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Accuracy and precision of computer-simulated tissue temperatures in individual human intracranial tumours treated with interstitial hyperthermia

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Abstract

Accurate knowledge of tissue temperature is necessary for effective delivery of clinical hyperthermia in the treatment of malignant tumours. This report compares computer-predicted versus measured intratumoral temperatures in 11 human subjects with intracranial tumours, treated with a conceptually simple 'conductive' interstitial hyperthermia system. Interstitial hyperthermia was achieved by the use of parallel arrays of implanted, electrically heated catheters. The tissue was warmed by thermal conduction and blood convection. Simulation of intratumoral temperatures was achieved by solving a modified bioheat transfer equation on a digital computer using a finite difference method. Comparison of intratumoral temperatures from simulations and measured values differed by about ± 0.75 ^{o}C. Further analysis of computed temperature distributions between catheters revealed a rapidly computable relationship between the local minimum tumour temperature and nearby catheter power and temperature that accounts for effects of varying blood flow. These findings suggest that 'on-line' prediction and control of local minimum tumour temperatures are feasible with the conductive interstitial technique.

Key words: cancer, closed loop, computer control, feedback, heat therapy, temperature distributions

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1. Introduction

The clinical use of hyperthermia therapy for the treatment of malignant tumours has progressed gradually during the past 10-15 years. Many institutions have reported dramatic tumour regression in patients treated with hyperthermia alone (Crile 1962, LeVeen et al. 1976, 1980, Manning et al. 1982, Storm et al. 1979) or in combination with radiation (Dethlefsen and Dewey 1982, Hahn and Kim 1980, Hornback et al. 1979, U et al. 1980). Despite these successes, the ability of local hyperthermia systems to elevate the temperature of tumours to cytotoxic levels has remained elusive. Limitations in equipment and instrumentation for heat delivery and control has led to the development of 'cold spots', which are areas that do not reach therapeutic levels (Oleson et al. 1984, Perez et al. 1988, Nussbaum 1982). A strong correlation has been demonstrated between the presence of cold spots in intratumoral temperature profiles and poor clinical results in the treatment of spontaneous cancer in pets (Dewhirst et al. 1984). Presumably, areas of tumours that do not reach cytotoxic levels, generally accepted to be above 42 °C, remain viable after treatment and may, in some cases, even be stimulated to grow more rapidly (Song et al. 1980).

One obvious technical solution to the presence of cold spots is simply to increase the power delivered until the probability of subtherapeutic temperatures is very low. Unless the tissue temperature elevation is uniform and strictly confined to the tumour, however, the price of such a solution is the overheating of nearby normal tissue (hot spots) and the possibility of intolerable pain, skin ulceration or other complications. Thus, to prevent both undesired cold spots in the tumour and undesired hot spots in adjacent normal tissue, precise control of a focused energy source is required. Such control has been stubbornly elusive with hyperthermia systems based on external microwave, radiofrequency, or even focused ultrasound technology applied to deep-seated tumours noninvasively. As a result, interstitial techniques that deposit power directly within neoplastic tissue have been increasingly employed (Meyer 1984).

This report describes patient-specific computer simulations of a conceptually simple technique for the generation of local hyperthermia with interstitially implanted catheters. Small-diameter (2×2 mm) interstitial catheters containing electrically resistive heating elements are implanted directly into a tumour in a uniform pattern with the aid of a template to gauge spacing (Baumann and Zumwalt 1989). Heating element lengths are matched to the dimensions of the tumour being treated, thereby limiting the power delivery to nearby normal tissue. The catheters are connected to a controllable power source, which under computer guidance, is altered to achieve the desired catheter temperature. The heating catheter's internal temperature is monitored via an internal thermistor. With this technique, energy is deposited only in the internal resistances of the catheters, not directly into the tissue. The tissue is warmed indirectly by simple thermal conduction and blood convection. This modality is known as interstitial conductive heating (Baumann and Zumwalt 1989). This technique produces temperature profiles similar to other conductive techniques such as ferromagnetic seeds (Stauffer et al. 1982, 1984). In the present study we used a mathematical model of heat transfer in order to describe and predict temperature distributions created by the interstitial array of heated catheters during individual patient treatments. The goals of the modeling project were to investigate the following.

1. The accuracy of the bioheat transfer equation model in the prediction of intratumoral temperatures between catheters.

2. Possible useful implantation geometries for heated interstitial catheters.

3. The electrical energy required to achieve therapeutic temperatures.

4. The effects of variations in local blood flow upon temperature distributions, with the aim of predicting blood flow changes and minimal tissue temperatures from clinically measurable parameters.

2. Computational methods

2.1. Bioheat equation

This study was performed using an iterative method for solving the bioheat transfer equation, first described by Pennes (1948), using the technique of finite differences. The partial differential equation used to describe the transient heat transfer of a control volume of tissue, small enough such that all thermal properties within it are uniform, is:

$$\dot{q}_{\mathrm{met}} + P + K_{\mathrm{ts}}\nabla^2 T + c_{\mathrm{b}} w_{\mathrm{b}}(T_{\mathrm{b}} - T) = \rho_{\mathrm{ts}} c_{\mathrm{ts}} \frac{\partial T}{\partial t}, \qquad (1)$$

where

$\dot{q}_{\mathrm{met}}$ is the specific rate of metabolic heat production (≈ 0 compared with other terms in the context of local heat therapy for cancer)

P is the power density delivered to tissue (= 0 for the conductive, interstitial modality)

K_{ts} is the tissue thermal conductivity

T is the temperature of tissue

c_b is the specific heat of blood

ω_b is the specific flow rate of blood in capillaries

T_b is the temperature of blood

ρ_{ts} is the mass density of tissue

c_{ts} is the specific heat of tissue

t is time.

At steady state, which in practice occurs after about 5-10 min of heating, $\partial T/\partial t \rightarrow 0$, and the differential equation for interstitial heat therapy of tissue reduces to the form,

$$K_{ts}\nabla^2 T + c_b w_b (T_b - T) = 0. \qquad (2)$$

On determination of boundary conditions for each control volume, the computational formulae were determined, using the Cartesian coordinate system and allowing heat transfer only in the x-y plane. This technique modeled temperature distributions in a two-dimensional mid-cross-section through an array of heated catheters embedded in tissue, for which the catheter separation was small with respect to heated lengths of the catheters, i.e. a simplified 'two-dimensional model'.

Each control volume had cross-sectional dimensions of Δx and Δy. The control volume thickness in the z-direction was assumed to be unity, and the volume of each node was $1\Delta x\Delta y$. The following is an example determination of the computational formula for an interior node at steady state. Heat transfer due to conduction was designated by N, S, E, and W (north, south, east and west) around the point of interest P (Figure 1). Energy must be conserved in each control volume. Thus, assuming no input power, the energy balance for point P is:

$$N + W + w_b c_b (T_b - T_P) - E - S = 0 \qquad (3)$$

where

$$N = \frac{K_N \Delta x (T_N - T_P)}{\Delta y} \qquad (4)$$

$$S = \frac{K_S \Delta x (T_P - T_S)}{\Delta y} \qquad (5)$$

$$E = \frac{K_E \Delta y (T_P - T_E)}{\Delta x} \qquad (6)$$

$$W = \frac{K_W \Delta y (T_W - T_P)}{\Delta x} \qquad (7)$$

where $K_{N, S, E, W}$ is the interface conductivity between a volume (N, S, E or W) and volume P (Incropera and Dewitt 1981).

For example, the interface conductivity between P and N is defined as:

$$K_{\text{int(N, P)}} = \frac{2K_N K_P}{K_N + K_P} \tag{8}$$

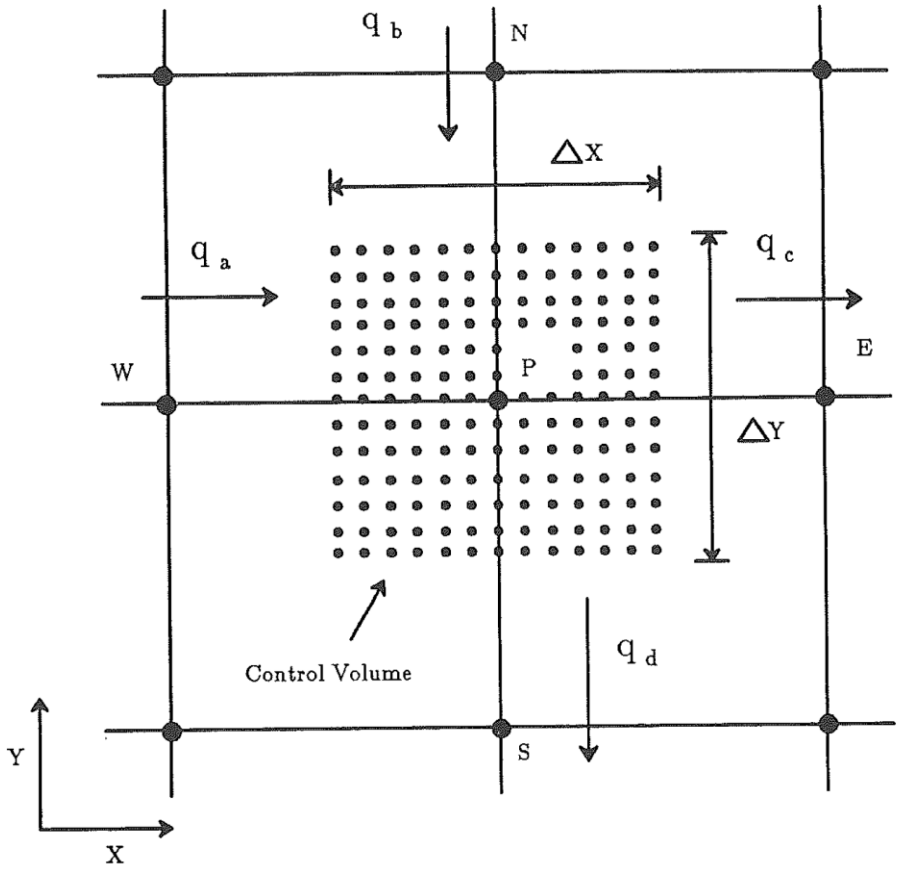

Figure 1. Control volume of node P for the two-dimensional coordinate model.

Thus, combining Equations (3) to (8), and dividing by the volume, a discretized equation is developed for the temperature at point P as a function of the surrounding temperatures and local perfusion as follows:

$$\frac{K_N(T_N - T_P)}{\Delta y^2} + \frac{K_W(T_W - T_P)}{\Delta y^2} = w_b c_b (T_b - T_P) + \frac{K_E(T_P - T_E)}{\Delta x^2} + \frac{K_S(T_P - T_S)}{\Delta x^2} \tag{9}$$

To simplify the expression one may assume all thermal conductivities are of equal value, K and introduce the change of variable $\Phi = T - T_b$, so that Equation (9) becomes:

$$\frac{K}{\Delta y^2}[2\Theta_P - \Theta_N - \Theta_W] + w_b c_b \Theta_P + \frac{K}{\Delta x^2}[2\Theta_P - \Theta_E - \Theta_S] = 0 \qquad (10)$$

Solving for Φ, the computational formula for the interior nodes becomes:

$$\Theta_P = \frac{\frac{K}{\Delta x^2}[\Theta_S + \Theta_E] + \frac{K}{\Delta y^2}[\Theta_N + \Theta_W]}{w_b c_b + 2\frac{K}{\Delta x^2} + 2\frac{K}{\Delta y^2}} \qquad (11)$$

The computational formulae for control volumes with different boundary conditions were determined in a similar fashion.

Using the bioheat transfer equation in the form of Equation (11), our computational strategy was to assume an initial thermal profile and update that estimate by successive iteration. The initial thermal profile was chosen as an exponential decay in temperature from each heating catheter. This selection is not mandatory to ensure convergence of the model; however, a good estimate of the temperature profile will decrease the computational time required to achieve the solution. When the difference between temperature estimates from one iteration to the next approaches zero, convergence to the steady-state solution is indicated. To further increase the rate of convergence, a method of successive over-relaxation (SOR) (Torrance 1985) was employed. This method adds a fraction of the difference between the current estimation and the previous estimation to the current estimation as shown below.

$$\Theta_P \leftarrow \Theta_P + \alpha(\Theta_P - \Theta_{P_{last}}) \qquad (12)$$

Selection of the constant, α, is limited to the interval [0, 1]. Proper selection of α, determined either by trial-and-error or analytically (Torrance 1985), allows for much faster convergence.

2.2. Resolution of simulations

In order to achieve accurate predictions of tissue temperatures in the presence of steep thermal gradients, the selection of the proper grid size proved to be very important. In exploratory calculations the number of grid points was slowly increased until there was negligible difference between plotted temperature profiles. A reasonable execution time (3-4 hours) on a Gould NP1 super-minicomputer was achieved with about 4000 nodes/cm^2 of simulated tissue. By these criteria a full three-dimensional simulation of the tissue would be unrealistic, requiring a

computation time > 10^6 days on the NP1 for a 9 x 9 x 9 cm volume of tissue. Hence, the modified two-dimensional simulations described above were performed for 11 patients and 14 treatment cycles to test the accuracy of the computational simulation of tissue temperatures during conductive interstitial heat therapy by comparing computed versus measured temperatures, and to explore approaches to future prediction and control of intratumoral temperature distributions.

Because the two-dimensional model presented above does not include the heat loss in the 'vertical' (z) direction, a single-catheter, three-dimensional model based on cylindrical coordinates was also developed to estimate such losses for catheters of different effective lengths. Comparison of results obtained from the two- and three- dimensional models allowed the vertical power loss to be quantified, for any given catheter spacing. This estimated vertical heat loss could then be added into the two-dimensional simulation to obtain a quasi-three-dimensional simulation without the computational cost of a full three-dimensional simulation.

3. Patient data acquisition

3.1. Patients

The 11 patients included in this report were treated with conductive interstitial hyperthermia between May and October 1988. There were seven men, ages 43-67 years and four women, ages 40-51 years. The tumour types diagnosed at the time of therapy included six glioblastoma multiformes, three anaplastic astrocytomas and two metastatic lesions. All patients were treated at Missouri Baptist Medical Center or St Luke's West Hospital in St Louis, Missouri, with approval from their Institutional Review Boards (IRB) and an investigational device exemption from the US Food and Drug Administration.

Patient selection criteria included local tumour recurrence after the application of appropriate standard therapy and an age greater than 15 years. All patients had conventional therapy prior to hyperthermia treatment, consisting of either surgery, radiation, brachytherapy, chemotherapy or some combination thereof. In all cases, hyperthermia treatment was initiated because other treatments failed to control the tumour. No concomitant therapy was given during hyperthermia.

3.2. Hyperthermia therapy

Hyperthermia was delivered according to a treatment protocol which consisted of one to three separate hospital admissions for multiple hyperthermia treatments (called treatment cycles). Subsequent treatment cycles were prescribed if the tumour continued to show contrast enhancement on the computed tomographic (CT) scans. Each treatment cycle consisted of delivery of hyperthermia 3 hours out of every 4 hours, six times a day until a total of 72 hours of hyperthermia had been delivered.

The hyperthermia catheters were implanted with a nominal 15 mm intercatheter spacing and triangular symmetry (Figure 2). A 15 mm intercatheter spacing allowed for satisfactory tissue temperatures and implantation. The number of catheters implanted varied with tumour size. Thus, each patient treatment was tailored to the tumour size and location. The number of heating

catheters implanted ranged from 6 to 17, with a median value of 11. In order to measure tumour temperatures between the heating catheters, small (OD 1.2mm) diameter temperature sensing (thermistor) probes were implanted as shown in Figure 3. Each temperature sensing probe contained four thermistors, spaced 1 cm apart. A minimum of two, and a maximum of 10, temperature-sensing probes were implanted with an average of four probes per patient and a total of 56 independent tissue temperature measurement sites. The temperatures measured by these stationary thermistor probes, in the steady state, were used as comparison points in the computer simulations to determine the accuracy and precision of the computer-generated temperature profiles.

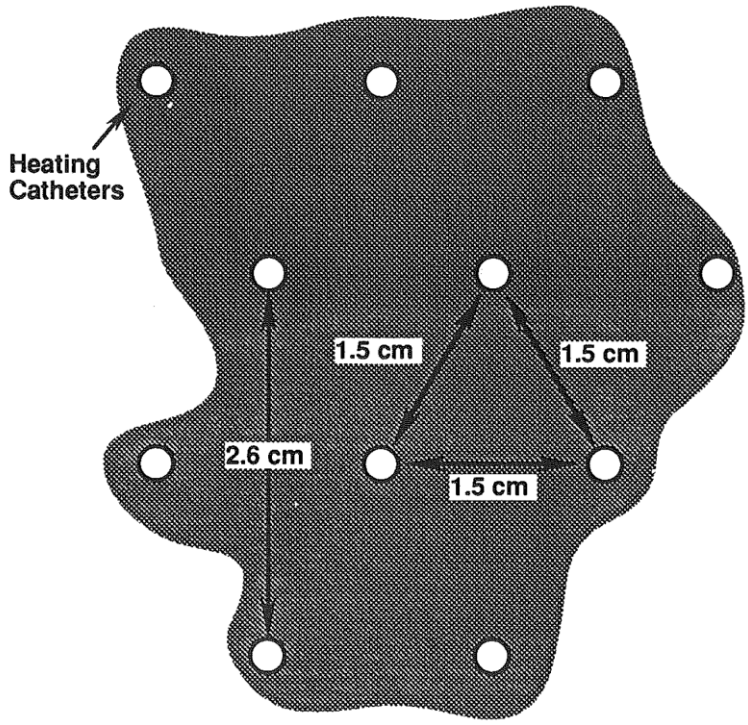

Figure 2. Nominal implantation geometry for heating catheters as seen in cross-section (not to scale).

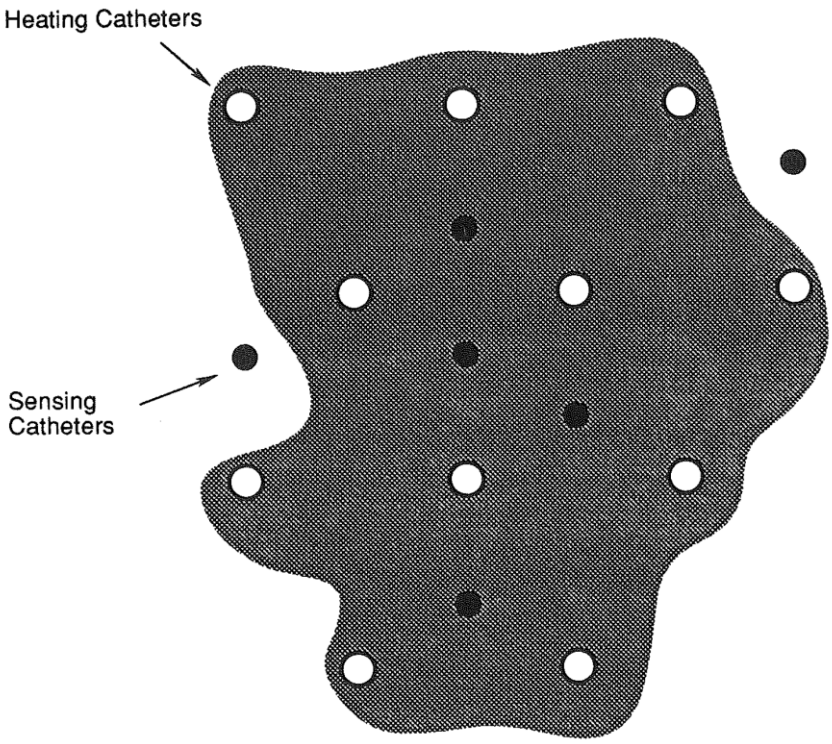

Figure 3. Nominal implantation of temperature-sensing catheters and heating catheters. Each temperature-sensing catheter is implanted in the centre of three heating catheters to measure the minimum tissue temperature.

In order to compare accurately temperatures measured by the implanted thermistor catheters, and accurately model the implantation of the heating catheters, non-overlapping sequential CT scans 3 mm thick were employed to obtain implantation geometries. Using the CT scan computer, intercatheter distances were determined for multiple points along the axes of the catheters. These distances were used as inputs into the computer simulation to accurately represent patient treatments. This technique allowed a more precise determination of the implanted catheter locations, thereby allowing a more precise model to be implemented. This high-resolution CT information was obtained in 11 patients, for whom 14 treatment cycles were included in the present analysis.

After implantation, each patient was awakened and transferred to the neurosurgical intensive care unit for recovery and subsequent treatment. After a complete neurological assessment, treatment parameters were entered into the hyperthermia treatment system computer (Volumetric Hyperthermia Treatment System-Cook, Inc., Bloomington, Indiana). Treatment parameters included patient data, location and heating section length of each implanted catheter, target catheter temperature, number of treatment fractions and the duration of each fraction. After preparing the patient for treatment, the implanted catheters were connected to the hyperthermia

generator and treatment commenced. During the course of treatment the delivered catheter powers and internal temperatures were continuously monitored and stored on magnetic disk for later data analysis.

3.3. Off-line simulation of tissue temperatures

Clinically obtained catheter powers, temperatures and initial perfusion estimates were used as inputs for the computer simulations. Other inputs included the dimensions of the heating area, control volume size, tolerance for determination of convergence and the value of α, as well as arterial blood temperature. Measured temperatures from the sensing catheters (non-heating) were then compared with corresponding simulated temperatures at the CT-verified locations.

Since the actual values of tissue perfusion in each patient were unknown, the following method was used to establish perfusion values. This method is based on the strong dependence of the change in heating catheter temperature per unit of applied power on the local blood perfusion near each catheter, demonstrated by the bioheat transfer equation and noted in general by others (Jain and Ward-Hartley 1984). The entire simulation volume was mapped into perfusion regions around each catheter (Figure 4). To determine the location of perfusion boundaries, a simple distance method was employed. The distance from a control volume to nearby catheters was determined and the node was assigned to the perfusion region of the closest catheter. An example of typical perfusion boundaries appears as Figure 4. Perfusion was estimated for each region by guided trial-and-error, in which successive perfusion values were tested in simulation to identify the specific perfusion value that allowed simulated catheter temperature and power dissipation to best match those actually measured in the clinic.

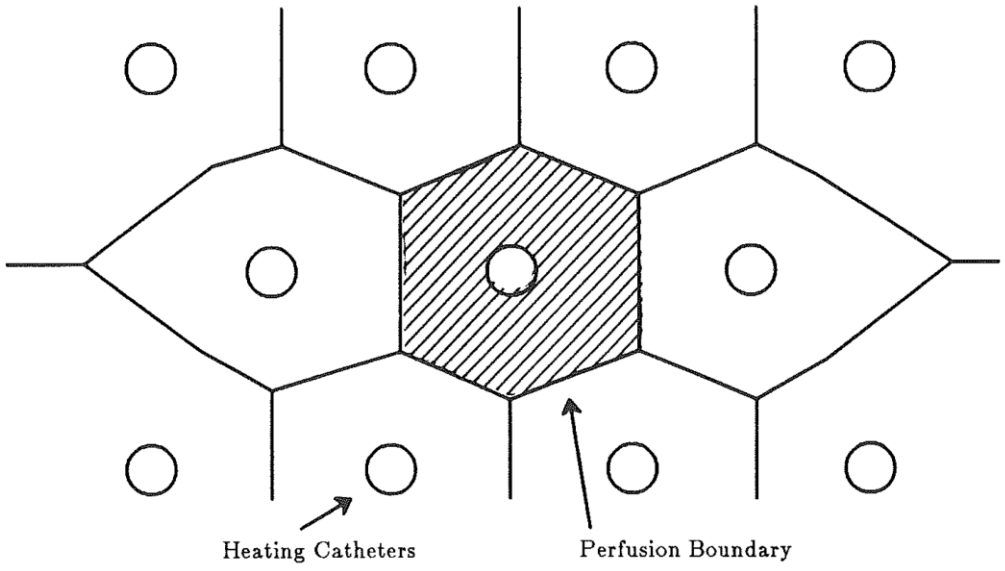

Figure 4. Local perfusion boundaries determined by the 'minimum distance' method.

Specifically, an initial reasonable guess for perfusion in each region was made and the computer simulations were allowed to run to convergence with input catheter powers equal to those measured clinically. Simulated catheter temperatures were then compared with the measured catheter temperatures for the selected perfusion values. The differences between measured and computed temperatures were used to update the perfusion estimates, for the perfusion zone around each catheter, and then the entire simulation was performed again. This iterative method was employed until the difference between the clinically measured and computer-simulated catheter temperature was less than 0.25 °C for each catheter. The resulting perfusion values, which reproduced the clinically measured set of 11 $\Delta T/P$ ratios for each catheter, were those used in the 'final' simulation of steady-state temperature distributions for a given patient treatment session.

Although this technique does not allow exact determination of local perfusions, since there may be blood flow variations along the catheter axis, it does allow determination of a perfusion rate that duplicates the heat flux found in the clinic. Simulated temperatures were then compared with measured tumour temperatures from implanted sensors (non-heating catheters) at known sites. The locations of the temperature sensors were determined from the CT scans, and the simulation temperature matrix was searched for the corresponding locations allowing direct comparisons of simulated and measured temperatures. The accuracy and precision of simulated temperatures were then assessed by histogram analysis of the distribution of difference terms, $T_{simulated} - T_{measured}$.

4. Results

Simulated and measured temperatures were analysed for 11 human subjects at a total of 56 discrete measurement sites. Figure 5 presents a hidden line plot of a typical temperature matrix determined from the computer simulation. Without correcting for 'vertical' heat loss (in the z-direction), we found the bioheat transfer equation model overestimated measured tumour temperatures with a mean error of 1.1 ^{o}C and a standard deviation of 1.3 ^{o}C. Figure 6 presents the histogram of difference terms, $T_{simulated} - T_{measured}$ for this strictly two-dimensional model.

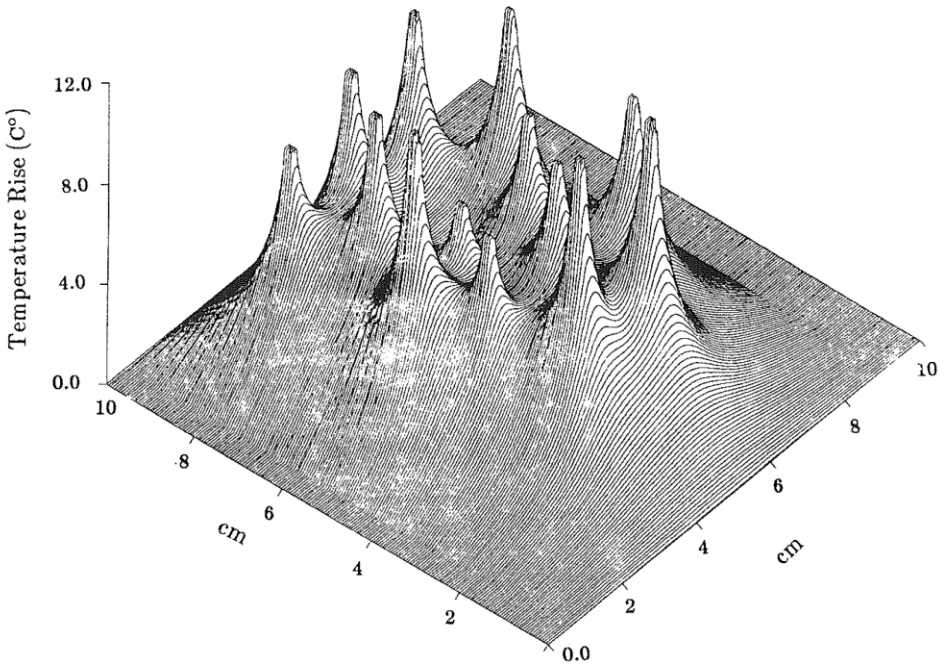

Figure 5. A temperature matrix from a typical treatment simulation. The high peaks correspond to the catheter temperatures and the lower valleys represent local minima in tumour temperature. Zero corresponds to arterial temperature. The temperature of each catheter was independently set to achieve the same valley temperature between heating catheters, thereby leading to different temperature peaks due to perfusion variations.

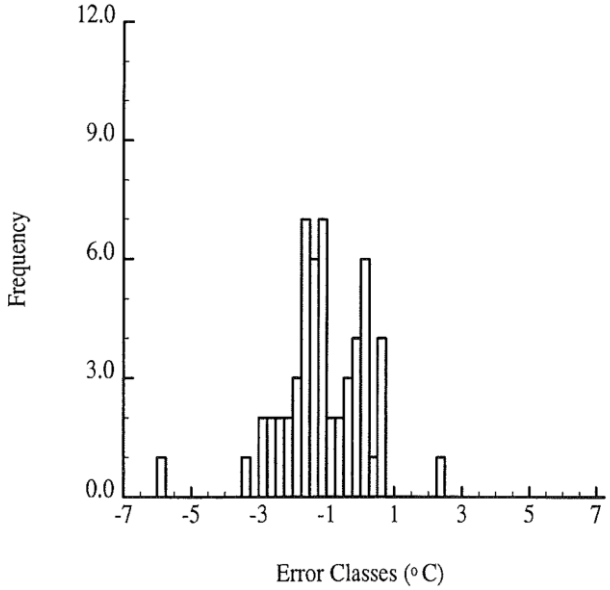

Figure 6. Histogram of temperature errors from direct comparison of measured and simulated temperatures from the two-dimensional Cartesian coordinate model.

Using the single-catheter, three-dimensional simulation we found that the heat loss in the vertical (Z) direction was, as expected, a function of both the catheter heating element length and the local perfusion. The amount of vertical heat loss was found to lie within 4-50% of total power dissipated. For a long catheter heating section (8 cm) and a low perfusion (1 ml/min per 100 g) the vertical heat loss was only about 4% of the total delivered power. However, with a short catheter heating section (2 cm) and a high blood flow rate (70 ml/min per 100 g) up to 50% of the delivered power was lost vertically. Applying the perfusion estimate from the two-dimensional simulation and the corresponding vertical heat loss found from the three-dimensional simulation, it was found that the resultant quasi-three-dimensional bioheat transfer equation again overestimated the measured temperatures, but the mean difference dropped to 0.3 ^{o}C with a standard deviation of 0.9 °C. Figure 7 presents the histogram of the difference terms with simulated temperatures computed by the modified model. Direct comparison of Figures 6 and 7 shows the marked advantage of the modified two-dimensional method in this particular problem. Figure 8 presents a comparison of the predictive value of the two-dimensional and quasi-three-dimensional models. On reviewing the simulated temperature profiles, we discovered that the overall temperature distributions were surprisingly uniform. Except for a thin sleeve of tissue surrounding each catheter heating element, broad, relatively flat zones of temperature elevation were achieved between the catheters, the levels of which were highly dependent on local perfusion (Figure 5). The greater the local blood flow, the lower the intercatheter temperatures. From the computer simulations a polynomial relationship was discovered between the ratio of catheter temperature elevation to catheter power and local perfusion. Figure 9 presents this relationship for various catheter temperatures, assuming 1.5 cm catheter spacing.

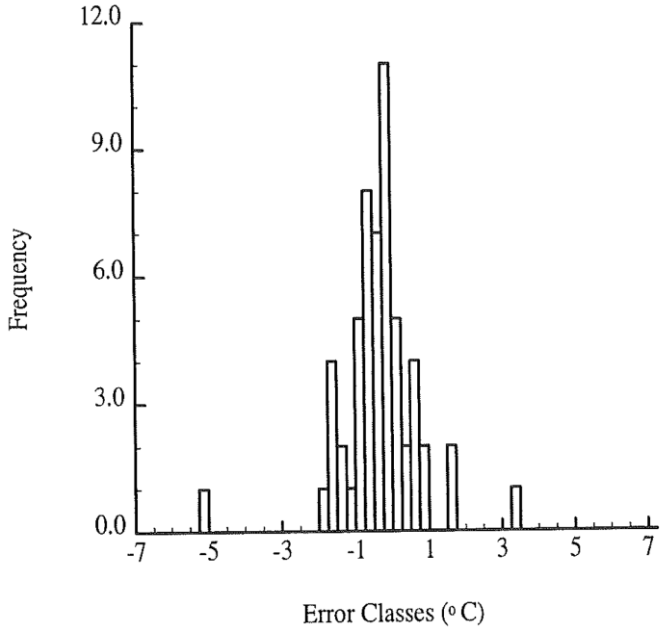

Figure 7. Histogram of temperature errors from direct comparison of measured and simulated temperatures from the quasi-three-dimensional model.

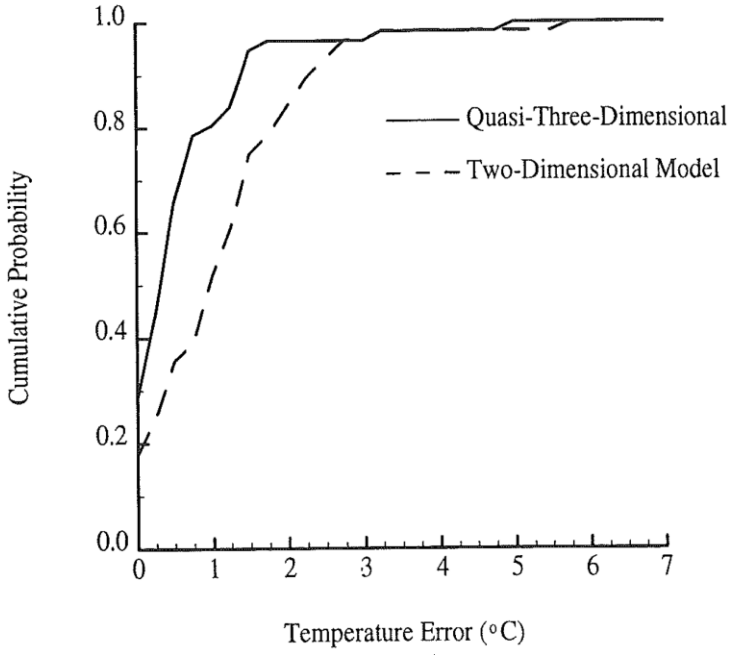

Figure 8. Comparison of two-dimensional and quasi-three-dimensional errors in temperature prediction. Notice that over 80% of all points (0.80 cumulative frequency) occur for the quasi-three-dimensional model at about 1 °C error, while in the two-dimensional model about 60% of all points lie within 1 °C error. The dashed curve represents the results of the two-dimensional model.

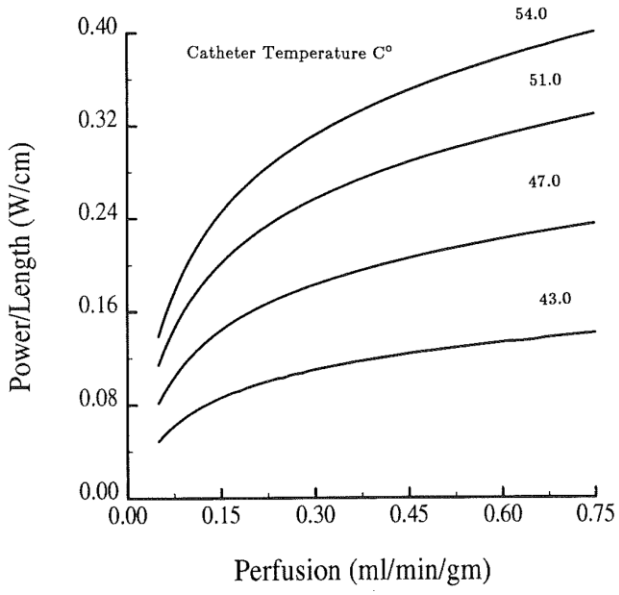

Figure 9. Catheter power per centimetre versus perfusion. For each catheter temperature there is a unique curve of power as a function of perfusion.

5. Discussion

The use of hyperthermia in the treatment of malignant tumours is based on a strong biophysical rationale. It is known that hyperthermia kills cells exponentially as a function of time and/or temperature. As a result, when temperature remains near the thermal death threshold, small differences in temperature can lead to large differences in cytopathological effect. A mere 1 ^{o}C change in treatment temperature can make a significant difference in the incidence of cure or recurrence (Sapareto 1982). Because effective treatment of cancer with hyperthermia is dependent on the abolition of cold spots (Dewhirst et al. 1984), more accurate and precise control of tissue temperatures during therapy is highly desirable.

The ability to predict tissue temperatures from clinically available data is a requisite first step to one technically attractive route to this goal: computer-assisted closed-loop controllers for hyperthermia applicators. According to this strategy a computer system would predict minimum tumour temperature from automatically measured patient data, and adjust input power repeatedly until the predicted minimum intratumoral temperature achieved the desired therapeutic target. The present investigation demonstrated that, in the case of the conductive interstitial modality at least, tissue temperatures may be predictable with sufficient accuracy and precision, to allow engineering work to proceed on closed-loop feedback control. In particular, for a given catheter spacing and catheter power, it appears possible to predict minimum tissue temperatures near each catheter from simple polynomial functions that can be determined in advance of treatment (in computations that take many hours) by solving the bioheat transfer equation for commonly used catheter spacings and geometries. These rapidly computable polynomials can be incorporated into software for on-line control during therapy.

This approach obviates the need for solving the complete bioheat transfer equation on-line, a task still often beyond the capabilities of present-day super-computers. The technical difficulties involved in eradication of cold spots without overheating adjacent normal tissue have been great barriers to the use of hyperthermia as a single-modality treatment of cancer. However, the results of this study show that with conceptually simple interstitial conductive heating, the possibility exists to predict and control minimum tumour temperatures, even in the presence of time-varying and non- uniform blood flow. This modality may also decrease the probability of trauma to the patient by minimizing the number of temperature-sensing catheters that must be implanted. Another possible advantage of this technique is the ability to tailor the thermal distributions to an irregular tumour volume.

This study found the bioheat transfer equation to be a good model for simulating temperature distribution in human patients, and with the quasi-three-dimensional technique presented results could be further improved. These results are consistent with results in previous reports (Charny and Levin 1988, Clegg and Roemer 1985, Olesen et al. 1984, Pantazatos and Chen 1978). Prediction and control of minimum intratumoral temperatures are important if neoplastic disease is to be treated successfully with hyperthermia. Direct measurement of complete temperature distributions cannot be achieved because of the large number of implanted temperature sensors required. However, continuous monitoring of input from a limited number of implanted catheters is possible with current technology. Numerical reconstruction and prediction of tissue

temperatures when applied to the relatively simple conductive interstitial modality become tractable for clinical use, and can be further reduced to the essential predictions of potential cold spots in the span of a few seconds. The application of these results may represent an important development for hyperthermia treatment, allowing tissue temperatures to be adjusted rapidly with a limited number of implanted elements. The accuracy and precision of these predictions seem sufficient for on-line closed-loop control for adjusting power to underheated regions in a guided fashion on a moment-to-moment basis.

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