Interstitial Hyperthermia of Brain Tumors

by

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Abstract

The goal of this research was to investigate the temperature distribution in brain tissue in the presence of arteriole flow from an array of 2.25 MHz interstitial ultrasonic waveguide applicators and an array of resistive wires. The temperature distribution was modeled using Finite Element Analysis under simplified conditions. The models predicted that it is possible to achieve therapeutic temperatures by adjusting the power at the surface of each applicator. However, due to the wide range of temperature in the spatial distribution at equilibrium, no conclusion can be made for the likely success of this method for realistic treatment. A human brain phantom was constructed to verify the modeling technique applied to heating by resistive wires. Good agreement was achieved between experiment and the simulation. The experimental data were used to predict the thermal dose, as a function of time, in representative regions of the tumour model.

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List of Abbreviations

EM ₄₃	Equivalent Minutes at 43°C
TID	Thermal Isodose
SAR	Specific Absorption Rate
ID	Inner diameter of arteriole
OD	Outer diameter of arteriole

Chapter 1

Introduction

Hyperthermia has a long history. The use of hyperthermia, such as burning the breast tumors by “fire stick” or “fire drill”, has been recorded as early as 3000 BC. The chemical caustics, hot metals and burning lenses, were the only means of inducing hyperthermia, until the nineteenth century [1]. Today, the most promising techniques for achieving high tissue temperatures are based on the interaction of electromagnetic waves or sound waves with tissues. Most of these technologies were developed in the 1970’s [2], and are still being improved upon today. The goal of this study is to investigate the feasibility of using an interstitial heating method in the treatment of brain gliomas. In this chapter the concept of thermal therapy, the proposed interstitial heating technique for treatment of gliomas, and the overall direction of the thesis will be presented.

1.1. Thermal Therapy

Hyperthermia is defined as a method for the treatment of cancer in which the temperature of tissue is elevated into the range of cytotoxic temperatures: *i.e.*, above 41°C. In conventional hyperthermia, the temperature of the target is raised to between 42°C and 45°C over a long period of time (about 60 min). It is usually used as an adjuvant treatment with other therapeutic modalities such as radiotherapy, chemotherapy, immunotherapy, and recently, gene therapy [3]. Several studies have shown that conventional hyperthermia increases the response of tumors to radiotherapy and chemotherapy, especially for radioresistant tumors, such as gliomas that have a large portion of hypoxic cells in low pH [4, 5]. Hyperthermia as a radiosensitizer can help to destroy malignant cells in a low pH, hypoxic or nutritionally deprived environment, and to induce apoptosis [6]. It has been shown that hyperthermia, both *in vitro* and *in vivo*, can inhibit tumor growth and induce apoptosis in gliomas and glioblastomas [7]. One of the challenges in hyperthermia is to overcome the problem of blood flow cooling in the tumor. Blood flow can reduce the temperature of the tumor below the cytotoxicity range.

Coagulative thermal therapy, or thermal therapy at higher temperatures, is applied in the range of 50°C to 80°C, over a short period of time (a few seconds). Thermal therapy, in this range of temperatures, immediately destroys tissue by denaturing protein in membranes or other cellular constituents (thermal coagulation), and by necrosis [7]. Therefore, this therapy could reduce the perfusion problem caused by blood flow. Coagulative thermal therapy, used alone, provides more effective control of the heat

distribution in a target than conventional hyperthermia. However, cold region adjacent to large blood vessels could still be produced [8].

Both conventional hyperthermia, applied over an extended period of time, and coagulative thermal therapy, applied over a short period of time, have the ability to produce the required thermal damage in the target.

Analysis of the cell survival curves (cell survival fraction versus heating time) at different temperatures has been shown that the cell killing by hyperthermia depends on time and temperature [4, 9]. It was observed that the cellular damage above 43°C exponentially depends on temperature and linearly on time. It is important in clinics to know how much heating time, for a given temperature, is required to obtain a specified level of thermal damage. In 1984, Sapareto and Dewey [9] by analysis the data obtained from many *in vitro* and *in vivo* studies, formulated a quantitative measure, the thermal dose for a given procedure, expressed as the heating time required to produce the same thermal isoeffect at a reference temperature of 43°C. The thermal isoeffect dose (TID) for temperatures between 42°C and 57°C is expressed as [10]:

$$t_{43} = \sum_{t=0}^{t=final} R^{(\bar{T}-43)} \Delta t \quad (1.1)$$

where t_{43} is the equivalent time at 43°C or Equivalent Minute at 43°C (EM_{43}), $\bar{T}$ is the average temperature during a small heating time of Δt , R is a constant, which is about 2 for temperatures greater than 43°C, and 4, for temperatures at 43°C and below. The different value of R below and above 43°C is related to the gradual development of

thermotolerance during heating to temperatures below 43°C [4]. It has been shown that a temperature rise of 1°C above 43°C requires 2-fold decrease in heating time to produce the same effect (isoeffect) as in a time t_0 at 43°C. Temperature rise of 1°C below 43°C requires 4-fold decrease in heating time, to produce the same effect as at 43°C.

The heat sensitivities of various tissues are different. Therefore the level of thermal damage for a given treatment is not the same in all tissues. TID only compares different possible thermal treatments for the same tissue. So, if the minimum required treatment for a specific tumor, or the maximum treatment that a given normal tissue can tolerate, is known, then treatment outcomes at other temperatures are predictable [9]. It was shown, that 20-240 EM₄₃ are required as thresholds to produce damage in different normal tissues, in various species [10].

In thermal therapy, the heat is usually delivered in tissue by one of microwave, laser or ultrasound sources. The goal in thermal therapy is to facilitate destruction of malignant tissue by localizing heat in the target with a minimum heating of surrounding normal tissue. Monitoring the temperature rise during treatment by temperature probes is quite invasive and therefore the number of probes that can be used is not enough to show adequately the temperature distribution during treatment. The possibility of detecting the temperature pattern by non-invasive imaging techniques such as MRI is under investigation. The temperature distribution during thermal therapy can in principle be predicted before treatment by using an appropriate thermal model [11-18].

1.2. Modeling of the Temperature Distribution

Mathematical models can be used to predict the temperature distribution in the target region and the surrounding normal tissue. This modeling requires knowledge of the power deposition pattern by a given heating source, the properties of tissue for calculating this pattern, the geometrical boundaries of target and normal tissue with their thermal conditions, the thermal properties of the tissue, blood perfusion, and the metabolic heat generation rate [19]. These models could be used to predict the power that is required at each source to produce TID's within a safe and effective range. The major problem with heating of the tumors is blood flow, which can take away heat from the heated region by convection. Usually ten to fifteen times more power is required to produce the same temperature elevation in a moderately perfused tissue than in a non-perfused tissue. An accurate modeling of the temperature distribution in the target requires a detailed knowledge of the real vasculature and perfusion of the target.

There are two main models of heat distribution in a perfused tissue: the Bioheat Thermal Equation (BHTE), proposed by Pennes in 1948 [11], and the Effective Thermal Conductivity Equation (ETCE), proposed by Weinbaum *et al.* in 1984 [13, 14]. These two models will be discussed in chapter 2. The BHTE considers the cooling effect of blood flow at the capillary level. Capillaries have a low blood velocity and quickly reach equilibrium with the heated tissue. This model assumes that blood enters the heated tissue at arterial temperature and leaves it at the local temperature of the heated tissue. Therefore blood acts as a heat sink when its temperature is less than the temperature of

the heated tissue. The ETCE is based on the idea that the major cooling occurs between the counter current vessels within the tissue, not the capillaries. In this model, the thermal conductivity of tissue is increased to include the heat transfer between vessels. These two models have been used and compared with each other [20-23]. The differences between the predictions of the two models increase with increasing blood flow.

Neither of these two models can predict the cooling effect encountered in the vicinity of large blood vessels. Significant cooling around large blood vessels has been demonstrated experimentally [8] and theoretically [24-26], by modeling discrete vessels. These vessels cause cold spots in well-perfused areas while there may be hot spots in necrotic regions. Hot spots usually cause pain, which limits how much heat can be transferred to cold spots. Discrete blood vessel models use the heat convection equation for calculating the cooling effect. Some of these models will be discussed in chapter 2.

The required temperature rise in a defined region over a specific period of time is usually achieved by one of the external, intracavitary, or interstitial techniques.

1.3. Interstitial Heating

Interstitial heating techniques are mainly used for the treatment of bulky deep-seated tumors that are difficult to reach by external or intracavitary methods. In interstitial heating, applicators are directly inserted into the target. Therefore this technique has the advantage of restricting the heat to the target volume, which produces less damage to

normal tissue. There are several interstitial heating sources for thermal therapy such as, RF, laser, microwave, ultrasound, and conduction sources [27].

Because of the short wavelength of ultrasound, it provides better localization and control of the temperature distribution than RF and microwave sources. It also provides a greater penetration depth than conduction devices [2]. Ultrasound in the frequency range of 0.5-10 MHz is usually used in thermal therapy. The possibility of using ultrasound for treatment of superficial and deep-seated tumors was reviewed by Hill [28]. Several interstitial ultrasonic applicators are under investigations. These applicators are categorized as catheter-cooled, direct-coupled, and waveguide applicators [3].

The first two types of applicators are based on the direct insertion of cylindrical piezoelectric tubes, which produce cylindrical ultrasound waves within the tissue. This configuration was proposed by Hynynen, in 1992 [29]. For these applicators the heating length can be controlled along the applicator for a given target, by adjusting the number of transducers in an array. Moreover, they can produce a good radial penetration depth (8-22 mm) in the target, because they have a cooling system that allows greater power at each transducer. They can be used with brachytherapy for the induction of hyperthermia. Fig. 1.1(a), shows a catheter-cooled applicator using 10 mm long, 1.2-1.5 mm OD, transducers. The transducers are typically inserted into a 13 or 14 gauge water-cooled brachytherapy catheter. The applied power to each transducer is adjustable [3, 27]. A diagram of direct-coupled applicators is depicted in Fig. 1.1 (b). For this applicator, an array of three 10 mm long, 1.8 - 2.5 mm OD, transducers is used. These applicators were

designed for use with remote afterloading brachytherapy: *i.e.*, thermobrachytherapy. In Fig. 1.1(b), the wall of the implant catheter is biologically and electrically insulated, so that it can be implanted directly in the target. The inner lumen is a remote afterloading brachytherapy catheter. The temperature at the interface of the tissue and the applicator is monitored by small thermocouples located on the surface of each transducer [3, 30].

Fig. 1.1. Diagrams of (a) catheter-cooled and (b) direct-coupled interstitial ultrasonic applicators [30].

These two applicators could produce therapeutic temperature distribution in the tumor. However, the design of these applicators is complicated. The control of electronics and

the water-cooling system in catheter-cooled applicators is difficult and the diameter of the direct- coupled applicators is quite large to be inserted into the tumor precisely [3].

The interstitial ultrasonic waveguide applicator was proposed by Jarosz in 1989 [31]. Fig. 1.2 shows the diagram of this applicator. The advantage of this design is that its small diameter hollow hypodermic needle, which can be inserted into a target precisely, is less invasive. This applicator is still in the design and testing phase.

Its current design consists of a piezoelectric plate that is impedance matched *via* a tapered transformer taper,^a to a waveguide. The ultrasound waves are transported by a waveguide to the desired site within the medium. The shielding (or cladding) shown in Fig. 1.2, contains a pocket of air that prevents the transmission of acoustic energy into the medium, before the surface waves reach the site. The piezoelectric plates for these kinds of applicators are typically resonant in the 1 to 3.5 MHz range, vibrating in thickness mode. The plate is under pressure from one side by a spring and the other side is attached to the taper *via* a layer of glue [32]. The glue layer has a thickness of $\lambda_L/2$, where λ_L is the wavelength of longitudinal ultrasound waves in the glue. The length of each section in the tapered transformer is an integral multiple of $\lambda_{Lt}/2$ for impedance matching purposes, where λ_{Lt} is the wavelength of longitudinal ultrasound waves in the taper [33]. It was assumed that the longitudinal mode of propagation of waves through the taper into the waveguide is converted into Rayleigh-type surface waves [34]. However, the quantitative

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^a Also referred as an acoustic transformer, velocity transformer or a truncated cone.

theoretical description of this conversion is very complex and has not been presented yet [35].

Fig. 1.2. Diagram of an interstitial ultrasonic waveguide applicator [32].

1.4. Interstitial Ultrasonic Waveguide Applicators in Treatment of Gliomas

Brain gliomas usually grow in those critical parts of the brain which are responsible for vital functions. It is difficult to remove these tumors, without damaging the normal surrounding tissue, by conventional surgery. Radiotherapy and chemotherapy are the usual alternative treatment methods used for such tumors. Unfortunately, gliomas are mostly radioresistant [5]. Some of them are also resistant to chemotherapy. For increasing the tumor response hyperthermia could be added to these treatment modalities.

These tumors are also highly vascularized near the surface [36]. There are theoretical and experimental studies on the vascular system of gliomas [36-39]. These studies are helpful in understanding the response of these tumors to different therapeutic methods. This is especially important for hyperthermia, because the presence of blood flow will cause cooling, which changes the effectiveness of the therapy [37]. Usually the central region of the tumor is necrotic due to the low blood flow rate and low nutrition that leads to cell death. The low blood flow rate at the center also decreases the convective heat transfer in this region [40]. In a study of blood flow around glioma tumors of 27 patients with tumor volumes between 5 and 175 cm³, using xenon computed tomography (XeCT), it was shown that the blood perfusion is lowest in the tumor core, and highest in the normal tissue adjacent to the tumor [38].

Producing hyperthermia alone for treatment of brain gliomas, by using an array of interstitial ultrasonic waveguide applicators, was proposed by Jarosz [32]. The interstitial ultrasonic waveguide applicators have the advantage of a small diameter antenna that can be inserted directly and precisely into the tumor. The interstitial ultrasonic techniques are usually preferred over external methods for these tumors because of high ultrasound absorption and impedance mismatch between air/skull interfaces, which (at least up to the present time) make the external ultrasonic methods ineffective. The possibility of using focused ultrasound for brain therapy is under investigation by Hynynen *et al* [41].

In a study of heating by 1 MHz interstitial ultrasonic waveguide applicators in a 240 cm³ static brain tissue phantom (non-perfused), a maximum 6°C temperature elevation in 180

min was achieved [35]. The feasibility of heating by 2.25 MHz applicators in a dynamic phantom (with some large blood vessels) is in progress. This treatment technique is in its initial stages and further research and development work will be required before it can be considered for clinical use. In this thesis the heating problem will be discussed.

1.5. Overview of Thesis

The final goal of this study is to investigate the feasibility of reaching the hyperthermic range of temperatures in a glioma tumor by using an array of interstitial ultrasonic waveguide applicators. Modeling of the temperature distributions in brain tissue in the presence of arterioles by an array of four 2.25 MHz ultrasonic applicators and an array of four resistive wires has been investigated. The geometry of the model and the position of the heat sources and the arterioles are based on the work done by Jarosz [42, 33]. The modeling was done with using an analytical solution for the heat transfer calculation in arterioles by approximating the blood flow in arterioles as the water flow in tubes. In previous studies by Jarosz [42, 43] the analytical solution of a solid cylinder that is transiently subjected to convection to the environment at a constant temperature was used for calculation of heat transfer in an arteriole. Although the assumption of solid moving rod for blood vessels with very small diameters (capillaries) could be valid, it was observed that this model overestimates the temperature around the larger blood vessels (arterioles). As an initial step to test the modeling, the heat distribution by resistive wires has been verified experimentally in a brain tissue phantom. The phantom that was used in this study had been built by Winter [44]. The thermal dose at selected locations in the

phantom was also calculated to investigate the thermal damage due heating by resistive wires.

In this chapter, we have discussed the general definition of hyperthermia and thermal coagulation, the concept of thermal damage and thermal modeling, the use of interstitial ultrasonic techniques for generating hyperthermia, and the possibility of using interstitial ultrasonic waveguide applicators for hyperthermia treatment of brain gliomas. Chapter 2 covers the heat production in tissue, thermal modeling of tissue, ultrasound absorption in brain tissue, and modeling of arteriole cooling using Jarosz's model. In Chapter 3, the simulation of heat propagation in brain tissue (using FEA) with and without arteriole cooling is presented. Chapter 4 covers the materials and methods used for our experiment of heating brain phantom by resistive wires. In Chapter 5, the results of this experiment with a comparison to the theory and thermal doses at selected locations in the phantom with and without arteriole flow are discussed. It is shown that the wide range of thermal doses may be expected in clinical applications. Chapter 6 concludes this thesis with a general overview and conclusion of our research, followed by a discussion of possible future directions of study.

Chapter 2

Thermal Modeling

The absorption of power within a tumor results in the generation of heat within the tumor volume. This then spreads by conduction, resulting in an overall increase in temperature, which with sufficient power deposition can achieve toxicity levels, above 45°C. The presence of blood vessels within the tumor, however, reduces the local temperature elevation by convection. The temperature around large blood vessels may drop below toxicity level and permit tumor regrowth. In this chapter, heat transfer by conduction and convection, bio-heat transfer models, and discrete blood vessel models, in particular the model that was used for modeling the heating of brain tissue by interstitial ultrasonic waveguide applicators in the presence of arterioles will be presented.

2.1. Heat Conduction

Heat is transferred in tissue mainly by conduction, and, to some extent, by convection. The rate of heat deposition in a stationary, homogenous, isotropic solid per unit volume

V , is equal to the sum of the rate of heat entering the volume, and rate of energy generation in the volume [45]: *i.e.*,

$$\rho c \frac{\partial T}{\partial t} = \nabla \cdot (k \nabla T) + Q, \quad (2.1)$$

where ρ (kg/m^3) is density, c ($J/kg^\circ C$) is the specific heat, k ($W/m^\circ C$) is the thermal conductivity, and Q is the heat generation rate. When the thermal conductivity, density and the heat capacity of the solid are constant, and the heat generation rate is independent of temperature, equation (2.1) can be simplified to the following linear form,

$$\frac{1}{\alpha} \frac{\partial T}{\partial t} = \nabla^2 T + \frac{Q}{k}, \quad (2.2)$$

where $\alpha = k / \rho c$ (m^2/s) is the thermal diffusivity [45], which represents how fast heat propagates within the medium. The thermal conductivity equation can be solved by considering the boundary conditions.

Fig. 2.1 shows a surface element of a solid that is subjected to conduction, convection, radiation, and external heat supply. To have an energy balance at the surface the heat loss should be equal to the total heat supply: *i.e.*,

$$q_n + q_{sup} = q_{conv} + q_{rad} \quad (2.3)$$

where $q_n = -k \partial T_s / \partial n$ (W/m^2), is the conduction heat flux vector normal to the surface element, q_{sup} is the energy supplied to the surface from an external source, $q_{conv} = h (T_s - T_\infty)$ is the heat loss at the surface, with temperature T_s , to the adjacent medium, with ambient temperature T_∞ , and heat transfer coefficient h ($W/m^2^\circ C$) and q_{rad} represents the

heat loss from the surface by radiation. When the q_{sup} and q_{rad} are negligible equation (2.3) simplifies to:

$$k \frac{\partial T_s}{\partial n} + hT_s = hT_\infty(r, t) \quad (2.4)$$

If $T_\infty(r, t) = f(r, t)$ and the first term on the left side of the equation is zero, then equation (2.4) will show the prescribed temperature at the boundary surface. If $hT_\infty(r, t) = f(r, t)$ and the second term in the left side of the equation is zero, then equation (2.4) represents a prescribed heat flux at the boundary surface [45].

Fig. 2.1. Diagram of the energy balance at the surface of a solid. $\hat{n}$ is the outward drawn unit normal vector [45].

2.2. Blood Flow

Heat distribution in tissue is also influenced by convection, arising from blood flow. Blood flowing inside blood vessels can be approximated by fluid flow in tubes. Fluid flow is usually categorized as laminar or turbulent. In laminar flow, fluid elements move

only in one direction, which is the flow direction. In turbulent flow, fluid elements move in all directions randomly as they move along the flow direction. Turbulent flow depends on the average velocity of the fluid, $\bar{u}$ (m/s), the density, ρ , the viscosity, μ (kg/ms), and the diameter of the tube, d . Usually the Reynolds number, Re , is used to show the limit of laminar/turbulent flow. This number is expressed by

$$Re(\bar{u}, d) = \frac{\rho \bar{u} d}{\mu} \quad (2.5)$$

The transition from laminar to turbulent flow occurs at about $Re \sim 2000$ to 2500 . Re for the aorta, which has the largest diameter and blood velocity, is 1063 in the case of steady flow. For other blood vessels Re is much smaller than 2000. Therefore under normal condition the turbulence may just occur in large blood vessels [46]. The possibility of turbulence also exists in diseased vessels. For the arterioles that were used in this study, Re is about 10, which is in the range of laminar flow.

When fluid with laminar flow enters into a tube, all of the fluid elements have the same non-zero velocity (entry flow). As the flow travels in the tube the velocity profile in cross section is rounded smoothly from zero at the walls to the maximum around the axis. When this velocity profile remains independent of axial distance, the fluid flow is fully developed (*i.e.*, $\partial u / \partial z = 0$). Fig. 2.2 shows the entry and the fully developed flow in a tube.

Fig. 2.2. Diagram of entry and fully developed flow in a tube [46].

Similarly, a thermally developed flow is defined as the condition where the dimensionless temperature profile at a cross section is independent of the axial position: *i.e.*,

$$\frac{\partial}{\partial z} \left[\frac{T(r, z) - T_w(z)}{T_m(z) - T_w(z)} \right] = 0 \quad (2.6)$$

where $T(r, z)$ is the local temperature of the fluid, $T_w(z)$ is the temperature of the wall, and $T_m(z)$ is the mean fluid temperature, defined as the temperature that would result at a cross-section if the fluid were thoroughly mixed to a uniform temperature:

$$T_m = \frac{\int_0^R T(r, z) u(r) r dr}{\int_0^R u(r) r dr} \quad (2.7)$$

where R is the radius of the tube and $u(r)$ is the velocity of the fluid.

The flow in the region where the temperature profile changes from its initial profile to the fully developed profile, is called thermally developing flow. If the Prandtl number, defined as the ratio of the kinematic viscosity and thermal diffusivity, is greater than one,

then the fully developed velocity profile is reached before a fully developed temperature profile. The Prandtl number of blood is 25 [46].

2.3 Heat convection

Heat convection refers to heat transfer in fluid by mixing one portion of the fluid with other portions due to movement of fluid mass [47]. If the fluid motion is due to density differences caused by temperature differences in the fluid, the process is called free or natural convection. If the fluid motion is caused by an external means such as a pump then the process is called forced convection. Heat convection by blood flow is assumed to be forced convection [46]. Blood flow takes heat away from the surrounding tissue and produce cold regions around large blood vessels. It is important to investigate the heat flow between blood and the surroundings. A blood vessel can be approximated by a circular tube and blood as fluid flowing through the tube. The temperature of the fluid could increase or decrease depending on the temperature of the tube wall.

The heat equation for the case of the fully developed laminar flow in a circular tube, with symmetric heat transfer, and constant fluid properties can be written as [48]:

$$\frac{\partial^2 T}{\partial r^2} + \frac{1}{r} \frac{\partial T}{\partial r} + \frac{\partial^2 T}{\partial z^2} = \frac{u(r)}{\alpha} \frac{\partial T}{\partial z} \quad (2.8)$$

where the right hand side of the equation represents the heat transport by mass flow. At the wall surface, the boundary condition can be expressed by equation (2.4). The heat transfer coefficient, h , becomes:

$$h = -k \frac{(\partial T / \partial n)_s}{(T_s - T_m)} \quad (2.9)$$

where T_s is the wall temperature at the surface and T_m is the mean fluid temperature (equation 2.7). h depends on the composition of the fluid, geometry, the velocity distribution across the cross section of the tube and the temperature differences. A parabolic velocity distribution is usually considered for a laminar tube flow that is expressed by:

$$\frac{u(r)}{\bar{u}} = 2 \left[1 - \left(\frac{r}{R} \right)^2 \right] \quad (2.10)$$

Equation (2.8) has been solved for two boundary conditions: constant wall temperature and constant heat rate per unit length of the tube. Nusselt in 1910 found that in the case of a very long tube with the assumption of no axial conduction ($\partial^2 T / \partial z^2 = 0$ in equation 2.8) and both fully developed velocity and temperature profiles, the local heat transfer coefficient, h , tends to a constant value [47]: *i.e.*,

$$Nu = \frac{h(z)d}{k} \quad (2.11)$$

where Nu is the Nusselt number or dimensionless heat transfer coefficient, and d is the diameter of the tube. The value of Nu is 3.66 if the temperature of the tube wall remains constant and is 4.36 if the heat flux through the wall is constant [47]. These values have been used to determine h , in the case of blood vessels [49]. In this study the Nusselt number of 3.66 was used for calculation of h in section 2.7.

When the laminar fluid flow is thermally developing, the problem is known as the Graetz problem. In this case the heat transfer coefficient, h , is not constant along the tube. This condition usually happens for the fluid whose Prandtl number is greater than 1. The solution to Equation (2.8) in this case and for the condition of constant wall temperature is given in Appendix A.

2.4. The Bioheat Transfer Equation (BHTE)

Accurate modeling of heat transfer in mammalian tissue is complicated due to several factors such as difficulties in considering the real geometry of the blood vessels, the blood velocity and the blood flow direction. The complication of heat transfer modeling is worse for tumors because usually the vascular geometry is more complicated, even chaotic. In 1948, Pennes proposed the Bioheat Thermal Equation (BHTE) for description of the spatial and temporal distribution of temperature in the human forearm [11]. This model is based on the assumption that heat transfer between tissue and blood vessels occurs at the capillary level. Capillaries have low blood velocity and a large cross-sectional area of heat exchange between tissue and blood. The BHTE is expressed by:

$$\rho_t c_t \left(\frac{\partial T}{\partial t} \right) = \nabla \cdot (k_t \nabla T) + Q_b + Q_m, \quad (2.12)$$

where ρ_t is the density of tissue, c_t is the specific heat of tissue, k_t is the thermal conductivity of tissue, Q_b is the rate of heat exchange between blood and tissue, and Q_m is the rate of metabolic heat generation. The blood term is considered as a heat sink. The quantity Q_b is defined as:

$$Q_b = c_b w_b (T_a - T) \quad (2.13)$$

where c_b is the specific heat of blood, w_b ($\text{Kg}/\text{m}^3\text{s}$) is the blood volumetric perfusion rate, and T_a is the arterial temperature. In this model, it is assumed that blood enters the heated region with the arterial temperature, usually 37°C , and instantly reaches thermal equilibrium with the local temperature of the heated tissue. Then, blood enters the venous system at the tissue temperature.

2.5. Effective Thermal Conductivity Equation (ETCE)

The Effective Thermal Conductivity Equation (ETCE) proposed by Weinbaum in 1984 [13, 14], is based on the assumption that most of the heat is conducted between counter-current vessels in the tissue. In contrast to BHTE, which assumes that most of the heat exchange occurs at the capillary level, in this model the major heat exchange between blood and tissue occurs in the intermediate size vessels, with diameters between 0.05 mm and 0.5 mm. In this model, the blood has reached thermal equilibrium before entering the capillaries [4]. In the ETCE the heat exchange between blood and tissue is expressed by an increase in the tissue thermal conductivity [13, 14]: *i.e.*,

$$\rho_t c_t \frac{\partial T}{\partial t} = \nabla \cdot (k_{eff} \nabla T) + Q_m, \quad (2.14)$$

where k_{eff} is the effective thermal conductivity of the tissue and Q_m is the rate of metabolic heat generation. Effective thermal conductivity is the increased tissue thermal conductivity taking account of conduction and convection by blood vessels. This quantity depends on blood velocity, direction, and vascular density. Effective thermal conductivity

is a tensor for real vascular geometry, but for isotropic vessel arrangements it is assumed to be a scalar. In this case the ETCE is called the scalar ETCE.

Both ETCE and BHTE have been used for prediction of temperature distributions in tissue. The ETCE showed the better agreement with experimental data in steady state and transient analysis done by Crezee *et al* [21, 50]. Roemer *et al* [20] by experiments in steady state and Kolios *et al* [23] by transient analysis showed better agreement between BHTE and experimental data. The lesion size predicted by BHTE model was also in better agreement with the published experimental data than of ETCE [51].

2.6. Discrete Blood Vessel Models

The aforementioned two continuum models do not take into account the cooling effect of individual large blood vessels in the heated tissue. Blood vessels with diameters larger than 0.5 mm have a large thermal equilibration length. This is defined as the axial distance required for blood to reach to $1/e$ of the surrounding maximum tissue temperature [52]. These vessels produce cold regions along their track in the heated tissue. The cold regions or untreated cells allow tumor regrowth. Therefore, it is necessary to consider the effect of such large blood vessels in the complete thermal modeling of heated tissue. Large blood vessels are usually modeled as discrete entities within the perfused tissue.

Kolios *et al.* [8], in experiment with porcine kidney tissue showed that even for a short period of heating time the large blood vessel could affect the temperature profile. The temperature gradient caused by these vessels depends on the vessel size and volumetric blood flow. They also concluded that large blood vessels could either heat or cool the tissue depending on their positions with respect to the heat source and the type of heat source. More localized heating sources produce larger temperature gradients across the vessels. The experimental results of Crezee *et al.* [50] with interstitial heating of perfused bovine tongues by hot water tubes with different level of perfusion, showed the necessity of including large blood vessels in modeling. They also concluded that for a higher level of perfusion more absorbed power away from the interstitial source is required for uniform temperature distribution and, therefore, hot water tubes could not be desirable heating sources.

Crezee and Lagendijk [49] modeled the heat distribution in a perfused cylindrical shaped tissue, using ETCE: *i.e.*, equation (2.14), together with a single large blood vessel at the center of the cylinder. The heat transfer between blood and tissue was calculated by using the heat transfer coefficient, h , for the two conditions of constant temperature and constant heat flux at the vessel wall. They showed that the minimum temperature in the tumor occurs around the vessel wall. The minimum temperature is sensitive to the effective thermal conductivity of the tissue, flow type, entrance effect and the vessel size. They also concluded that a higher level of tissue perfusion reduces the amount of cooling around the vessel and increases the probability of uniform heating [51].

This was also concluded by Kolios *et al.* [25]. The geometry of their model was also a heated, perfused cylindrical shaped tissue with a large blood vessel at the center. The heated tissue was also surrounded by another unheated cylindrical shaped tissue. The unheated tissue was kept at the basal temperature at its radial boundaries. The tissue was modeled with both BHTE (equation 2.12) and ETCE (equation 2.14) for different levels of perfusion and for uniform power deposition in the heated region. The Finite Difference Method was used for calculating the temperature distribution [25]. They concluded that decreasing the volumetric flow in the vessels reduces the cooling effect of the large blood vessels. The advantage of their model is that for their procedure, the heat transfer coefficient h , required by Crezee and Lagendijk method, which depends on the temperature gradient (equation 2.9) and the boundary conditions, is not required. In general if the temperature gradient changes, the heat transfer coefficient should also change. Moreover, the numerical values of h were found for a steady state condition that should not be used for transient analysis [52], which is especially important for modeling of temperature distribution during coagulative thermal therapy (see section 1.1).

Modeling with more blood vessels in tissue has been done by Kotte, *et al.* [53] and Van Leewen *et al.* [26]. They have developed a 3D artificial vessel network to predict the temperature distribution more accurately. This model could be used for the discrete vasculature of each specific patient. In this method the vessels can be simulated as 3D curves.

Jarosz [42, 43] modeled the temperature distribution in non-perfused tissue coupled with some large blood vessels. The geometry of this model is quite complicated. The non-perfused tissue was represented by 70% of adult brain volume. Heating was introduced by four interstitial ultrasonic waveguide applicators inserted in the tissue, each surrounded by some large blood vessels. The model calculates the heat transfer in the non-perfused tissue by using BHTE (equation 2.12), and the blood vessels were assumed in quasi-equilibrium with the tissue. The temperature distribution in the blood vessel was calculated, with the approximation of symmetric heating of the vessel wall and no temperature change in the axial direction. In this method heat transfer between tissue and blood was calculated by using the solution for transient heat transfer within a solid cylinder, initially at a uniform temperature, and subjected to convection to the environment at a constant temperature [42]. The heat transfer coefficient, h , was needed for this calculation. This value for a moving solid was assumed as $\rho c \bar{u}$ [33].

In the present study, the modeling of heat transfer was done using Jarosz model but with a different method of coupling large blood vessels in tissue. A detailed explanation of this model will be presented in the following section.

2.7. The Discrete Blood Vessel Model of Heat Transfer by Interstitial Ultrasonic Waveguide Applicators

In this model, it was assumed that the interstitial ultrasonic waveguide applicators are inserted in a non-perfused brain tissue with a number of discrete large blood vessels (arterioles) located in the vicinity of each applicator. Ultrasound heat production in tissue is the result of the absorption of ultrasound energy.

Fig. 2.3 shows an interstitial ultrasonic waveguide applicator that generates cylindrical ultrasound waves. The intensity of the outgoing cylindrical waves generated by the applicator drops off as $1/r$, with an exponential attenuation factor. Then the absorbed power per unit volume [29], or volumetric Specific Absorption Rate (SAR), is given by [32];

$$g(r, z) = aI_0(z) \frac{R}{r} e^{-\mu(r-R)}, \quad (2.15)$$

where I_0 is the initial intensity, a is the power absorption coefficient, and μ is the ultrasonic power attenuation coefficient. The attenuation coefficient has absorption and scattering terms. In the case of hyperthermia, the scattered energy also contributes to tissue heating [29]. Therefore, all of the energy lost from the ultrasound is absorbed by tissue. The absorption coefficient is frequency dependent and is expressed by,

$$\alpha_a = a f^n, \quad (2.16)$$

where α_a is absorption coefficient, f is frequency (in MHz), and a and n are tissue dependent constants. The value of n for brain tissue is 1.20 – 1.46 in the frequency range of 1-6 MHz [54].

Fig. 2.3. Cylindrical symmetry around the interstitial waveguide applicator, where $2R$ is the diameter of the waveguide, and r is the radial distance from the central axis, z , of the waveguide.

The geometry of the model and the location of blood vessels were defined for the special case of brain gliomas. In this model, cylindrical shaped arterioles were positioned parallel to the applicators. For the investigation of the cooling effect of the arterioles in the heated tissue, they were located close to the applicators, due to the relatively small heating volume of applicators and the tumour necrotic condition (see section 1.4).

In this model the BHTE is combined with a model for calculating the cooling effect of discrete blood vessels. The BHTE (equation 2.12) is written as [43]

$$\rho c \frac{\partial T}{\partial t} = \nabla \cdot (k \nabla T) + w_b c_b (T_a - T) + \sum_{i=1}^4 \langle g_i(r, z) \rangle_z + Q_m, \quad (2.17)$$

where for a non perfused tissue $w_b C_b (T_a - T)$ is zero. The average term, $\langle g_i(r, z) \rangle_z$, is the z averaged volumetric SAR around the i th applicator (equation 2.15), and the summation term, $g = \sum \langle g_i(r, z) \rangle_z$, is a sum over the contributions of four applicators. In short, this term represents the major component of the heat generation rate in tissue. In this study a uniform I_0 was assumed along each applicator. The Q_m was assumed negligible. This equation was solved under steady state conditions.

The steady state heat transfer into arterioles is taken into account by some approximations. It is assumed that the arterioles are heating symmetrically and there is no ultrasonic power deposition in the vessels. The blood flow is laminar, the velocity profile is fully developed and temperature profile is developing.

This method starts with an assumed temperature for a cylindrical layer of tissue that surrounds a blood vessel, and a mean blood temperature to make a first estimate of the temperature of the arteriole wall.

The temperature of the assumed cylindrical layer can be found by solving equation 2.17 using Finite Element Analysis (FEA) without considering the heat transfer to arterioles (the detailed description of the procedure will be discussed in chapter 3). The temperature of the assumed cylindrical layer is taken from the nodes that represent the cylindrical tissue layer in the FEA model. After that, the method of Crezee *et al.* [49] is used to calculate the inner arteriole wall temperature. In Crezee's method, ETCE is used for heat

transfer in the tissue. However, in our model the microvasculature perfusion is not taken into account: *i.e.*; $k_{eff} = k$. The steady state radial heat equation for an arteriole, with inner radius a , and outer radius w , which is surrounded by a cylindrical tissue layer with radius b can be written [49]:

$$k \left(\frac{d^2 T}{dr^2} + \frac{1}{r} \frac{dT}{dr} \right) = 0 \quad a < r < b \quad (2.18)$$

where $k = k_w$ (wall) for $a < r < w$ and $k = k_t$ (tissue) for $w < r < b$. The heat flux should be continuous at all boundaries:

$$-k_w \left(\frac{dT_w}{dr} \right) = -k_t \left(\frac{dT_t}{dr} \right) \quad r = w \quad (2.19)$$

$$-k_w \frac{dT}{dr} = h(T_a - T_m) \quad r = a \quad (2.20)$$

where k_t is tissue thermal conductivity, k_w is wall thermal conductivity, T_a is the temperature at the inner wall, T_m is the mean blood temperature and h is the heat transfer coefficient, which can be replaced by the Nu number from equation (2.11). The Graetz solution can be used to find the mean blood temperature, T_m , and the local Nusselt number, $Nu(z)$, along the arteriole length (Appendix A). Crezee *et al.* [49] used Graetz solution to express the solution of Equation 2.18 in the form:

$$T_a(z) = T_m + (T_b - T_m) \left\{ 1 + \frac{1}{2} Nu(z) \left[\left(\frac{k_b}{k_w} \right) \ln(w/a) + \left(\frac{k_b}{k} \right) \ln(b/w) \right] \right\}^{-1} \quad (2.21)$$

where $T_a(z)$ is the inner wall temperature, T_b is the temperature of the assumed cylindrical tissue layer, k_b is blood thermal conductivity. After calculating the inner arteriole wall temperature, using equation 2.21, this temperature is used to perform a second FEA. This procedure of calculating and iterating is repeated until convergence is achieved, that

is, no further temperature changes in the wall temperature are seen. A diagram of the procedure is depicted in Fig. 2.4. A detailed description of the method and the results will be presented in the next chapter.

Fig.2.4. The diagram of the procedure for calculating blood vessel temperature.

Chapter 3

Finite Element Analysis of Heat Transfer in Tissue

Finite Element Analysis (FEA) can provide an approximate solution for differential equations: *e.g.*, for modeling heat transfer problems. The most important advantage of this method is its ability to solve problems involving heterogeneous tissue properties with irregular shaped organ boundaries. In this study, a commercially available FEA software package Algor¹, was used to obtain a numerical solution of the discrete blood vessels model, as discussed in chapter 2. An analytical solution was used for heat transfer in large blood vessels. The details of the model, boundary conditions, and the resultant temperature distributions will be discussed in this chapter.

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¹ Algor, Pittsburgh, PA.

3.1. Finite Differences and FEA Techniques

Finite differences and Finite element analysis are the common numerical methods of solving a differential equation, in a specially defined region of interest, by replacement of the differential equation by a set of algebraic equations, which relates dependent variables at the neighboring nodes in the region.

In the finite difference technique, the region of interest is approximated by grid points. The derivatives of the dependent variable at each point can be expressed by a set of algebraic equations based on the dependent variable on the adjacent nodes. Then the solution of the differential equation is estimated by solving the set of algebraic equations at each point.

In FEA the region of interest is approximated by a number of finite elements. Each element provides nodes at the intersection of the element's boundaries. The change of dependent variable with location inside each element is expressed by an interpolation function. This function is substituted into an equivalent integral and integrated. Then the integration result over each element is combined with that of other elements by a set of algebraic equations [55]. FEA is the newer technique and has the advantage of being more flexible in dealing with boundary conditions, inhomogeneous problems and non-uniform meshing.

3.2. Description of our 3-D Mesh

A finite element mesh is usually built by subdividing the region of interest to quadrilateral or triangular elements. Our 3-D model, which represents 70% of an adult human brain, by volume, consisted of 4902 nodes and was created by using the Algor software package, used for thermal FEA analysis. Our model is based on the assumption of a tumor close to the base of the frontal lobe: *i.e.*, in the region of the brain that has the largest cross-sectional area [56]. Fig. 3.1(a) shows the mesh that was created based on these assumptions. The dimensions of the model are shown in Fig 3.1(b). The brain volume has been divided into quadrilateral bricks with rectangular walls. The height of each brick depends on the position of the brick in the volume. The volume has different layers, and the height of each brick is equal to the height of the layer in which it lies. This model has five layers, totaling 6 cm in height. The height of the bottom layer is 2.5 cm. The height of the middle layers is 0.5 cm, totaling 1.5 cm in height. Finally, the height of the top layer is 2 cm.

In this model, four different tissue types were included: skull, brain tissue, arteriole wall, and blood. The thermal conductivity, density, and specific heat of each of them are given in Table 3.1. The initial temperature of brain tissue, arterioles, and skull were set at a basal temperature of 37°C. Modeling has been done for two kinds of heating elements: an array of four interstitial ultrasonic applicators and an array of four resistive wires. The heat source in the model could also be changed to other interstitial heating modalities by some modifications in the model.

Fig. 3.1. (a) A 3-D mesh representing the 70% of the adult brain volume. The four vertical lines, in the z direction, represent the position of four interstitial heating elements in the mesh. (b) A cross-section of the model showing the dimensions of the model.

Tissue Type	Density, ρ (g/cm^3).	Thermal Conductivity, k ($W/m\ ^\circ C$).	Specific Heat, c_p ($J/g\ ^\circ C$).
Skull (Plexiglas)	1.18	0.25	2.15
Brain tissue	1.05	0.528	4.18
Arteriole wall	1.1	0.476	4.18
Blood	1	0.492	4.18

Table 3.1. Density, thermal conductivity, and the specific heat of the tissue types used in our modeling [33, 42, 54].

3.2.1. Modeling of Ultrasonic Applicators

An array of four interstitial waveguide applicators, with operating frequencies of 2.25 MHz, was applied. They are represented by the four long dark cylinders shown in Fig. 3.1(a). These applicators were positioned to the right of the middle line of the frontal lobe yielding asymmetric boundary conditions that lead to an asymmetrical temperature distribution [32]. The applicators are arranged vertically in the z (axial) direction, to form a square box, with a corner to corner dimension of 2.4 cm and a height of 3.5 cm. The radiating parts of the applicators are 1.5 cm in length, upwards from the base of the array. Fig. 3.2(a) shows the spatial layout of the applicators within the brain. It can be assumed that the 2.25 MHz ultrasonic waves in tissue remain in the near field for the above dimensions and there is no beam divergence above and below the radiating part.

Each applicator is surrounded by three arterioles each 6 cm long, 0.96 mm outer diameter (OD), 0.58 mm inner diameter (ID), aligned parallel to the applicators. Each set of three arterioles forms an equilateral triangle in cross section, with the applicator at the center of the triangle. Fig. 3.2(b) shows the position of arterioles around one applicator. No other arterioles were considered in our modeling. The location of arterioles in the model is depicted in Fig. 3.3.

Fig. 3.2. Diagram of applicator array (a) and the position of arterioles around each applicator (b).

Fig. 3.3. Position of the arterioles around each applicator in the mesh.

The heat generation rate, or SAR, in the tissue for our ultrasonic applicators drops off quickly with distance (equation 2.15). The SAR pattern generated by each applicator was incorporated into our model, shown in Fig. 3.4. An initial SAR value was assumed at the applicator. This value for the modeling without blood flow was 0.430 W/cm^3 . The initial SAR value for the case of modeling with blood flow is given in Table. 3.2. Each circle shown in Fig. 3.4 represents a contour line, along which the SAR is constant. The ratio of the SAR values along each “SAR-Contour” to the SAR value at the surface of the applicator is given in Table 3.3. This ratio drops off to about 0.05, at roughly 10 mm from each applicator, which reduces the heating volume to effectively a small volume around each applicator. Therefore, an array of four applicators increases the treatment volume effectively bounded by the array.

Applicator	SAR at the applicator (W/cm^2)
DR (Dorsal Right)	0.430
DL (Dorsal Left)	0.470
FR (Frontal Right)	0.547
FL (Frontal Left)	0.538

Table 3.2. The SAR values at the surface of each ultrasonic applicator for modeling with blood flow. The insert on the right shows the positions of the applicators, along with their associated arterioles.

Fig. 3.4. The SAR pattern around each applicator. In this diagram, the mesh radiates outwards in a circular fashion, from the central applicator. The circles or “SAR-contours” are labeled 1 through 10. These “SAR-contours” extend vertically only as far as the applicator’s antenna, forming cylinders of constant SAR.

“SAR- Contour”.	Radius (mm).	Ratio of the SAR at Different Distances to the SAR at the applicator.
1	0.600	1.00
2	0.760	0.80
3	1.096	0.55
4	1.491	0.40
5	1.965	0.30
6	2.880	0.20
7	3.757	0.15
8	5.406	0.10
9	7.353	0.07
10	9.702	0.05

Table 3.3. The ratios of the “SAR- Contour” values to the SAR value at the applicator operating at 2.25 MHz. The SAR-Contour numbers are presented in Fig. 3.4.

3.2.2. Modeling of Resistive Wires

The resistive wires were assumed cylindrical in shape, with a height of 6 cm and diameter of 2.3 mm. The surfaces of the wires were assumed to remain at a constant 12°C above the basal temperature. In this case, there is no volume absorption power.

3.3. Analysis of temperature distribution in the Mesh

Our 3-D mesh was encoded into an Algor file, as an isotropic medium, with the tissue types and SAR values given in section 3.2. The Algor transient heat transfer analysis routine was used for steady state modeling. The total analysis time for each run was 10 hours.

To take into account the cooling effect of arterioles, the temperature distributions within the arterioles were calculated separately (*cf.*, Section 2.7). In our FEA modeling, first the steady state heat transfer analysis was done without considering the blood flow. In this analysis the initial temperature of the arterioles was assumed to be the initial temperature of the surrounding tissue. Second, the final temperatures of the outer cylindrical tissue-shells, which surround the outer arteriole walls (Fig. 3.5), were used to calculate the temperature of the inner arteriole walls, using the Crezee, *et al.* [49] solution (equation 2.21). Third, the calculated inner wall temperatures were assigned to the inner arteriole walls in the FEA model. The FEA analysis was then continued, and the second and third steps repeated, until convergence. Table 3.4 shows an example of

the results obtained, for 6 iterations, for an arteriole in the Dorsal Right region. As one can see, the temperature fluctuation decreases with each iteration.

Fig. 3.5. The position of arteriole inside the four nodes tissue element.

Tissue Node No.	Temperature after First Iteration (°C)	Temperature after Second Iteration (°C)	Temperature after Third Iteration (°C)	Temperature after Fourth Iteration (°C)	Temperature after Fifth Iteration (°C)	Temperature after Sixth Iteration (°C)
α	45.1	43.9	43.4	43.2	42.8	42.8
β	46.1	45.0	44.5	44.2	43.9	43.8
γ	46.4	45.3	44.8	44.3	44.2	44.2
ϵ	45.5	44.3	43.8	43.5	43.2	43.2

Table 3.4. The temperatures at the tissue surrounding the arteriole walls, after each iteration for the modeling of temperature distribution by resistive wires. The arteriole is shown in Fig. 3.5.

3.4. Results and Discussion

The temperature distribution in the 3-D mesh, for an array of four ultrasonic interstitial applicators and an array of four resistive wires, without blood flow is shown in Figs. 3.6 (a) and 3.6 (b), respectively. The maximum tissue temperature elevation in the vicinity of each ultrasonic applicator was about 14°C.

Figs. 3.7 (a) and 3.7 (b) show the temperature distributions in the presence of blood flow for an array of four interstitial ultrasonic applicators and an array of four resistive wires, respectively. Although the arterioles are located very close to the heating elements, local cold spots are still seen around them. The maximum tissue temperature elevation is about 9.2°C around each ultrasonic applicator. The presence of blood flow not only reduced the maximum temperature elevation in the heated volume, but also produced local cooling. The temperature distribution in the presence of blood flow is more affected for modeling with resistive wires (Fig. 3.7(b)). In this case, because a constant temperature was assumed at the wires without any power deposition in the tissue, the temperature gradient caused by arterioles is larger. Therefore the probability of producing cold spots around the arterioles is more when the heat source is a resistive wire. This demonstrates the importance of choosing the type of heat source for treatment.

Usually, in thermal therapy planning, a uniform heat distribution in the tumor volume is required. Also, the whole tumor volume is expected to reach the therapeutic range of temperature within the planned therapy time.

Fig. 3.6. Temperature distribution in the middle layer of the model, without including the cooling effects of arterioles (a) Produced by an array of four 1.5 cm long ultrasonic applicators. The temperature at each applicator site is 51°C. These temperatures fall off fairly quickly, once outside of the heating volume, and approach a basal or boundary temperature of 37°C. (b) Produced by an array of four 6 cm long resistive wires. The temperature of each wire is 49°C.

Fig. 3.7. Temperature distribution in the middle layer of the model, including arteriole flow (a) Produced by an array of four 1.5 cm long ultrasonic applicators. The maximum temperature at each applicator site is 46.5°C. (b) Produced by an array of four 6 cm long resistive wires. The temperature of each wire is 49°C.

Figs. 3.8 and 3.9 show the temperature distribution in the middle plane of the source region along different axes, vectors A, B, C, D (these vectors are depicted in Fig. 3.3), for the case of ultrasonic applicators and resistive wires. The temperature at the center of the symmetry of the heating elements is 45°C and 44°C for the ultrasonic applicators and resistive wires, respectively. These temperatures in Fig. 3.8(a) and (b), are achieved over 1.4 cm around the center of symmetry of the heating elements along vectors A and B. In Fig. 3.9(a) and (b) these temperatures are roughly achieved for 4.2 cm around the center of the symmetry of the heating elements along vectors C and D. From these figures, it can be concluded that the power adjustment at the ultrasonic applicators and temperature adjustment at the resistive wires could produce the required therapeutic temperature in the heated region. The power deposition pattern of ultrasonic heating could provide more uniform temperature and more temperature increase in the center of the heated region. However, it should be noted that there is no arteriole along the vectors A, B, C, D (Fig. 3.3). Therefore Figs. 3.7 and 3.8 do not show any local temperature gradient caused by arterioles. The local cold area around arterioles exists for both ultrasound and resistive heating. The temperature at a position in the vicinity of an arteriole in our model is about 43°C .

The following chapter describes the experiment that was carried out to verify these calculations.

Fig. 3.8. The temperature distribution versus distance along the vectors A and B in the presence of arterioles. The origin is at the center of the square formed by (a) four ultrasonic applicators and (b) four resistive wires.

Fig. 3.9. The temperature distribution versus distance along the vectors C and D in the presence of the arterioles. The origin is at the center of the square formed by the four (a) ultrasonic applicators and (b) resistive wires.

Chapter 4

Materials and Methods

A phantom was designed based on the specifications of an adult human brain to verify the FEA of heat transfer in brain tissue produced by an array of interstitial ultrasonic applicators [44]. As an initial step, an array of resistive wires was replaced by the ultrasonic applicators in a phantom of the same design. In this chapter, detailed descriptions of the equipment, materials and methods will be presented: *e.g.* resistive wires, brain tissue phantom, arteriole tubes, and microthermistors.

4.1. Resistive Wires as Heating Elements

A 4.060 Ω /ft, 0.32 mm diameter, 80 cm length of Inconel resistive wire was coated with an insulating paint and cut in four equal length sections. Each section was bent in half and inserted into 1.1 mm OD, 0.8 mm ID, 10 cm long hollow glass capillary tubes^a. A

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^a KIMAX-51 Capillary tubes.

power supply^b was used to supplying power to these wires. A set of preliminary tests was done for estimate the required input power on each resistive wire for production of 12°C temperature elevation in a piece of phantom gel. The temperature was monitored by a microthermistor at each capillary tube. Fig. 4.1 shows the diagram of the test setup.

Fig. 4.1. Block diagram of the circuit used to find the required input power of resistive wire.

4.2. Brain Tissue Phantom

The phantom that was used in this experiment was made of a gel consisting of 9.1% gelatin^c by mass, in ethylene glycol.^d The gelatin and ethylene glycol were mixed together at 90°C, until the gelatin became completely dissolved. The cooling process required 24 hours to reach room temperature.

According to previous studies of the properties of the phantom [44] the melting point is 39°C, the thermal conductivity is (0.55 ± 0.12) W/(m°C) and the ultrasound attenuation coefficient is (0.089 ± 0.010) Np cm⁻¹ MHz⁻¹. The average thermal conductivity and

^b HEATHKIT model IP-12 DC.

^c Sigma Chemical Type B from bovine skin .

^d The phantom that was used in this experiment had been designed and built in the previous studies [42].

ultrasound attenuation coefficient of brain are $0.527 \text{ W}/(\text{m}^\circ\text{C})$ and $(0.086 \pm 0.020) \text{ Np cm}^{-1} \text{ MHz}^{-1}$ respectively. The dimensions of the phantom and of our FEA mesh were based on 70% of the adult brain volume. A picture of the phantom is shown in Fig. 4.2.

Fig 4.2. The phantom used in this experiment.

4.3. Arteriole Tubing

The arterioles in this experiment were made of Intramedic Polyethylene Tubing with an inner diameter of 0.581 mm and outer diameter of 0.965 mm, yielding a wall thickness of 0.192 mm. These dimensions of the arterioles were chosen based on the ratio of wall thickness to the inner diameter of real arterioles. This ratio does not change with aging, even though the vessel sizes do. The ratio, obtained from cross-sectional photographs of cranial vessels is approximately 0.2 [44]. The plastic tubing that was used in this experiment has a ratio of 0.33 [44]. The velocity of the blood is proportional to the size of the vessels [44]. According to color Doppler ultrasound imaging, the blood flow rate of

the venous vessels in the brain is in the range of 3.0-9.2 cm/s [57]. Since arterioles have a moderate size, a nominal value of 4.9 cm/s was chosen as the blood flow rate for the arterioles in our experiment [44].

Since 89% of human blood is water, in our experiment water was used to simulate blood. The water was circulated in the plastic tubing by means of a pump.^e The arterioles have been positioned in the phantom at the same locations used in the FEA model.

4.4 The Skull

Plexiglass (poly methyl methacrylate) was used to simulate the human skull in our experiment. A frame of plexiglass, with the dimensions of the human brain cross-section, used in our FEA model, was filled with our phantom tissue gelatin solution. The thermal conductivity of plexiglass is comparable to that of the human skull. Holes were drilled into the Plexiglas for the positioning and supporting applicators, arterioles, and microthermistors.

4.5. Assembly and Calibration of Microthermistors

Microthermistors were used as temperature sensors in the phantom experiment. These are made of ceramic semiconductors. They are nonlinear elements and have a negative

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^e Cole Parmer Master Flex Model 7016-21, Chicago, IL.

temperature coefficient: *i.e.*, the resistance of a microthermistor decreases as the temperature increases.

Eleven 111-202CAK-B01 microthermistors^f with a bead size of 200 μm , with two 50 μm thick wire leads were used in this experiment. Each microthermistor was placed in a 24-gauge stainless steel needle. The perturbation in temperature measurements by the needles is very small due to poor conductivity of stainless steel material. The needles were beveled to 70° on one side as shown in Fig. 4.3, with the microthermistors placed inside the bevels. For pulling microthermistors through the needle, two wires were soldered to the microthermistor leads. One of the leads was coated with an insulating paint. The microthermistor beads were then protected with a layer of epoxy before being inserted into water for calibration. It is recognized that microthermistors themselves produce perturbations in the results of temperature measurements. However, since they are very small, it can be assumed that the perturbation is also small.

Fig. 4.3. A microthermistor position in a stainless steel needle.

^f Fenwell Electronics, Milford, MA.

The resistance, R_μ , of a microthermistor drops off exponentially with the inverse of its absolute temperature [58]:

$$R_\mu = A e^{\beta/T}, \quad (4.1)$$

where A and β are constants and T is the absolute temperature.

The microthermistors were calibrated by using the voltage divider circuit shown in Fig. 4.4 to give the constants A and β .

Fig. 4.4. The voltage divider circuit for calibration of the microthermistors. Here, V_i is the input voltage, V_o is the output voltage, R is a constant resistance, and R_μ is the resistance of the microthermistor.

The microthermistors were immersed in water with a calibrated thermolinear element.^g The temperature of the water was elevated to 20°C above room temperature, using an electric heater controlled by a VARIAC transformer. The temperature of the water was monitored by using a standard mercury thermometer. The output voltage was adjusted to

^g YSI Inc. Yellow Springs Ohio. The thermolinear element is a semiconductor used for precisely measuring temperature.

produce a 20°C temperature elevation over a period of 2 hours. The water was then allowed to cool back to room temperature over an additional period of 2 hours. A data acquisition system^h, executed in MATLAB 5.0 environment, was used during the heating and cooling phases to determine $R_\mu(T)$, by measuring V_{out} and T as a function of time.

$R_\mu(T)$ is related to V_{out} by the voltage divider equation,

$$V_{out} = \frac{R_\mu}{R + R_\mu} V_i, \quad (4.2)$$

where R and V_i are kept constant. The theoretical curve was then fitted to the data to determine A and β in equation 4.1 using linear regression. The calibrated microthermistors were then inserted into the phantom at different locations. Fig. 4.5 shows the location of the microthermistors in the phantom. Nine microthermistors (Nos. 2, 3, 4, 6, 7, 8, 9, 10, 11) were positioned in the middle plane of the model, as defined in our FEA modeling (Chapter 3) for temperature analysis. Microthermistors numbers 2, 3, 6, 7 were located in the DR region for monitoring the temperature distribution in the vicinity of the DR wire toward the boundary of the DR and DL quadrants.

Microthermistors Nos. 3 and 6 specifically show the temperature across one of the internal arterioles in this quadrant. Microthermistors numbers 6, 8, 9, and 11 were positioned in the vicinity of an arteriole in the DR, DL, FL and FR regions, respectively. These microthermistors are equidistant from a heat source and show the temperature near arterioles in different regions. Microthermistor number 4 was placed at the boundary of

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^h DATASCAN 7010 and 7020, Measurement System Ltd. Pl., UK.

the FL and FR quadrant to check the temperature elevation of the phantom at the boundary of the two lower quadrants that are located close to the boundary of the wall. Microthermistor number 10 detects the temperature elevation at the center of the heated region. The other two microthermistors, number 1 and number 5, were positioned in planes 0.5 cm below and above the microthermistor number 10 respectively. The coordinates of the microthermistor positions are given in Table 4.1. The accuracy of positioning was to within ± 0.3 mm.

Microthermistor No.	X(mm)	Y(mm)	Z(mm)
1	44.3	50.0	25.0
2	21.9	63.2	30.0
3	20.2	63.4	30.0
4	10.0	3.6	30.0
5	10.0	50.0	35.0
6	17.7	63.9	30.0
7	13.4	64.4	30.0
8	-5.7	67.7	30.0
9	-7.7	67.7	30.0
10	10.0	50.0	30.0

Table 4.1. The coordinates of microthermistors in the phantom. The coordinates of the center at the square defined by the resistive wires, are (10, 50, 0) mm.

Fig. 4.5. Diagram of the position of microthermistors 1 through 11 in the phantom (top view).

4.6. Heating Procedure

An array of four resistive wires, encapsulated in the capillary tubes, was inserted into the phantom with arterioles and microthermistors in place. Fig. 4.6 is a picture of the experimental set up. Each resistive wire was inserted in the phantom to a depth of 6 cm. The wires were connected in series and attached to the power supply. The current and voltage of the power supply were adjusted to rapidly achieve a 12°C temperature rise at the capillary tubes. They were manually adjusted to maintain the $(12.0 \pm 0.2)^{\circ}\text{C}$ temperature elevation for about 90 min. This temperature, at the surface of capillary tubes, was chosen so as not to exceed the melting point of the phantom: *i.e.*, 39°C. The temperature at one of the capillary tubes was monitored by a microthermistor (number 2), 1.2 mm away. Because of the symmetry in the heating region of the phantom, as explained in chapter 3, the temperature is assumed to be the same, at this distance, for the other three capillary tubes, so no other microthermistors were used for monitoring the maximum phantom temperature.

A data acquisition system was used for temperature measurements. Given the calibration factors for each of the microthermistors, a MATLAB program dynamically computed the temperature values from their individual voltage readouts. The result was a graph of microthermistor temperatures versus time, shown in Figs. 5.1 to 5.4. These graphs will be presented in the next chapter.

Fig. 4.6. The experimental set up for temperature measurement in the brain phantom.

Chapter 5

Results and Discussion

FEA modeling of the heat distribution in a brain tissue phantom, in the presence of arterioles, was verified by a series of experiments. In this chapter, the FEA of the heat distribution, in a brain tissue phantom, produced by an array of four resistive wires, along with experimental results, will be presented.

5.1. Temperature Distribution in the Phantom

The temperature in the phantom, without water flow, was measured for periods of 60 and 90 minutes. Figs. 5.1 and 5.2 show the temperatures of ten microthermistors (numbers 1 through 10), at various locations in the phantom, as a function of time. The positions of the microthermistors are shown in Fig. 4.5. For the first three minutes, the microthermistors show the temperature of the phantom at room temperature. The initial temperature of the phantom in each experiment was estimated as the average of the microthermistor temperatures at $t = 0$. The initial temperature of the phantom in Fig. 5.1

is $(25.1 \pm 0.2)^{\circ}\text{C}$ and in Fig. 5.2 is $(26.2 \pm 0.3)^{\circ}\text{C}$. The instrumental uncertainties are negligible.

In Fig. 5.1, the maximum $(12.0 \pm 0.2)^{\circ}\text{C}$ temperature elevation was achieved by applying 4.2 W total power for 1380 seconds. The power was then manually adjusted for the following 2040 seconds to maintain the maximum temperature elevation. The final applied power was 2.6 W. Fig. 5.2 depicts the temperature in the phantom during a period of 5400 seconds. During this time 4.8 W was applied for about 420 seconds, to reach the required 12°C temperature elevation at the position of microthermistor No.2. The current was then adjusted to maintain this elevation. The final applied power was 2.1 W. The combined results are also shown in table 5.1. The differences between Figs. 5.1 and 5.2 are due to the initial applied power that was applied to the wires and the heating time. In Fig. 5.1, the initial power is lower and the total heating time shorter.

Fig. 5.3 and 5.4 show results of the temperature measurement in the phantom with flowing water. The first 180 seconds show the temperature of the phantom at room temperature: *i.e.*, $(22.5 \pm 0.2)^{\circ}\text{C}$ in Fig. 5.3 and $(25.3 \pm 0.3)^{\circ}\text{C}$ in Fig. 5.4. In both curves, the temperature of the phantom at the position of microthermistor No.2 was then increased by 12°C , over a period of 480 seconds by 5.5 W applied power. Then the power was adjusted to maintain the $(12.0 \pm 0.2)^{\circ}\text{C}$ temperature elevation over a period of 4920 seconds. The final applied powers were 3.2 W for Fig. 5.3 and 3.5 W for Fig. 5.4. Table 5.2 shows the final temperature of each microthermistor, corresponding to Figs. 5.3 and 5.4.

Fig. 5.1. The temperature versus time in the brain tissue phantom for the first run without water flow. The numbers correspond to the microthermistor numbers.

Fig. 5.2. The temperatures versus time in the brain tissue phantom for the second run without water flow. The numbers correspond to the microthermistor numbers.

Final temperature elevations corresponding to Fig.5.1		Final temperature elevations corresponding to Fig. 5.2	Mean temperature rise $\pm 0.2^{\circ}\text{C}$
Micr. No.	Temperature $\pm 0.2^{\circ}\text{C}$	Temperature $\pm 0.3^{\circ}\text{C}$	
1	8.5	8.7	8.6
2	11.9	12.3	12.0
3	11.7	11.6	11.7
4	7.3	9.4	7.9
5	8.6	9.3	8.8
6	9.7	9.5	9.7
7	9.1	9.0	9.1
8	9.3	8.6	9.1
9	7.1	7.2	7.1
10	8.7	8.9	8.8

Table 5.1. The final temperature elevation of each microthermistor taken from Figs. 5.1 and 5.2.

Final temperature elevations corresponding to Fig.5.3		Final temperature elevations corresponding to Fig. 5.4	Mean temperature rise $\pm 0.2^{\circ}\text{C}$
Micr. No.	Temperature $\pm 0.2^{\circ}\text{C}$	Temperature $\pm 0.3^{\circ}\text{C}$	
1	6.2	6.9	6.4
2	12.2	12.0	12.1
3	10.4	11.2	10.6
4	6.2	7.4	6.5
5	6.7	6.5	6.7
6	5.5	6.9	5.9
7	6.3	7.1	6.5
8	5.9	6.3	6.0
9	5.0	4.9	4.9
10	6.7	6.2	6.6

Table 5.2. The final temperature elevation of each microthermistor taken from Figs. 5.3 and 5.4.

Fig. 5.3. The temperature versus time in the brain tissue phantom for the first run in the presence of water flow. The numbers correspond to the microthermistor numbers.

Fig. 5.4. The temperature versus time in the brain tissue phantom for the second run in the presence of water flow. The numbers correspond to the microthermistor numbers.

5.2. Results

For the comparison between experimental and theoretical results, it is best to visualize the thermal data as a function of position with respect to a single heating element by mapping the temperature values into the dorsal-right (DR) quadrant of the applicator array. The insert in Fig. 5.5 depicts this mapping. Microthermistors numbers 2, 3, 6, and 7 are placed along a radial direction, toward the dorsal-left, from the DR resistive wire. Microthermistors numbers 8 and 9 are mapped from the dorsal-left (DL) and frontal-left (FL) quadrants, respectively. These microthermistors are also along a radial direction from the DR resistive wire, but they point up to the right. Microthermistor No. 4 is mapped from the boundary of the FL and frontal-right (FR) quadrants to the left edge of the DR quadrant, horizontally, away from the DR resistive wire. Microthermistor No. 10 is at the center of the symmetry of the heating region. Microthermistors numbers 1 and 5 are mapped to the same position as of No. 10 from a layer 5 mm above and below, respectively. Since all of the aforementioned measurement points are now represented within the same quadrant, a radial plot can be made, which gives an overall representation of the data.

Fig. 5.5. The location of the microthermistors numbers 1 through 10 in our phantom. The insert box shows the position of microthermistors, mapped to the dorsal- right (DR) region, which will be used for analysis purposes.

Figs. 5.6 and 5.7 show the thermal data as a function of distance, from the DR resistive wire, without and with arteriole blood flow, respectively. Each experimental data point in these figures is the weighted average of the final temperatures of each microthermistor (taken from tables 5.1 and 5.2). The standard deviation of the mean of each data point was calculated by [59]:

$$\sigma_{\mu} = \sqrt{\frac{1}{\sum_{i=1}^N \frac{1}{\sigma_i^2}}} \quad (5.2)$$

where the σ_i values are the uncertainty at each final temperature. The accuracy of the positioning of each microthermistor was ± 0.3 mm. This was converted into the temperature uncertainty in simulation by interpolating with respect to neighboring nodes. As an example the temperature of the neighboring nodes around microthermistor No. 6 are shown in table 5.3. The errors in the temperature of each simulated result, due to uncertainty in positioning, are shown in Figs. 5.6 and 5.7. The simulated data are also presented in table 5.4.

The agreement between experiment and theory for microthermistors numbers 2, 3, 6, and 7 seems reasonable for both of the figures. The temperature at these microthermistors in Fig. 5.7 drops about 3.5°C lower than in Fig. 5.6, as one crosses the arteriole region. The temperature perturbation caused by the arteriole reduces the temperature elevation around the arteriole to 6°C. The distance of microthermistor No. 6 is just 0.5 cm away from the heat source, which is 12°C temperature above basal temperature.

Fig. 5.6. The temperature of the microthermistors as a function of radial distance from the DR wire, obtained from experiment and simulation, without arteriole blood flow. The splines, connecting microthermistors numbers 2, 3, 6, 7 are just for guiding the eye. Very small errors are plotted as zero.

Fig. 5.7. The temperature of the microthermistors as a function of distance from the DR wire, obtained from experiment and simulation, with arteriole blood flow. The splines, connecting microthermistors numbers 2, 3, 6, 7 are just for guiding the eye. Very small errors are plotted as zero.

Distance from Microthermistor No. 6 (cm)	Temperature rise (°C)
0.25	6.9
0.35	6.3
0.19	6.3
0.35	6.5
0.25	6.9
0.27	6.7
0.16	6.6
0.27	7.2

Table 5.3. The simulated temperatures at the nodes around microthermistor No. 6 in the presence of water flow.

Microthermistor No.	Temperature rise (°C) corresponds to Fig. 5.6	Temperature rise (°C) corresponds to Fig. 5.7
1	9.4 ± 0.0	7.3 ± 0.0
2	12.0 ± 0.2	12.0 ± 0.0
3	11.0 ± 0.0	10.8 ± 0.3
4	7.9 ± 0.4	6.6 ± 0.1
5	9.4 ± 0.0	7.1 ± 0.0
6	9.7 ± 0.1	6.3 ± 0.0
7	9.1 ± 0.0	6.5 ± 0.0
8	9.6 ± 0.1	6.3 ± 0.1
9	7.8 ± 0.0	6.2 ± 0.1
10	9.4 ± 0.0	7.2 ± 0.0

Table 5.4. The temperatures at the position of microthermistors from simulation. Very small errors are set to zero.

Microthermistor No. 4 is located midway between the FL and FR resistive wires. The agreement between theory and experiment is good in both figures. Microthermistors numbers 4 and 7 show roughly the same temperature in Fig. 5.7. Both of these microthermistors are located almost on a line running between two arterioles and are, therefore, shielded from the heat sources. In Fig. 5.6 the temperature at microthermistor No. 7 is about 1.5°C higher than that of microthermistor No. 4. Microthermistor No. 4 is located in the region close to frontal boundaries, which is closer to the boundaries of the phantom (the wall).

Microthermistors numbers 6, 8 and 9 are very close to arterioles and have the same distance from an arteriole. These microthermistors also have the same distance from the DR, DL and FL heat sources, respectively. The experimental results for microthermistors numbers 6 and 8 are in good agreement with the simulation. These two microthermistors roughly show the same temperature. Microthermistor No. 8, which is closer to the boundary, shows a slightly lower temperature. The discrepancy between experiment and simulation is worse for microthermistor No. 9 in both figures. This microthermistor is located in the frontal part of the heating region that is closer to the boundaries of the phantom. This microthermistor also shows the lowest temperature compared to the other two microthermistors, because the temperature gradient towards the phantom wall is steeper for the former.

Microthermistors No. 10, 1 and 5 are located on the same vertical line. Microthermistor No. 10 is located at the center of the source region. Microthermistor No. 1 is located 0.5

cm above No. 10 and is 2 cm below the top of the phantom wall. The experimental temperature at this microthermistor is roughly 0.2°C lower than the temperature of No. 10 in Fig. 5.6 and 0.4°C lower than that of No. 10 in Fig. 5.7. Microthermistor No. 5 is located 0.5 cm below No. 10 and 2.5 cm above the base of the phantom. The experimental temperature at this microthermistor is the same as the temperature of No. 10 in Fig. 5.6 and 0.4°C more than No. 10 in Fig. 5.7. The different temperatures at No. 10, 5 and 1 in experiment are related to the position of these points with respect to phantom wall. In other words, a temperature gradient exists from the top to the bottom of the phantom due to a slight temperature difference between the top and the bottom of the phantom.

To estimate the thermal damage it is necessary to calculate the thermal dose in the target. The thermal dose at the location of the microthermistors in the phantom was calculated by using equation 1.1. For this calculation, Δt was 3 minutes, and the initial temperature of the phantom was assumed to be at the basal temperature of the body *i.e.*, 37°C . The thermal dose at the position of microthermistors numbers 4 and 10 with and without water flow is depicted in Fig. 5.8. For heating time of 60 minutes, the accumulated thermal dose at the location of microthermistors number 4 and 10 without water flow are 129 EM_{43} and 193 EM_{43} , respectively. These values reduce to 29 EM_{43} and 50 EM_{43} in the case of the experiment with water flow. Fig. 5.9 shows the thermal dose versus heating time for microthermistors numbers 6, 8 and 9 with and without water flow. Each of these microthermistors is located close to an arteriole. The lower temperature around an arteriole reduces the thermal damage. For the heating time of 60 minutes, the

accumulated thermal doses in the case of the experiment without water flow are 393 EM_{43} for microthermistor number 6, 64 EM_{43} for microthermistor number 8 and 38 EM_{43} for microthermistor number 9. These values reduce to 28 EM_{43} 29 EM_{43} and 8 EM_{43} , respectively for the experiment with water flow. The thermal dose at microthermistor No. 2 is about 3600 EM_{43} in both experiments with and without water flow.

Fig. 5.8. Thermal dose at the location of microthermistors numbers 4 and 10 with and without water flow.

Fig. 5.9. Thermal dose at the location of microthermistor numbers 6, 8, 9 with and without water flow.

5.3. Discussion

The main discrepancies between experiment and theory appear to be in two regions: close to the boundaries of the phantom, and in the vertical direction. The phantom boundaries are made of plexiglass, which does not remain at constant temperature during the experiment. Furthermore, the assumption of no heat exchange between plexiglass and air

is not realistic. The heat exchange between plexiglass and air was not considered in our FEA modeling. The discrepancies between simulation and experiment increase, as one gets closer to the boundaries of the phantom.

Experimental results show that there is a temperature gradient in the vertical direction. The result of the simulation in the case without blood flow, does not predict any temperature gradient in the vertical direction. The simulation in the presence of blood flow predicts a vertical temperature gradient because of the model of heat transfer to the arterioles. However, it seems that the model underestimates the temperature gradient when compared to experiment. The discrepancies between experiment and theory in vertical direction could be also because of the non-uniform heating within the resistive wires. In general more microthermistors along the vertical direction and around the phantom boundaries are required to investigate the temperature variations in these two regions.

However, the model in most parts seems to be in agreement with the experimental results. It was used under some unrealistic approximations, such as symmetric heating of the arterioles that is not the case for interstitial heating. Furthermore, the approximation of a cylindrical tissue layer around each arteriole was not a good approximation in our FEA. The asymmetric heat transfer in arterioles (equation 2.8 with addition of ϕ term) could be calculated using Finite Difference Method (FDM). The details of the calculation and preliminary results are presented in Appendix B. This model is not dependent on the heat transfer coefficient. Fig. 5.10 shows the prediction of the model compared to experiment

after 3 iterations. The model seems to be slow in converging to the solution when it is coupled with FEA. This might be related to the fact that the mesh is very coarse around arterioles in FEA model. Also it is critical how the boundary conditions are defined. The assumption of the adiabatic boundary condition for the blood at the bottom of the phantom is not realistic. The results would be improved if the arterioles were extended to a longer length and outside the phantom. This could push the adiabatic boundary condition far away from the significant regions of the phantom.

The reduction of thermal dose in the experiment with water flow shows the importance of considering the large blood vessels in modeling. Usually about 60 EM₄₃ is required for lesion production [51]. In our experiment with resistive wires and in the presence of water flow during 60 minutes heating time the thermal doses at the microthermistors numbers 10, 4, 6, 8 and 9 have not reached to this limit. For the same heating time the thermal dose at the microthermistor No.2 was too high (about 3600 EM₄₃). In a longer heating time, it might be possible to reach the required thermal dose for lesion production at the location of all microthermistors, but the high accumulated dose around microthermistor No. 2 would probably exceed the tolerance of the normal tissue close to this location. This is especially important when the heating elements were positioned close to the boundaries of the tumor.

There are some sources of errors in the experiment that can affect the agreement between experiment and simulation. The arteriole's cooling is sensitive to blood velocity. Therefore any error in estimation of water velocity flowing through arterioles will affect

the results. Also the thermal conductivity and the specific heat capacity of the phantom, arterioles, and water can affect the results.

Fig. 5.10. The temperature of the microthermistors as a function of distance from the DR wire in the presence of arteriole flow, obtained from experiment and simulation where the finite difference method was used for heat transfer within the arterioles. The splines, connecting microthermistors numbers 2, 3, 6, 7, are just for guiding the eye. Very small are plotted as zero.

Chapter 6

Conclusion and Future direction

6.1. Conclusion

The discrete blood vessel model, which was proposed by Jarosz [42], has been used for the prediction of the temperature distribution in brain tissue with some modifications in the method of heat transfer calculation in arterioles. Two types of heat sources were considered for modeling: an array of four 2.25 MHz interstitial ultrasonic waveguide applicators and an array of four resistive wires. In this model three cylindrical shaped arterioles were placed, parallel to, and around each heating element. The FEA simulation of steady state heat transfer without and with blood flow, showed that the temperature in the heated region bounded by the heating elements could be in the therapeutic range by adjusting the power at the ultrasonic applicators, and the temperature at the resistive wires. However it should be recalled that the thermal damage to biological tissue, in addition to temperature, depends on time, and it is very important to heat the tissue uniformly. There is always a thermal dose tolerance for the normal tissue around the

tumor. Therefore only increasing the temperature at the heating elements until the therapeutic temperature is achieved throughout the tumor volume may result in exceeding the thermal dose tolerance of the normal tissue around the heating elements. It was also observed that the arterioles produce a cold region around themselves. The temperature perturbation caused by arterioles is greater for the case of resistive wires than for ultrasonic applicators. Therefore the probability of producing cold spots around the large blood vessels is higher in the case of resistive wires than for ultrasonic applicators. Clearly the power deposition pattern of the heat source plays an important role in the temperature distribution in the region of interest.

However, although the model predicts satisfactory results, we cannot conclude that it is ready for clinical application. In fact it should be noted that this model neglects the microvasculature perfusion, which is an unrealistic assumption for brain tissue. In this model, BHTE or ETCE do not really give significantly different results. Furthermore the assumption of cylindrical arterioles, parallel to the applicators is artificial, especially for the complex vascular geometry of tumors. Arterioles in this model were only assumed very close to the heat source. The cooling effect of these vessels was not investigated in the regions farther from the heat source. The assumption of a necrotic region at the center of tumor may be valid, but for accurate modeling the possibility of having blood vessels in other areas should be also considered. Furthermore, the model that was used for calculation of heat transfer to the individual arterioles is based on the assumption of constant arteriole wall temperature and a symmetric heating of the arteriole. The model also uses the numerical value of the heat transfer coefficient, h for calculation. In short,

the present model could only be considered as an initial step towards modeling of temperature distribution produced by interstitial heating of gliomas. It does, however, confirm the importance of consideration of the arterioles in treatment planning, where under treatment of even small regions can have serious consequences.

An experiment was set up to verify our FEA modeling. In this experiment, the heat source was an array of four resistive wires, which produced a maximum 12°C temperature elevation, above room temperature. The results of this experiment were then compared with the FEA simulation. In general a good agreement was seen between the experimental results and the simulation. The largest discrepancies between experiment and simulation were in the areas that are closer to the boundaries of the phantom and in the vertical direction. It was concluded that the definition of the boundaries in our model is not really matched with the experiment. Also the non-uniform heating along the resistive wires and the temperature gradient in the vertical direction caused by blood flow could be the reasons for these discrepancies. Furthermore the low node density around arterioles in our FEA modeling could lead to an inaccurate estimation of temperature, especially in the vertical direction and around arterioles. Inaccurate estimate of the specific heat capacity, thermal conductivity of the phantom and the blood velocity in arterioles may also cause discrepancies.

6.2. Future Direction

The modeling of heat transfer could be improved in many ways to more realistically simulate a specific tissue. Microvasculature perfusion should be included in realistic modeling. An investigation should be done on the size and the velocity of the large blood vessels in the tumor to be considered. A finer mesh is required, especially around the arterioles and the heating elements. The heat transfer to the arterioles can be calculated without assumption of symmetric heating and constant arteriole wall temperature using one of the Finite Difference Method (FDM) or FEA. However, coupling the results of FDM to FEA is time consuming and inefficient. Either FEA or FDM codes can be written to calculate the heat transfer for the whole model. Also, the newer version of the commercial software that was used in this study, Algor, has the ability to couple the fluid flow and heat transfer analysis. This software can be used for transient and steady state heat transfer analysis, without separately modeling the heat transfer in large blood vessels. The transient analysis is especially important for thermal dose investigation on the heated region.

It is critical to redefine and control the boundary conditions in the experiment. Using plexiglass at the boundaries of the phantom adds complications to the experiment and the definition of the boundary conditions in the model. A water bath can be used to keep the temperature of the boundaries at a constant temperature.

Since the final goal of the study is to propose a method for treatment of gliomas, it is necessary to investigate the real vasculature geometry and the blood flow rate of these tumors for modeling. Since it is very difficult to provide the vasculature geometry in a phantom, a real perfusable tissue should be used for experimentation instead of a phantom. It is also necessary to determine the range of thermal dose that is required for treatment, and which can be tolerated by normal tissues before reaching any conclusion about the likely success of the method as a treatment technique.

Appendix A:

The Graetz Problem

The Graetz problem is defined for heat transfer to a laminar fluid that flows through a circular tube. The fluid is assumed to have constant properties, fully developed velocity profile and developing temperature profile. The temperature is constant along the tube wall and axial heat conduction is neglected. The heat equation is expressed by:

$$\frac{\partial^2 T}{\partial r^2} + \frac{1}{r} \frac{\partial T}{\partial r} = \frac{u(r)}{\alpha} \frac{\partial T}{\partial z} \quad (\text{A.1})$$

where $u(r)$ is the laminar velocity and α is the thermal diffusivity. The boundary conditions are as follows:

$$\frac{\partial T}{\partial r} = 0 \quad \text{at} \quad r = 0 \quad (\text{A.2})$$

$$T = T_w \quad \text{at} \quad r = a \quad (\text{A.3})$$

$$T = T_e \quad \text{at} \quad z = 0 \quad (\text{A.4})$$

where T_w is wall temperature and T_e is the initial temperature. The solution of temperature distribution and Nusselt number for this problem, is given by [60]:

$$\theta_m = \frac{T_m - T_w}{T_e - T_w} = 8 \sum_{n=0}^{\infty} \frac{G_n}{\lambda_n^2} \exp(-2\lambda_n^2 \frac{z}{d Pe}) \quad (\text{A.5})$$

$$Nu = \frac{\sum_{n=0}^{\infty} G_n \exp(-2\lambda_n^2 \frac{z}{d Pe})}{2 \sum_{n=0}^{\infty} (\frac{G_n}{\lambda_n^2}) \exp(-2\lambda_n^2 \frac{z}{d Pe})} \quad (\text{A.6})$$

where θ_m is the dimensionless mean fluid temperature, T_m is the mean fluid temperature, G_n represent eigenvalues and λ_n represents eigenconstants. The first ten G_n and λ_n are given in Table A.1. In equations (A.5) and (A.6), z is the axial distance, d is the diameter of the tube and Pe is the Peclet number that is defined by:

$$Pe = Re \cdot Pr \quad (\text{A.7})$$

where Re is Reynold number and Pr is Prandtl number:

$$Re(\bar{u}, d) = \frac{\rho \bar{u} d}{\mu}, \quad (\text{A.8})$$

$$Pr = \frac{\mu c_p}{k} \quad (\text{A.9})$$

where $\bar{u}$ is the average velocity, ρ is density, μ is the dynamic viscosity, k is the fluid thermal conductivity and c_p is the specific heat of fluid.

Figs. A.1 and A.2 show the normalized mean blood temperature and the Nusselt number versus the axial distance for the arterioles with inner diameter of 0.58 mm and the length of 6 cm.

N	G_n	λ_n
0	0.7488	2.7044
1	0.5438	6.6790
2	0.4629	10.6734
3	0.4154	14.6711
4	0.3829	18.6699
5	0.3587	22.6691
6	0.3396	26.6687
7	0.3241	30.6683
8	0.3110	34.6681
9	0.2998	38.6679
10	0.2901	42.6677

Table A.1. The eigenvalues and eigenconstants for a circular tube [60].

Fig A.1. The normalized mean fluid temperature versus axial distance.

Fig. A.2. Nusselt Number versus the axial distance.

Appendix B:

Arteriole Heat Transfer Calculations

using FDM

The Finite Difference Method (FDM) was used to solve the steady state heat equation for blood vessels (laminar flow and fully developed velocity profile). The heat equation for these vessels can be written as;

$$u(r) \frac{\partial T}{\partial z} = \alpha_b \left(\frac{\partial^2 T}{\partial r^2} + \frac{1}{r} \frac{\partial T}{\partial r} + \frac{\partial^2 T}{\partial z^2} + \frac{1}{r^2} \frac{\partial^2 T}{\partial \phi^2} \right) \quad \text{for } r < R_b \quad (\text{B.1})$$

and

$$\nabla^2 T = 0 \quad \text{for } R_b < r < R \quad (\text{B.2})$$

where R_b is the radius of the inner blood vessel wall, R is the radius of the outer blood vessel wall, and $u(r)$ represents the radial blood velocity profile: *i.e.*,

$$u(r) = 2\bar{v} \left[1 - \left(\frac{r}{R_b} \right)^2 \right] \quad (\text{B.3})$$

where $\bar{v}$ is the average blood velocity. These equations must be solved for the following boundary conditions,

$$T(r, z, \phi) = 0 \quad \text{at } 0 < r < R, \quad z = 0, \quad 0 < \phi < 2\pi, \quad (\text{B.4})$$

$$\frac{\partial T(r, z, \phi)}{\partial z} = 0 \quad \text{at } 0 < r < R, \quad z = L, \quad 0 < \phi < 2\pi, \quad (\text{B.5})$$

$$-k_b \frac{\partial T_b(r, z, \phi)}{\partial r} = -k_w \frac{\partial T_w(r, z, \phi)}{\partial r} \quad \text{at } r = R_b, \quad 0 < z < L, \quad 0 < \phi < 2\pi, \quad (\text{B.6})$$

and

$$T(r, z, \phi) = f(r, z, \phi) \quad \text{at } r = R, \quad 0 < z < L, \quad 0 < \phi < 2\pi. \quad (\text{B.7})$$

In FDM, the first and second derivatives of a function, $u(x)$ at node i , can be defined by the following equations,

$$\frac{du(x)}{dx} = \frac{u_i - u_{i-1}}{\Delta x} \quad (\text{B.8})$$

and

$$\frac{d^2 u(x)}{dx^2} = \frac{u_{i+1} - 2u_i + u_{i-1}}{(\Delta x)^2}, \quad (\text{B.9})$$

respectively, where Δx is very small and is the distance between node i and its adjacent nodes. Fig. B.1 shows the function $u(x)$ at the node i and its neighbors.

Fig. B.1. The function $u(x)$ about the i th node, position x_i .

A blood vessel with radius R and length L was discretized by n_r points in R , n_z points in L , and n_ϕ points in 2π . *i.e.*,

$$r_i = (i-1)\Delta r \quad \Delta r = R/(n_r - 1) \quad \text{and} \quad 2 \leq i \leq n_r - 1, \quad (\text{B.10})$$

$$z_j = (j-1)\Delta z \quad \Delta z = L/(n_z - 1) \quad \text{and} \quad 2 \leq j \leq n_z - 1, \quad (\text{B.11})$$

and

$$\phi_k = (k-1)\Delta\phi \quad \Delta\phi = 2\pi/(n_\phi - 1) \quad \text{and} \quad 2 \leq k \leq n_\phi - 1. \quad (\text{B.12})$$

The points $i = 1, n_r$, $j = 1, n_z$, and $k = n_\phi$ are handled by the aforementioned boundary conditions. The temperature derivatives in equation (B.1) can be written in terms of equations (B.8) and (B.9): *i.e.*,

$$\begin{aligned} & \frac{T_{i+1jk} - 2T_{ijk} + T_{i-1jk}}{(\Delta r)^2} + \frac{T_{ijk} - T_{i-1jk}}{r_i \Delta r} + \frac{T_{ij+1k} - 2T_{ijk} + T_{ij-1k}}{(\Delta z)^2} + \frac{T_{ijk+1} - 2T_{ijk} + T_{ijk-1}}{r^2 (\Delta\phi)^2} \\ & - \frac{u(r_i)}{\alpha_b} \frac{T_{ijk} - T_{ij-1k}}{\Delta z} = 0 \end{aligned} \quad (\text{B.13})$$

where

$$u(r_i) = 2\bar{v} \left[1 - \left(\frac{i-1}{n_b-1} \right)^2 \right], \quad (\text{B.14})$$

where

$$n_b = (n_r - 1) \frac{R_b}{R} + 1 \quad (\text{B.15})$$

Using equations (B.10) through (B.12), and solving for T_{ijk} , the temperature at each internal node (inside the blood vessel) can be written as,

$$\begin{aligned} T_{ijk} = & \frac{1}{\xi_i} \left\{ T_{i+1jk} + \left(\frac{i-2}{i-1} \right) T_{i-1jk} + \tau^2 T_{ij+1k} + (\eta_i + \tau^2) T_{ij-1k} \right. \\ & \left. + \frac{1}{4\pi^2} \left(\frac{n_\phi - 1}{i-1} \right)^2 (T_{ijk+1} + T_{ijk-1}) \right\} \end{aligned} \quad (\text{B.16})$$

where

$$\xi_i = \frac{1}{2\pi^2} \left(\frac{n_\phi - 1}{i-1} \right)^2 + \frac{2i-3}{i-1} + \eta_i + 2\tau^2, \quad (\text{B.17})$$

$$\eta_i = \frac{2\tau\bar{u}R}{\alpha_b(nr-1)} \left[1 - \left(\frac{i-1}{n_b-1} \right)^2 \right], \quad (\text{B.18})$$

and

$$\tau = \left(\frac{n_z - 1}{n_b - 1} \right) \frac{R}{L}. \quad (\text{B.19})$$

The temperatures at nodes for $z = L$, $r < R_b$ can be obtained by using the fictitious technique [45]. In this technique it is assumed that the region is extended to $L + \Delta z$.

Therefore, there is a fictitious node n_z+1 at a fictitious temperature $T_{i n_z+1 k}$. The boundary condition (equation B.5) can be written by:

$$\frac{T_{i n_z+1 k} - T_{i n_z k}}{\Delta z} = 0 \quad (\text{B.20})$$

For eliminating the $T_{i n_z+1 k}$, another equation is required that can be provided by solving equation (B.13) for the case of $j = n_z$:

$$\begin{aligned} T_{i n_z+1 k} = & \frac{1}{\tau^2} \left\{ \xi_i T_{i n_z k} - T_{i+1 n_z k} + \left(\frac{i-2}{i-1} \right) T_{i-1 n_z k} + (\eta_i + \tau^2) T_{i n_z-1 k} \right. \\ & \left. + \frac{1}{4\pi^2} \left(\frac{n_\phi - 1}{i-1} \right)^2 (T_{i n_z k+1} + T_{i n_z k-1}) \right\} \end{aligned} \quad (\text{B.21})$$

The temperature at $T_{i n_z k}$ can be written by eliminating the $T_{i n_z+1 k}$ from equations (B.20) and (B.21):

$$\begin{aligned} T_{i n_z k} = & \frac{1}{\xi_i - \tau^2} \left\{ T_{i+1 n_z k} + \left(\frac{i-2}{i-1} \right) T_{i-1 n_z k} + (\eta_i + \tau^2) T_{i n_z-1 k} + \right. \\ & \left. \frac{1}{4\pi^2} \left(\frac{n_\phi - 1}{i-1} \right)^2 (T_{i n_z k+1} + T_{i n_z k-1}) \right\} \end{aligned} \quad (\text{B.22})$$

Similarly, the temperatures for the nodes at $z = L, R_b < r < R$ are

$$\begin{aligned} T_{i n_z k} = & \frac{1}{\xi_i - \tau^2} \left\{ T_{i+1 n_z k} + \left(\frac{i-2}{i-1} \right) T_{i-1 n_z k} + \tau^2 T_{i n_z-1 k} \right. \\ & \left. + \frac{1}{4\pi^2} \left(\frac{n_\phi - 1}{i-1} \right)^2 (T_{i n_z k+1} + T_{i n_z k-1}) \right\} \end{aligned} \quad (\text{B.23})$$

The temperatures for nodes at $r = R_b$ are

$$T_{n_b j k} = \frac{1}{k_b + k_w} (k_b T_{n_b-1 j k} + k_w T_{n_b+1 j k}) \quad (\text{B.24})$$

where R_b contains n_b nodes. Temperature of the nodes at $r = R$ is:

$$T_{n_r j k} = T_{j k} \quad (\text{B.25})$$

where $T_{j k}$ at $r = R$ are obtained from our FEA iteration.

The $T_{j k}$ in the neighborhood of $r = 0$ were defined by using the heat equation in Cartesian coordinates, which one-to-one mapped to our special case for $n_\phi = 4$. The mapping is shown in Fig. B.2.

$$T_{1 j k} = \frac{1}{\chi} \left\{ \frac{T_{2 j 1} + T_{2 j 2} + T_{2 j 3} + T_{2 j 4}}{(\Delta r)^2} + \frac{T_{1 j+1 k} + T_{1 j-1 k}}{(\Delta z)^2} + u(r_2) \frac{T_{1 j-1 k}}{\Delta z} \right\} \quad (\text{B.26})$$

$$T_{1 j 1} = T_{1 j 2} = T_{1 j 3} = T_{1 j 4} \quad (\text{B.27})$$

where

$$\chi = \frac{4(\Delta z)^2 + 2(\Delta r)^2}{(\Delta z \Delta r)^2} + \frac{u(r)}{\Delta z} \quad (\text{B.28})$$

Similarly, the temperature at $z = L$ and $r = 0$ can be written as

$$T_{1 n z k} = \frac{(\Delta z)^2}{\chi(\Delta z)^2 - 1} \left\{ \frac{T_{2 j 1} + T_{2 j 2} + T_{2 j 3} + T_{2 j 4}}{(\Delta r)^2} + \frac{T_{1 j-1 k}}{(\Delta z)^2} + u(r) \frac{T_{1 j-1 k}}{\Delta z} \right\}. \quad (\text{B.29})$$

For solving the FDM, the relaxation technique was used. The relaxation algorithm can be found in Numerical Recipes [61]. Temperatures at $r = R$ and $\phi = 90^\circ, 180^\circ, 270^\circ$ and 360° from the results of FEA were used as inputs in our FDM code. The FDM calculated temperatures at $r = R_b$ were then used in FEA as the boundary conditions for the next FEA iteration.

Fig. B.2. The one-to-one correspondence of the Cartesian and cylindrical coordinates for the temperature at the core of blood vessels. For our special case of $n_\phi = 4$ we have the one-to-one correspondence $T_{i j 1} = T_{i j 2} = T_{i j 3} = T_{i j 4} = T_{x y z}$, $T_{i+l j k} = T_{x+l y z}$, $T_{i+l j k+1} = T_{x y+l z}$, $T_{i+l j k+2} = T_{x-l y z}$, $T_{i+l j k+3} = T_{x y-l z}$, $T_{i j+l k} = T_{x y z+l}$, and $T_{i j-l k} = T_{x y z-l}$.

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