transfer processes in the tissues, as can be appreciated by reading the work of Pennes (44), which is intended to predict the general characteristics of temperature distributions over "large distances" in the body. From a more fundamental thermal viewpoint, tissue can be thought of as a stationary solid/liquid tissue matrix (i.e., the extravascular space consisting of the cellular structures and the interstitial fluids) through which the vascular tubes are interposed. Fundamental conservation of energy principles would then give separate equations for the stationary tissue matrix in which no velocities exist (neglecting the small velocities associated with lymph movement and plasma filtration in the extravascular space),

$$-\nabla \cdot (k \nabla T) + \frac{\partial T}{\partial t} = Q_p + Q_m$$  \hspace{1cm} (B)

and for the moving blood inside the vasculature,

$$-k_b \nabla^2 T_b + \rho_b \frac{\partial T_b}{\partial t} + \rho \nabla \cdot \mathbf{U}_b \cdot \nabla T = Q_p$$  \hspace{1cm} (C)

where $\mathbf{U}_b(t, t)$ is the blood velocity. To solve this set of coupled equations (including the matching boundary conditions of the tissue/blood interfaces) is a formidable task. To solve them exactly, one would need to have: (a) a complete description of the anatomy of all of the vascular components in the region of interest (i.e., knowledge of the diameters, lengths, and positions of all of the arteries, arterioles, capillaries, venules, and veins); and (b) a complete description of the velocity field—$\mathbf{U}_b(t, t)$—within each such vessel. This requires a considerable amount of information which is unavailable at present, and even if it were known, the computational task would be monumental. The accomplishment of such
a task is even more difficult when one reflects on the types of tube-flow situations for which complete analytical solutions are available in the engineering literature. These are available primarily for laminar flow of simple fluids in regular, geometric channels (e.g., circular tubes). For the case of pulsatile flow of two-phase blood (solid and liquid components) in flexible tubes, the difficulties can easily be sensed. This situation is analogous to turbulent flow problems in engineering, for which a complete velocity profile is not known and various approximations are used. Thus, some approximation is clearly needed in the bioheat transfer calculations. Pennes compressed all of the perfusion information into the single blood perfusion term \( w_0(T - T_\text{b}) \), where, in general, \( w = w(f, T) \) and \( T_\text{b} = T_{\text{b}}(f, t) \). Pennes checked the validity of this approximation by comparing the temperatures predicted by the equation to experimentally measured temperatures in the human forearm. In his approach, the blood perfusion term \( (W) \) in equation (A) was adjusted until the predicted temperatures agreed well with the measured temperatures. Since the perfusion values \( (W) \) which are needed to get good agreement between the predicted and measured temperatures agreed well with known perfusion magnitudes \( (\text{ml/100 g/min}) \) for muscle tissues, Pennes considered that his model was a good approximation to the actual thermal processes present in the tissue. This general process (of adjusting \( W \) and, sometimes, \( T_\text{b} \) until predicted and measured temperatures agree “well”) has been followed by several investigators to model experimental results. The most complete such study was recently reported by Sekins et al. (49) for a 2-dimensional model of a microwave-heated thigh (Chart 2). In their results, blood perfusion was modeled as a function of temperature, so that during the initial power-on transient, the blood perfusion varied with time. Their results (Chart 3) showed that not only did the temperatures agree well, but the predicted perfusion values agreed well with measured perfusion values (xenon clearance). While such studies illustrate that, in some situations, the thermal processes inside tissues can be well represented by the bioheat transfer equation, for reasons of both physical consistency in the equation and practical considerations in hyperthermia, various investigators have proposed extensions of or alternative formulations to the bioheat transfer equation (see Refs. 11, 31, and 54 for recent proposals). From the practical point of view in hyperthermia, the main question is: Are there any extremes of temperature (i.e., low tumor temperatures, which would indicate that an inadequate treatment was occurring, or high normal tissue temperatures, indicating that tissue damage was occurring) that are not predicted by the bioheat transfer equation? While this is a difficult question to answer in general, there is one anatomical feature which is not included in the bioheat transfer equation which could cause low tumor temperatures in many situations—the possible presence of “large” blood vessels containing relatively cool blood that is reducing temperatures in the adjacent tumor tissue. This problem (the effect of the presence of large vessels) has been modeled by Chato (10) for general applications and, more recently, by Lagendijk (34) and Lagendijk et al. (35) for hyperthermia applications. It is also possible to approximate the presence of such vessels using the bioheat transfer equation by raising \( W \) to large values in locations where such vessels occur.

**Comparative Thermal Dosimetry**

The purpose of comparative thermal dosimetry is to determine which power deposition modalities (or configurations for a given modality) are most appropriate for heating certain classes of tumors. This is a general question, which is not restricted to the analysis of which modality or configuration to use for a particular patient. Instead, a broader question is asked, which is concerned with how different heating modalities and configurations compare in their abilities to properly heat general classes of tumors (e.g., deep versus superficial) in various anatomical locations and for general classes of patients (e.g., thin versus obese).

The overall approach (Chart 1) is to determine the power deposition patterns of the various heating systems with respect to the region of interest and then use this information in a numerical model of the bioheat transfer equation to calculate the resulting temperature distributions. Since we are interested in general situations, typical standardized values of tissue properties can be used, as can idealized anatomical models of “average” patients. Only (a) the nature of the thermal model of the tumor, which is highly dependent upon blood flow conditions, and (b) the characteristics of the perfusion response of normal tissues to temperature (see Chart 1) remain significant unknowns. Nevertheless, these can be treated systematically as well, as will be discussed below, again using standardized tumor and patient models.

The first task is to determine the power deposition distribution. Guy (23) introduced the use of tissue-equivalent electromagnetic phantoms, along with thermography, to study these distributions experimentally. Simple homogeneous or layered phantoms can be used to verify the theoretical principles of the power deposition patterns and to compare one instrument against another, while more complicated phantoms (38, 40, 49) using realistic dimensions and anatomical features can be used to study the effect of heterogeneities on the power deposition field. With
proper registration, the SAR distribution, as determined experimentally, can be superimposed on a thermal model of the tissues, and the temperature patterns can be computed (21).

Similarly, the SAR distributions can be computed, analytically in some geometrically simple cases and numerically in general. Examples of these calculations have been performed for magnetic induction, capacitive induction, phased-array electromagnetic induction, interstitial current fields, interstitial microwaves, ferromagnetic implants, and ultrasound (see Refs. 51 and 52 for current reviews).

In order to compare the abilities of different heating modalities to properly heat various classes of tumors, a standardized method of comparison is needed. That is, a standardized criterion for adequate heating must be established in order to properly evaluate the capabilities of a given method. We have developed one such criterion (the acceptable power band approach) and applied it to several different heating modalities (24, 25, 39).

This technique uses the range of absorbed power values that give proper tumor and normal tissue temperatures as the measure of success in heating a tumor. An acceptable temperature distribution is defined by the following criteria, as outlined in our latest modification: (a) In a successful clinical treatment, the coldest part of the tumor must be above some minimum acceptable temperature \( T_{\text{min, acc}} \) for an effective treatment to have occurred. This condition is consistent with the basic definition of “hyperthermia” and is borne out in clinical results for both spontaneous animal treatments (17, 18) and human clinical trials (42). (b) There exists a maximum tumor temperature \( T_{\text{max, acc}} \) that a clinician will not exceed in practice because of concern over possible damage to adjacent normal tissue, especially given the limited information obtainable from presently available thermometry, and over possible complications resulting from rapid tissue necrosis that can result in infection-prone voids. (c) Finally, there are limiting maximum temperatures for normal tissues above which normal tissue damage occurs (3, 36). To explain the application of these criteria, consider Chart 4, which is an idealized curve for a given tumor in a fixed location with all normal and tumor blood perfusions constant, with the tumor being heated by a fixed modality. The only independent variable is the magnitude of the applied power. As that magnitude is increased, temperatures everywhere in the region where power deposition occurs increase. Chart 4 shows the percentage of the tumor volume that is at temperatures between the minimum acceptable value \( T_{\text{min, acc}} \) and the maximum acceptable value \( T_{\text{max, acc}} \) versus the power absorbed in the tumor. At very low power values, the tumor remains cold throughout, and the percentage of the tumor between \( T_{\text{min, acc}} \) and \( T_{\text{max, acc}} \) is zero. As the magnitude of the power is increased, temperatures in the hottest portions of the tumor begin to rise above \( T_{\text{min, acc}} \) and the above percentage becomes finite. As power is increased further, a higher percentage of the tumor rises to acceptable temperatures until, at some power \( Q_{\text{acc}} \), 50% of the tumor is between \( T_{\text{min, acc}} \) and \( T_{\text{max, acc}} \). Increasing power to \( Q_{\text{acc}} \), a situation is reached in which 100% of the tumor is within the acceptable temperature range. This is the specified condition for a proper treatment. As power is increased even further, the overall temperatures still increase, and the tumor temperatures (although rising) still stay between \( T_{\text{min, acc}} \) and \( T_{\text{max, acc}} \). Eventually, a power is reached \( Q_{\text{acc}, \text{ tum}} \) beyond which the hottest portions of the tumor exceed \( T_{\text{max, acc}} \) and, thus, the percentage of the tumor volume between \( T_{\text{min, acc}} \) and \( T_{\text{max, acc}} \) decreases. For the situation shown in Chart 4, the range of powers that give acceptable tumor heatings for 100% of the tumor is

\[
\Delta Q_{\text{acc}} = Q_{\text{acc}, \text{ tum}} - Q_{\text{acc}}
\]

This quantity \( \Delta Q_{\text{acc}} \) is used as the measure of success in heating a tumor (the acceptable power range).

Note that, for some situations, those in which a very wide range of temperatures exists in a tumor, no condition may be reached where \( \Delta Q_{\text{acc}} \) is greater than zero. That is, before the coldest portion of the tumor has reached \( T_{\text{min, acc}} \), the hottest portion has exceeded \( T_{\text{max, acc}} \). Then, since \( Q_{\text{acc}, \text{ tum}} < Q_{\text{acc}, \text{ tum}} \), we have \( \Delta Q_{\text{acc}} = 0 \). In such cases, the tumor being simulated cannot be properly heated by the power deposition pattern being analyzed. In such circumstances, it may become appropriate to analyze the ability of the power deposition system to properly heat smaller portions of the tumor, say, 50%, by the measure

\[
\Delta Q_{\text{acc}} = Q_{\text{max, tum}} - Q_{\text{max, acc}}
\]

Furthermore, normal tissue-limiting temperatures can affect the size of the acceptable power range \( \Delta Q_{\text{acc}} \) that yields a proper range of tumor temperatures; i.e., as power is increased in the foregoing manner, the normal tissue temperatures are, in general, increasing also. Thus, at some power value, the limiting temperature in a normal tissue region may be exceeded. For example, if the maximum acceptable power is limited by excessive temperatures in the visceral tissue, then this power is denoted by \( Q_{\text{acc, vs}} \). Similar limits on the power deposition are denoted by \( Q_{\text{max, mus}}, Q_{\text{max, fat}}, \) and \( Q_{\text{max, sk}} \) for the muscle, fat, and skin regions. Thus, in general, if the temperatures in region \( i \) limit the amount of power that can be applied, then this power value is denoted by \( Q_{\text{acc, i}} \). If a normal tissue-limiting condition is reached before the hottest portion of the tumor exceeds the maximum allowable temperature \( i.e., Q_{\text{max, i}} < Q_{\text{max, tum}} \), then the size of the acceptable power range is given by

\[
\Delta Q_{\text{acc, i}} = Q_{\text{max, i}} - Q_{\text{min, acc}}
\]

For our studies, the normal tissue-limiting temperatures were...
taken as 44° for the skin, fat, and muscle regions and 42° for the viscera region (3, 36), while $T_{\text{min, soc}}$ and $T_{\text{max, soc}}$ were set at 42° and 60°, respectively. Since the exact boundaries of a tumor will probably be irregular and will not be known exactly, some normal tissue adjacent to a tumor will generally be heated along with the tumor in clinical situations. Thus, a 1-cm band of normal tissue surrounding the tumor was allowed to exceed the above normal tissue limiting conditions in our latest application. Note that, in general, the size of the acceptable power range is given by

$$ΔQ^{100}_{\text{soc}} = Q_{\text{max, soc}} - Q_{\text{min, soc}}$$  \hspace{1cm} (G)$$

where $Q_{\text{max, soc}}$ is given by either $Q_{\text{max, tum}}$ or $Q_{\text{max, i}}$ (where $i$ can represent any of the normal tissues), depending on the particular situation.

The results of such an analysis are given in terms of the acceptable power range ($ΔQ^{100}_{\text{soc}}$), which is plotted in terms of the average power absorbed in the tumor (watts/cu cm). To obtain the range of powers absorbed in the tumor (in watts) that gives acceptable temperature distributions, one needs to multiply the given results (watts/cu cm) by the tumor volume. Furthermore, for any given power deposition device (and configuration), there is a proportional relationship between the power absorbed in the tumor and the total power applied to the patient. Thus, if one knows this proportionality factor, the results given could be converted to values observed on a power meter. That is, the range of powers given by $ΔQ^{100}_{\text{soc}}$ can be thought of as proportional to the range of power meter readings which will properly heat a tumor. These values range from the lowest applied power that will raise the coolest part of the tumor to an acceptable temperature (i.e., the power $Q_{\text{min, soc}}$), to the maximum applied power which does not cause excessive normal (or tumor) tissue temperatures (i.e., $Q_{\text{max, soc}}$). The above approach to obtain $ΔQ^{100}_{\text{soc}}$ is a formalized version of the steps used by clinicians in heating tumors or in attempting to heat tumors. That is, after a heating modality is set up to treat a patient, power is applied, and the temperatures are noted. The power amplitude is then increased until an acceptable temperature distribution is reached, if it can be, which is often not possible given the current limitations on power deposition equipment. In an aggressive therapy, the power amplitude would be increased until a limiting condition was reached, thus yielding an experimental value for $ΔQ^{100}_{\text{soc}}$ for that clinical situation (tumor, patient, and heating modality and configuration). This general process is what is being simulated in the determination of $ΔQ^{100}_{\text{soc}}$.

The use of a computer to calculate the temperature profiles and thus determine the acceptability (or unacceptability) of a heating method depends upon the existence of a thermal model of a tumor. Since tumors can have a range of properties and blood flows, the designation of a single general model is impossible. However, it is possible to conceive of a tumor perfusion model that is easy to heat by a given modality, i.e., that gives a large $ΔQ^{100}_{\text{soc}}$. Similarly, it is possible to conceive of a tumor model that has perfusion characteristics that make it difficult to heat by that modality, i.e., that gives $ΔQ^{100}_{\text{soc}} = 0$, or low values. Thus, we can possibly construct limiting case tumor perfusion models that bracket the characteristics of a real tumor. For many situations, the uniform blood flow model shown in Chart 5 represents an easy-to-heat perfusion pattern, and the annular blood flow model is a hard-to-heat perfusion pattern. To verify the validity of this concept, we generated many tumor models in which the blood flow pattern was set randomly by computer. Except in a few cases in which extreme blood flow patterns resulted, the results of the heating as characterized by the $ΔQ^{100}_{\text{soc}}$ parameter were intermediate between the limiting case models of uniform blood flow and annular blood flow, which indicates that these 2 tumor perfusion patterns can be used as limiting or bracketing case models between which the results for most other tumor perfusion patterns will lie.

As an example of applying the acceptable power range method, Chart 6 shows the temperature pattern to be expected from uniform power deposition in the pelvis with an annular blood flow tumor perfusion model (25). Similarly, Chart 7 shows the temperature pattern to be expected from magnetic induction heating with concentric coils at 13.56 MHz for the same exact case. The results of acceptable power band analyses of these 2 heating modalities are given in Charts 8 and 9, which show the size of the acceptable power band (in terms of total absorbed power; given by the magnitude of the vertical bars) for 3 tumor sizes and 3 normal tissue perfusion magnitudes for the annular tumor perfusion model. The results are shown for the tumor located in the 5 positions shown in Chart 10. From these results, the 2 power deposition patterns can be compared in terms of their relative abilities to properly heat tumors.

In terms of the predictive value of such general models, the validity of this approach is becoming apparent clinically as well. For example, large necrotic tumors often have very nonuniform temperatures. If temperatures are measured at only a few points, the therapist may feel that successful heating was achieved and may even observe rapid regression of the tumor. Nevertheless, the likelihood of a long duration of response is small if low tumor temperatures are present elsewhere in the tumor. The general trends predicted by the above model of the concentric coil apparatus (inability to properly heat deep-seated pelvic and abdominal tumors because of low tumor temperatures and high normal muscle and fat tissue temperatures) have also been predicted by another set of simulations for these general tumor models.

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Bioheat Transfer Simulations in Hyperthermia

Chart 6. Predicted temperature distribution for an annular blood flow tumor model located just off the body axis and heated by a method that gives uniform power deposition. Curves a, b, and c, normal tissue, blood perfusion of 1.0, 2.5, and 5.0 kg/cu m/sec, respectively. PR, peripheral region; IR, intermediate region; NC, necrotic core. Reproduced from Ref. 25 by permission of Pergamon Press, Ltd.

Types (50). The general simulation predictions have also been borne out by clinical trials (41). Additionally, Gibbs (22) and Oleson (5) have compared directly temperatures measured along radial paths from the deepest aspects of tumors to the surface for cases which have been heated both with concentric magnetic induction and with a method of relatively uniform power deposition (BSD Annular Phased Array). Chart 11 gives one example and shows that the temperature patterns are consistent with the general characteristics of the models. Also, the range of powers needed to acceptably heat tumors using ferromagnetic seeds, as predicted by this modeling approach (39), is consistent with clinical results in animal head and neck tumors.7 It is of interest to note that the above simulation predictions were performed before the clinical data were available. Thus, even though the simple thermal models used had many limitations, they were still capable of predicting the general clinical results obtained.

Prospective Thermal Dosimetry

Once a comparative evaluation is completed and a heating modality is chosen for a particular patient, we become interested in individual treatment planning. The concepts remain the same as in the previous category, except that now we require the characteristics to be specifically those of the patient rather than those for generalized, typical models. Parametric analysis is used for tailoring the treatment to the patient rather than for elucidating the sensitivity of the model to errors or for comparing the general features of various modalities.

The first task is to locate the tumor and the general anatomical features of the surrounding normal tissues through use of CT...
scans or other imaging techniques. Typical values from the literature can be assigned to the normal tissues. Properties of tumor tissues can be estimated based upon any information that might be available on its constituents, such as the concentration of water or lipids. The power deposition pattern then must be determined for the region to be treated. Detailed phantoms based upon the CT scans can be constructed, and the SAR can be determined by using the thermographic technique of Guy (23) discussed previously. Alternatively, the SAR distribution can be computed numerically for the individual patient. This has been done for high-frequency heating using both capacitive and magnetic induction by Armitage et al. (2), for magnetic induction by Hill et al. (26), and for the BSD annular phased array by Iskander et al. (27). Additionally, Arcangeli et al. (1) have used optimization techniques to refine the heating patterns from an array of applicators at 915 MHz.

In treatment planning, the actual blood flow in the normal tissues, as well as in the tumor, that will be present during the treatment is still a significant unknown, so it is presently impossible to compute the isotherms that will result. Nevertheless, it might be possible to use the bracketing case tumor model concept and hence establish if the heating technique in question has a reasonable chance of producing an acceptable heating of the tumor. Initially, both the uniform blood flow model and the annular blood flow model could be used to represent the tumor. If additional information is available on the location of major vessels, it could be incorporated into the models as well. If the computer simulation indicates that the most difficult-to-heat tumor perfusion model can be heated acceptably, then it is probable that the method will work on a real tumor located similarly in the patient. Conversely, if the easiest-to-heat tumor perfusion model cannot be heated by the method, then it is unlikely that the method would work in a real case. Of course, if the results of the model computations are mixed, then either further development of the models is necessary or the physician and physicist together must exercise their judgment as to the level of risk. While definite answers cannot be given as in radiation dosimetry, at least some basis for judgment is provided. [As an aside, it should be noted that this difference with radiation treatment planning arises directly from the lack of knowledge of what the

Chart 9. Results for concentric coil magnetic induction heating for the annular tumor perfusion model. ML, muscle temperature limited; FL, fat temperature limited; VL, visceral temperature. Reproduced from Ref. 24 by permission of Pergamon Press, Ltd.

Chart 10. A, schematic diagram of pelvic model. Positions 1 through 5 are the tumor locations used. Reproduced from Ref. 24 by permission of Pergamon Press, Ltd. B, annular tumor perfusion model. Three regions are assumed: necrotic core where \( W = 0 \), an intermediate region with \( W = W_0/2 \), and a highly perfused periphery with \( W = W_0 \). \( W_0 \) is the normal tissue perfusion rate. Reproduced from Ref. 25 by permission of Pergamon Press, Ltd.

Chart 11. Temperature distribution measured in a patient with a large broncho- genic carcinoma heated by 3 different methods: C-coil, a concentrically aligned magnetic induction coil (Magnetrode); APAS, the BSD annular phased array; and H-coil, a coaxially aligned pair of coils arranged with one anterior and one posterior to the patient. The latter method is not discussed here.
patient’s blood perfusion will be during the treatment. In hyperthermia, the power delivered (analogous to the radiation delivered) can be determined, in principle, before the treatment. However, the efficacy of hyperthermia resides not on the power delivered, but on the temperatures reached, which are a result of the net differences between power delivered and power removed.

From calculations such as these, it will eventually be possible to optimize the treatment protocol prior to therapy so that the patient is likely to receive maximum benefit at minimal risk. One additional feature of this approach is that the models should be able to indicate the places where thermometer probes need to be placed in order to properly monitor the treatment procedure. The risk of not measuring at points of high temperature in normal tissues or in cool locations within the tumor, such as near a major vessel, will be reduced. It is clear that advances in the area of prospective thermal dosimetry will require development of the ability to be able to predict (before a hyperthermia treatment) what each patient’s tissue perfusion will be during the treatment.

**Concurrent Thermal Dosimetry**

Concurrent thermal dosimetry represents the monitoring and control of temperatures during the actual treatment. We presume that, for some time to come, noninvasive tomographic thermometry will not be feasible. A real difficulty to be faced by any such noninvasive technique is the necessity of adequate space around the patient to have sophisticated multiperture-heating equipment, as well as temperature-monitoring equipment. In addition, the noise rejection requirements on any tomographic thermometry system will be extremely high if it is to perform in the presence of intense heating fields. Thus, temperatures must be monitored with invasive probes, resulting in the basic question of concurrent thermal dosimetry: How can one control the complete temperature field based on measurements at a finite number of points?

The general principles of thermometry as they relate to hyperthermia have been reviewed in a number of references (e.g., Refs. 5 to 7, 14, 15, and 32). An excellent compilation of recent advances in thermometry is given in Ref. 48. Measurements in intense electromagnetic or ultrasonic heating fields require special considerations to avoid serious errors, although the former is, in general, more difficult than the latter. The problem which we address here is related to the need to sample many places using invasive methods in order to characterize the complete thermal field. Since patients cannot be expected to tolerate more than a few interstitial probes, it becomes necessary to sample several points along a track. Two methods have been used in recent years. The first is to use pull-back techniques within a catheter. This is convenient, and once a steady state is reached, it can be performed manually with simple probes and a readout instrument. Significant errors can occur with this technique, especially in the presence of steep gradients. Presumably, with proper thermal contact media introduced into the catheter, this can be minimized. Alternatively, multiple-sensor probes are being used in a number of places. These are extremely helpful, in that their location can be determined precisely and they remain fixed throughout the treatment. An automated system is required to monitor the large number of sensors that can be used in such a system.

Proper thermal monitoring and control in the clinic thus should be configured as in Chart 12. Multiple-sensor probes should be placed within the region to be heated, along with single-sensor probes to monitor other specified points such as core temperatures or critical points within the field. Placement of the probes under CT or other diagnostic scanning devices will help both in ensuring that the probe is in the desired location and in assisting in the later analysis of the data. To properly control the complete temperature field, boundary condition information will need to be determined accurately (e.g., see Ref. 49).

Control of hyperthermia treatments in most centers to date consists of simple gain control of power by reference to a single temperature sensor. Lee et al. (37) recently described a multiple-array configuration of interstitial microwave antenna with 4 independent amplifiers controlled by 4 sensors. Also, Samaras (47) recently described a modified PID controller applied to intracranial microwave hyperthermia. A more general approach would be to use many sensors to control the amplitude and phase of several applicators in order to achieve dynamic control of the power deposition field. Arcangeli et al. (1) have described the use of phase and amplitude optimization methods to arrive at a configuration of 915-MHz applicators for heating a lesion on the thoracic wall. While their paper is more properly part of the previous 2 aspects of thermal dosimetry, it suggests the power and versatility possible if an analogous optimization were carried out under real-time computer control of the heating apparatus. The ultimate goal is thus to be able to control the complete

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**Chart 12.** System diagram indicating the characteristics required for a computerized data acquisition and control system for hyperthermia therapy which is coupled to a larger mainframe computer for data analysis and data base management (from Ref. 9).
temperature fields in an optimal manner. To do this, mathematical models of the treatment process are needed, as are advanced control algorithms. These latter approaches will first include multi-input/output programs, state estimators, and, eventually, distributed system algorithms.

Retrospective Thermal Dosimetry

Retrospective thermal dosimetry is the computation of the isothermal distributions and the accumulated thermal dose that were attained during a completed treatment. While these distributions eventually may be computed and displayed during the treatment, in the immediate future, they are more likely to be calculated after the treatment due to the size and speed of the computer programs required. These distributions will be used as the basis of dose calculations, against which response will be correlated. An additional application will be to use experimental data taken during a treatment to normalize the predictions of the model calculations in any subsequent treatment planning phase.

The first step is to refine the modeled SAR distributions by using the initial heating transient to determine the SAR at the locations of the thermometer sensors using

\[ \rho C \frac{dT}{dt} = \rho \text{(SAR)} \]  

(1)

(It can be shown\(^8\) that the same information can be obtained from power-off cooling transients.) This information can then be used in the numerical model of the bioheat transfer equation to compute complete temperature distributions. The actual blood flow values may still be unknown, but the blood flow parameter can be adjusted automatically (through optimization techniques) in the model in order to force the computed temperatures to agree with the real values at the measurement locations. As an illustration of the technique (19), we considered the case of a dog thigh heated with microwaves at 2.45 GHz with a waveguide aperture. The skin surface was cooled with ambient air blowing through the waveguide. Thermometer probes were inserted along the axis of symmetry at 0.1-cm intervals beginning at 0.5 cm below the surface, continuing to a depth of 5.5 cm, and in the femoral artery. The experiments were run at constant power. Measured temperatures are given for the 2 hottest probes as a function of time in Chart 13. From the initial temperature transients, the local SAR was computed and was fitted to a smooth function versus depth in the tissue, in this case, an exponential. Chart 14 shows the measured temperatures at 5 depths (the points) and the predicted temperature distributions (the smooth curves) that resulted for 2 times during the experiment, namely, at the first maximum in Chart 13 and at the first minimum. Chart 15 gives the values of blood flow that were predicted by the model for the 2 times. In this particular model, blood flow was taken as a constant throughout the 1-cm region surrounding each temperature probe. This application is a simple physical situation to treat, and so, in itself, is not exciting; nevertheless, it does suggest that reasonable numerical models can possibly be used for interpolation between measured points, even when blood perfusion magnitudes are unmeasured. This state (temperature) and parameter (blood flow) estimation algorithm (19) minimizes the differences between specified known experimental temperatures (measured or from simulated experiments) and computed temperatures from the model for the measurement locations. The first test of the method was based upon well-defined experiments, such as that just described. The second test made use of temperature profiles which were based on solutions of the bioheat transfer equation for simulated experiments. The estimation algorithm is given a set of trial values for blood flow, a set of tissue parameters, and a set of temperatures. The estimation algorithm and the routine run to see how well the simulated temperature profile can be reproduced. Under these circumstances, the estimated blood flow values will be in error, such that the effects of erroneous tissue properties are

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just compensated (19). Since the temperature distribution is the primary desired end point for thermal dosimetry (rather than knowledge of properties or blood flows), this compensation effect is encouraging. Of course, to the extent that the correct parameters are used, the blood flow patterns will be calculated accurately.

Using a different state and parameter estimation algorithm, some studies in progress here suggest that temperature maxima and minima can be determined at other than the measured points. Thus, the methodology appears to be capable of extrapolation as well. This capability will be important in determining unmeasured temperatures at tumor boundaries. These ideas need to be developed and tested further, both numerically and experimentally, but we are optimistic that complete temperature fields can be characterized reasonably well from knowledge of temperatures measured at several points, knowledge of the anatomical and geometrical configurations present, and modestly sophisticated numerical models. This problem is similar to the thermal tomography problem (12, 13, 33, 43); however, the additional invasive temperature measurements in hyperthermia make this problem appear easier. This general problem of calculating complete temperature distributions from measured temperatures at a few locations remains a fundamental problem in hyperthermia research. It is a difficult problem which will require considerable effort to solve.

Finally, once isotherms are computed and once a definition of thermal dose is selected, it is possible to compute isodose lines for the treatment.

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Appendix: “Heat” and “Heating”

The words “heat” and “heating” are used in the hyperthermia literature with a variety of implied meanings, which results in a certain amount of vagueness and confusion in interpreting results. Thermodynamically, the concept of “heat” is precisely defined as an energy transfer process (thus, the commonly used term “heat transfer”); i.e.,

Heat, like work, is energy in the process of being transferred. Heat and work are not “stored” within matter; they are “done on” or “done by” matter. Energy is what is stored, and work and heat are two ways of transferring energy across the boundaries of an assembly. Once energy has gotten into an assembly, it is impossible to tell whether the energy was transferred as heat or as work. The term “heat of a substance” is thus as meaningless as “work of a substance” (45).

Unfortunately, the literature contains some remnants of the caloric theory of heat, in which heat was pictured as a conserved substance. In present thermodynamic theory, heat is not conserved and is not a property of matter. Still, some handbooks tabulate “heats of the liquid,” “sensible heats,” and “latent heats.”

Thus, given this accepted definition of heat transfer as an energy transfer process (rather than heat as a stored quantity), the use of “heat” as a noun implying an accumulated, stored quantity should be avoided. This occurs in the following phrases: “heat dose,” “heating treatment,” “the effects of heat,” “heat plus radiation,” “heat plus chemotherapy,” etc.

What is generally meant by the word “heat” in those phrases is related to the elevation of temperature for sustained periods of time. Thus, “heat” could be replaced by “hyperthermia” to more clearly describe the phenomena of interest.

Additionally, the word “heating” seems to be used alternately to mean both “increasing the temperatures of” some object (the accepted, common usage) and “depositing energy into” some object. While, in some situations, these meanings are compatible—for example, at the start of a hyperthermia treatment, energy will be deposited into the patient (e.g., by microwaves) and the patient’s local temperatures will rise—in others, they are not—for example, in the hypothetical patient above, after some time, an equilibrium temperature distribution will be reached and, although energy is still being deposited into the patient by microwaves, the patient’s temperatures are not increasing. That is, in the latter case, while energy is being added to the patient by microwaves, an equal rate of energy removal is occurring due to heat transfer outside the treatment area by thermal conduction and convection to the circulating blood.

Thus, 2 separate verbs are needed to indicate the phenomena of (a) “increasing the temperature of”—here, the word “heating” is adequate—and (b) “depositing energy into an object” by, usually, electromagnetic or ultrasonic means. In the latter case, phrases such as “energy deposition” and “power deposition” should be used rather than “heating.”

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Applications of Bioheat Transfer Simulations in Hyperthermia

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