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Heating in Biothermal Systems

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1. Introduction

Heat therapy is a traditional healing method. The first written reference to hyperthermia occurred in an Egyptian papyrus scroll 5000 years ago (Hall & Cox, 2003). In this chapter, we planned to introduce promising medical treatments which applied thermal energy in living tissues to raise tissue temperatures to therapeutic temperatures. The treatments, based on duration of time, were classified into low-temperature level in the range of 41~45°C (hyperthermia or thermal therapy) and much higher temperatures (thermal ablation treatments) than previous one.

Heating in the biothermal systems involves two primary heat transport modes: thermal conduction and convection. Extreme complicating living vasculatures and organs make heating the target volume and raising temperature to therapeutic temperature at the target volume difficult and, thus, a challenging task.

In this chapter, we will introduce thermal models which were used to describe biothermal systems. One of well-known models, Pennes bio-heat transfer equation (PBHTE) was initially introduced in 1949. Up until now, it still is used widely by research groups around the globe, to deal with temperature or heat that associated with human or living creatures. As well as other models which also described the impact of thermally significant blood vessel (or vascular system) and blood perfusion during treatments will also be introduced in this chapter.

The heating methods that deposited the thermal energy in transport medium (i.e. solid tumor, tissues and liquid so forth) will also be addressed. For example, high-intensity focused ultrasound (HIFU) is one of popular non-invasive method which could deposit heat into deep seated tissue region.

Lastly, we addressed promising future in combining other treating modalities (such as drug treatment) with hyperthermia. It has shown significant results for medical treatments in curing patients with cancers.

2. Heat transport

Thermal transport modes in bio-thermal systems involve three typical modes: conduction, convection and radiation. Limitation and restrictions of therapeutic temperatures on heating (or freezing) subjects are first, to remove tumorous tissues and at the same time without damaging the normal tissues. Table 1 shows significance of thermal transport modes in

typical components of bio-thermal systems, as our subject of discussion refers to cancer treatments using heat. Thermal diffusion plays a dominant transport mode in tissues, and convection is less significant as blood perfuses in solid tissues at capillary level vessels which are small in size and blood within are in slow motion.

	Conduction	Convection	Radiation
Tissues	Significant	Less Significant	Insignificant
Bones	Significant	Insignificant	Insignificant
Blood vessels	Less Significant	Significant	Insignificant
Skins	Insignificant	Significant	Significant

Table 1. Significance of thermal transport modes in typical components of vio-thermal systems

3. Mathematical modelings

To accurately describe physical phenomena in living tissues, we have to rely upon mathematical models (or bio-heat transfer formulation). There are many significant models appeared in history during the development of heating in tissues. Those models help us in analyzing temperature management in treatment planning with accuracy. We introduced them here:

3.1 Pennes bio-heat transfer equation (PBHTE)

In 1948, Pennes (Pennes, 1948) performed a series of experiments which measured temperatures on human forearms of volunteers, and derived a thermal energy conservation equation: the well known bio-heat transfer equation (BHTE) or the traditional bio-heat transfer equation. It is written as

$$\nabla \bullet k\nabla T + q_p + q_m - Wc_b(T - T_a) = \rho c_p \frac{\partial T}{\partial t} \tag{1}$$

where T(°>°C) is the local tissue temperature; T_a (°C) is the arterial temperature; c_b (J/kg/°C) is the blood specific heat; c_p (J/kg/°C) is the tissue specific heat; W(kg/m^3/s) is the local tissue blood perfusion rate; k(w/m/°C) is the tissue thermal conductivity; ρ(kg/m^3) is the tissue density; q_p(w/m^3) is the energy deposition rate; and q_m (w/m^3) is the metabolism, which is usually very small compared to the external power deposition term q_p (Roemer et al, 1988). The term $Wc_b(T-T_a)$, which accounts for the effects of blood perfusion, can be the dominant form of energy removal when considering heating process. It assumes that the blood enters the control volume at some arterial temperature T_a, and then comes to equilibrium at the tissue temperature. Thus, the blood leaves the control volume it carries away the energy, and hence acts as an energy sink in hyperthermia treatment.

Although Pennes' equation is an approximation equation and it does not have a physically consistent theoretical basis, it is surprisingly that this simple mathematical formulation predicted temperature fields well in many application situations. The reasons why PBHTE has been widely used in hyperthermia modeling field are two important factors: one is its mathematical simplicity and the other is its ability to predict the temperature field reasonably in applied fields.

Nevertheless, the equation does have some limitations. It does not, nor was it ever intended to, handle several physical effects. The most significant problem is that it does not consider the effect of the directionality of blood flow, and hence does not describe any convective heat transfer mechanism.

3.2 The Chen and Holmes (CH) model

Several investigators have developed alternative formulations to predict temperatures in living tissues. In 1980, Chen and Holmes (Chen and Holmes, 1980) derived the one and it has a very strong physical and physiological basis. The equation can be written as,

$$\nabla\bullet(k+k_p)\nabla T + q_p + q_m - Wc_b(T-T_a) - \rho_b c_b u\bullet\nabla T = \rho c_p \frac{\partial T}{\partial t} \tag{2}$$

Comparing this equation with Pennes' equation, two extra terms have been added. The term $-\rho_b c_b u\bullet\nabla T$ is the convective heat transfer term, which accounts for the thermal interactions between blood vessels and tissues. The term $\nabla\bullet k_p\nabla T$ accounts for the enhanced tissue conductive heat transfer due to blood perfusion term in tissues, where k_p is called the perfusion conductivity, and is a function of blood perfusion rate. The blood perfusion term $-Wc_b(T-T_a)$ shown in CH model, accounts for the effects of the large number of capillary structures whose individual dimensions are small relative to the macroscopic phenomenon under their study. Relatively CH model has a more solid physical basis than Pennes model. However, it requires knowledge of the details of the vascular anatomy and flow pattern to solve it, and that was an extreme complicating task.

3.3 The Weinbaum and Jiji (WJ) model

In 1985, Weinbaum and Jiji (Weinbaum and Jiji, 1985) proposed an alternative mathematical formulation of the bio-heat transfer equation. Their formulation is based on their observations from vascular network of rabbit thighs that blood vessels which are significant for heat transfer in tissues always occur in counter-current pairs. Hence, the major heat transfer mechanism between blood and tissues is the "incomplete counter-current heat exchanger" between thermally significant arteries and veins (with diameters about 50-500μm). Their formulation uses tensor notation and it can be written as

$$\rho c\frac{\partial\theta}{\partial t} - \frac{\partial}{\partial x_i}\left[(k_{ij})_{eff}\frac{\partial\theta}{\partial x_j}\right] = -\frac{\pi^2 n a^2 k_b^2}{4\sigma k} Pe^2 l_j \frac{\partial l_i}{\partial k_j}\frac{\partial\theta}{\partial x_j} + Q_m \tag{3}$$

where θ is the local temperature, ρc is the volume average tissue density and specific heat product, a is the local blood vessel radius, σ is a shape factor for the thermal conduction resistance between adjacent counter-current vessels, n is the number density of blood vessels of size a, k_b is the blood thermal conductivity, Pe is the local Peclet number (=2 ρ_b cnau/k_b), us is average blood flow velocity in the vessels and l_i is the direction cosine of the ith pair of countercurrent vessels. $(k_{ij})_{eff}$ is the effective conductivity tenor element, which is given by,

$$(k_{ij})_{eff} = k(\delta_{ij} + \frac{\pi^2 n a^2 k_b^2}{4\sigma k^2} Pe^2 l_i l_j) \tag{4}$$

where δ_{ij} is the kronecker delta function, and k is the tissue thermal conductivity. Clearly, this equation represents one of the most significant contributions to the bio-heat transfer formulation. But, in practical situations, this equation needs detailed knowledge of the sizes, orientations, and blood flow velocities in the countercurrent vessels to solve it and that presents a formidable task. Furthermore, there are several issues related to the WJ model. First, thoroughly comparison for both predicted temperatures and macroscopic experiments are required. Secondly, the formulation was developed for superficial normal tissues in which the counter-current heat transfer occurs. In tumors, the vascular anatomy is different from the superficial normal tissues, and therefore a new model should be derived for tumors. Some (Wissler, 1987) has questioned the two basic assumptions of WJ model: first, that the arithmetic mean of the arteriole and venule blood temperature can be approximated by the mean tissue temperature; and second, that there is negligible heat transfer between the thermally significant arteriole-venule pairs and surrounding tissue.

3.4 Thermally significant blood vessel model

As CH and WJ models presented, many investigators (Baish et al, 1986; Charny and Levin, 1990) during late 1980, questioned mostly on blood perfusion term or how to estimate blood temperature and local tissue temperatures where blood vessels (counter-current vessels) are involved. As arterial and veinous capillary vessels are small, their thermal contributions to local tissue temperatures are insignificant. However, some larger vessel sizes than the capillaries do have thermally significant impacts on tissue temperatures in either cooling or heating processes. Several investigators (Chato, 1980; Lagendijk, 1982; Huang et al, 1994) examined the effect of large blood vessels on temperature distribution using theoretical studies. Huang et al (Huang et al, 1996) in 1996 presented a more fundamental approach to model temperatures in tissues than do the generally used approximate equations such as the Pennes' BHTE or effective thermal conductivity equations. As such, this type of model can be used to study many important questions at a more basic level. For example, in the particular hyperthermia application studied herein, a simple vessel network model predicts that the role of counter current veins is minimal and that their presence does not significantly affect the tissue temperature profiles: the arteries, however, removed a significant fraction of the power deposited in the tissue. The Huang's model used a simple convective energy balance equation to calculate the blood temperature as a function of position,

$$\dot{M}_i c_b \frac{dT_b}{dx_i} = \dot{Q}_{ap} - h_i A_i (T_b - T_w) \tag{5}$$

Here, $\dot{M}_i$ is the mass flow rate of blood in artery i, c_b is the specific heat of blood, $T_b(x_i)$ is the average blood temperature at position x_i, x_i indicates the direction along the vessel I (either x, y or z depending on the vessel level). $\dot{Q}_{ap}$ is the applied power deposition x_i, h_i is the heat transfer coefficient between the blood and the tissue, A_i is the perimeter of blood vessel i, and $T_w(x_i)$ is the temperature of the tissue at the vessel wall. For the smallest, terminal arterial vessels a decreasing blood flow rate is present giving the energy balance equation,

$$\dot{M}_i c_b \frac{dT_b}{dx_i} = \dot{Q}_{ap} - h_i A_i (T_b - T_w) - \frac{d\dot{M}_i}{dx_i} c_b T_b \tag{6}$$

The blood leaving these terminal arterial vessels at any cross-section is assumed to perfuse the tissue at a constant rate. The detailed description is shown in Huang (Huang et al, 1996). As to venous thermal model, for all of veins except the smallest terminal veins, the above equation (5) holds. For the smallest veins, the T_b replaced by the venous return temperature, $T_{vr}(x_i)$. In the presented study this temperature is taken to be average temperature of four tissue nodes adjacent to the terminal vein in the plane perpendicular to that vein,

$$T_{vr} = \frac{1}{4}\sum_{i=1}^{4} T_{i,adj} \tag{7}$$

For tissue matrix thermal equations, they can be explained most succinctly by considering the Pennes Bio-Heat Transfer Equation as the most general formulation,

$$-k\nabla^2 T + \dot{W}c_b(T - T_a) = \dot{Q}_{ap} \tag{8}$$

Here, k is the thermal conductivity of the tissue matrix, T(x,y,z) is the tissue temperature, $\dot{W}$ is the "perfusion" value and T_a is the arterial blood temperature at some reference location.

3.5 Others

A few studies (Leeuwen et al, 2000; Devashish and Roemer, 2006; Baish, 1994) have modeled the effect of collections of a large number of parallel vessels or of networks of vessels on the resulting temperature distributions. Those were developed in attempt to describe the impact of blood vessels and to properly predict heat transfer processes in bio-thermal systems in a more accurate way.

4. Numerical modelings

As mentioned above the mathematical models for actual thermal problems of interest in hyperthermia or thermal ablation are too complicated to be conveniently solved with exact formulas. The majority of unsolved problems in medical fields is governed by non-linear partial differential equations. In most cases, one thereby reduces the problems to rather simplified models which can be exactly analyzed, for example, analytical solution of the 3D Pennes equation presented by Liu (Liu, 2001; Liu and Deng, 2002) using multidimensional Green function, and 1D transient Pennes equation by Shih et. al. (Shih et al, 2007) using the Laplace transform. But occasionally such an approach does not suffice. Consequently, specialists have recently devoted increasing attention to numerical, as opposed to analytical, techniques. Nowadays one of the major challenges for thermal ablation and hyperthermia simulation is the incorporation of the very detailed information coming from biophysical models into the numerical simulations. Thanks to advanced imaging techniques, accurate tumor static models including detailed description of all vascular matrix objects are currently available. Unfortunately, most of the discretization methods commonly used in computer simulation, mainly based on structured grids, are not capable to represent the detailed geometry of such treatment regions or other complicated entities such as microvascular matrix, horizontal wells, and uniformity, etc. The complexity of multidimensional heat transfer problems in hyperthermia suggests the application of numerical techniques. Several numerical methods have been used in engineering and

science fields; finite difference method, finite element method, finite volume approach, etc. (Morton and Mayers, 2005; Derziger, Peric, 2001; Thomas, 1995; Minkowycz et al, 1988; Anderson et al, 1984).

4.1 Finite difference method

Several mathematical models were discussed above to describe the continuum models of heat transfer in living biological tissue, with blood flow and metabolism. The general form of these equations is given by:

$$\rho c \frac{DT}{Dt} = \rho c \left(\frac{\partial T}{\partial t} + V \bullet \nabla T \right) = \nabla \bullet k \nabla T - w_b c_b (T - T_a) + Q \tag{9}$$

The partial differential equations for thermal ablation or hyperthermia are discretized at the grid point by using the finite difference approximation using Pennes equation.

$$\rho c \frac{\partial T}{\partial t} = k \nabla^2 T - w_b c_b (T - T_a) + Q \tag{10}$$

The Pennes equation is solved with the finite difference formulation when the exact geometry is not particularly important or when the fundamental behavior of a bio-thermal system is analyzed, in particular with heterogeneous and at times anisotropic thermal properties. Define an *Nx* x *Ny* x *Nz* lattice in the (x, y, z) plane that spans our region of interest in 3D with dimension of L*x* x L*y* x L*z* as shown in Figure 2. Let *Nx*, *Ny* and *Nz* be the numbers of equally spaced grid points in the *x*-, *y*-, and *z*-directions, respectively, and $\{x_{ijk} := (i\Delta x, j\Delta y, k\Delta z)\}$ the grid points in the computational domain, where Δx = L*x*/*Nx*, Δy = L*y*/*Ny*, and Δz = L*z*/*Nz*.

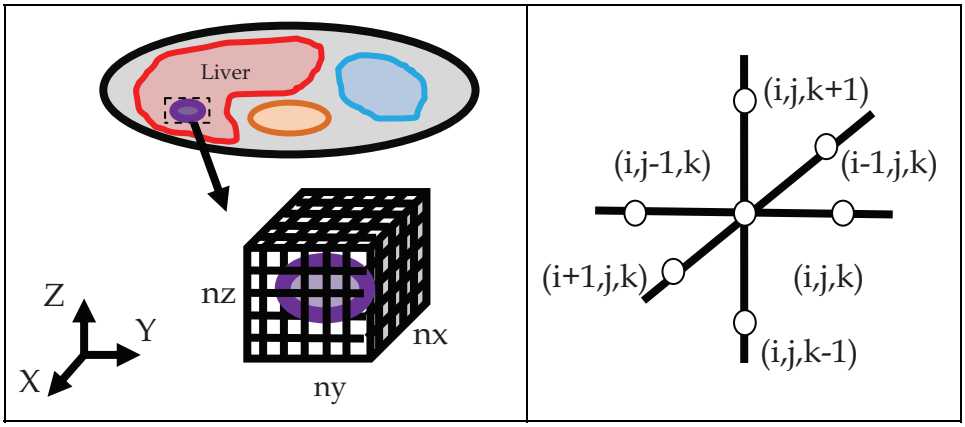


Fig. 1. Schematic representation of the grid system using a finite difference scheme

In a typical numerical treatment, the dependent variables are described by their values at discrete points (a lattice) of the independent variables (e.g. space and/or time), and the partial differential equation is reduced to a large set of difference equations. It would be useful to revise our description of difference equations. Let Γ be the elliptic operator and Π a finite difference approximation of Γ with *p*th order accuracy, i.e.,

$$\Gamma T = k\nabla^2 T - w_b c_b T \tag{11}$$

$$\Pi T \approx \Gamma T + O(h^p)$$

where h = max{Δx, Δy, Δz}. Then the semi-discrete equation corresponding to Equation (11) reads $\rho c \frac{\partial T}{\partial t} = \Pi T + Q + w_b c_b T_a$. To integrate in time, one can use the two-level implicit time-stepping scheme:

$$\rho c \frac{T^{n+1} - T^n}{\Delta t} = \Pi\left(\frac{1}{2}T^{n+1} + \frac{1}{2}T^n\right) + Q^n + w_b c_b T_a \tag{12}$$

where Δt is the time step size and T^n is the discrete solution vector at time $t^n = n\Delta t$. This numerical scheme is known as the Crank–Nicolson scheme (Crank and Nicolson, 1947). It yields a truncation error at the nth time-level: $Error = O\left(\Delta t^2 + h^p\right)$. In the matrix form we can represent (2) as:

$$\left(I - \frac{\Delta t}{2\rho c}\Pi\right)T^{n+1} = \left(I + \frac{\Delta t}{2\rho c}\Pi\right)T^n + \frac{\Delta t}{\rho c}(Q^n + w_b c_b T_a) \tag{13}$$

That is at time t^{n+1} the discrete solution is given by:

$$T^{n+1} = \left(I - \frac{\Delta t}{2\rho c}\Pi\right)^{-1}\left[\left(I + \frac{\Delta t}{2\rho c}\Pi\right)T^n + \frac{\Delta t}{\rho c}(Q^n + w_b c_b T_a)\right] \tag{14}$$

Obviously other standard techniques for numerical discretization in time have also been used. For instance the unconditionally stable Alternating Direction Implicit (ADI) finite difference method (Peaceman and Rachford, 1955) was successfully used in the solution of the bio-heat equation in (Qi and Wissler, 1992; Yuan et al, 1995).

4.2 Finite element method

When an analysis is performed in complex geometries, the finite element method (Dennis et al, 2003; Hinton and Owen, 1974) usually handles those geometries better than finite difference. In the finite element method the domain where the solution is sought is divided into a finite number of mesh elements. (for example, a pyramid mesh, as shown in Figure 3). Applying the method of weighted residual to Pennes equation with a weight function, ω, over a single element, Λ_e results in:

$$\oint_{\Lambda_e} \omega\left[\rho c \frac{\partial T}{\partial t} - \nabla \bullet k\nabla T + w_b c_b (T - T_a) - Q\right] d\Lambda_e = 0 \tag{15}$$

A large but finite number of known functions are proposed as the representation of the temperature. The (shape) functions are constructed from simple interpolation functions within each element into which the domain is divided. The value of the function everywhere inside the element is determined by values at the nodes of that element. The temperature can be expressed by,

$$T^{(e)}(x,y,z,t)=\sum_{i=1}^{Nr}N_i(x,y,z)T_i(t) \tag{16}$$

Or in a matrix form, $T^{(e)}(x,y,z,t)=\left[N(x,y,z)\right]\{T(t)\}$

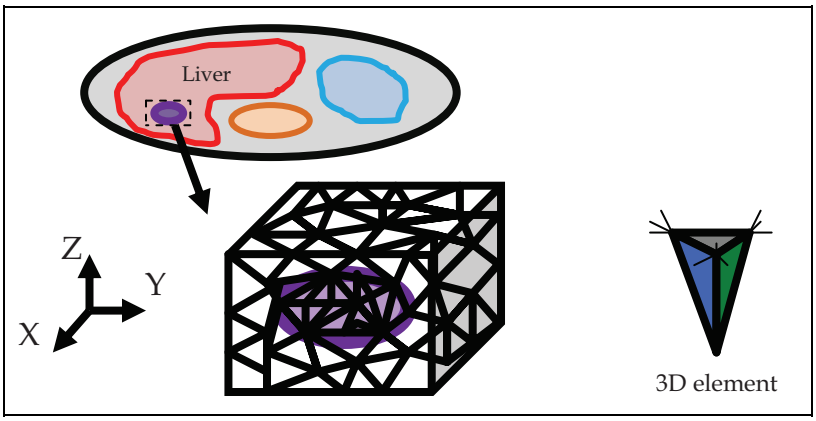


Fig. 2. Schematic representation of the mesh element system using a finite element scheme

In Eq. (16), i , is an element local node number, Nr is the total number of element nodes and N(x,y,z) is the shape function associated with node *i*. Applying integration by parts into Eq. (15) one can obtain

$$\oint_{\Lambda_e}\omega\left[\rho c\frac{\partial T}{\partial t}+w_b c_b(T-T_a)-Q\right]d\Lambda_e+\int_{\Lambda_e}\omega k\nabla T\bullet\nabla N_i d\Lambda_e-\int_{\Gamma_e}\omega(k\nabla T\bullet\hat{n})N_i d\Gamma_e=0 \tag{17}$$

Here, Γ_e is the surface element. Using the Galerkin method, the weight function, ω, is chosen to be the same as the interpolation function for T. Evaluation of each element and then assembling into the global system of linear equations for each node in the domain yields

$$[M]\left\{\dot{T}\right\}+[K]\{T\}+[W]\{T\}=\{R\}+\{P\},$$

$$\text{or } [M]\left\{\dot{T}\right\}+[A]\{T\}=\{B\}$$

where

$$M_{ij}=\int_{\Lambda_e}\omega\rho cN_iN_j d\Lambda_e,\ K_{ij}=\int_{\Lambda_e}\omega k(\nabla N_i\bullet\nabla N_j)d\Lambda_e,\ W_{ij}=\int_{\Lambda_e}\omega W_b c_b N_iN_j d\Lambda_e,$$

$$P_i=\int_{\Gamma_e}\omega k(\nabla\sum_{j=1}^{Nr}T_jN_j\bullet\hat{n})N_i d\Gamma_e,\ R_i=\int_{\Lambda_e}\omega Q_iN_i d\Lambda_e,\ A_{ij}=K_{ij}+W_{ij},\ B_i=R_i+P_i$$

This set of equations cane be solved with any kind on numerical integration in time to obtain the approximate temperature distribution in the domain. For instance one can use the Crank-Nicolson algorithm,

$$\left(\frac{1}{2}[A]+\frac{1}{\Delta t}[M]\right)\{T^{n+1}\}=\left(\frac{1}{2}[A]+\frac{1}{\Delta t}[M]\right)\{T^{n}\}+\frac{1}{2}\left(\{B^{n+1}\}+\{B^{n}\}\right) \quad (18)$$

where the superscript n+1 denotes the current time step and the superscript n, the previous time step.

4.3 Finite volume method

Finite volume methods are based on an integral form instead of a differential equation and the domains of interest are broken into a number of volumes, or grid cells, rather than pointwise approximations at grid points. Some of the important features of the finite volume method are thus similar to those of the finite element method (Oden, 1991). The basic idea of using finite volume method is to eliminate the divergence terms by applying the Gaussian divergence theorem. As a result an integral formulation of the fluxes over the boundary of the control volume is then obtained. Furthermore they allow for arbitrary geometries, using structured or unstructured meshing cells. An additional feature is that the numerical flux is conserved from one discretization cell to its neighbor. This characteristic makes the finite volume method quite attractive when modeling problems for which the flux is of importance, such as in fluid dynamics, heat transfer, acoustics and electromagnetic simulations, etc.

Since finite volume methods are especially designed for equations incorporating divergence terms, they are a good choice for the numerical treatment of the bio-heat-transfer-equation.

The computational domain is discretized into an assembly of grid cells as shown in Figure 4.

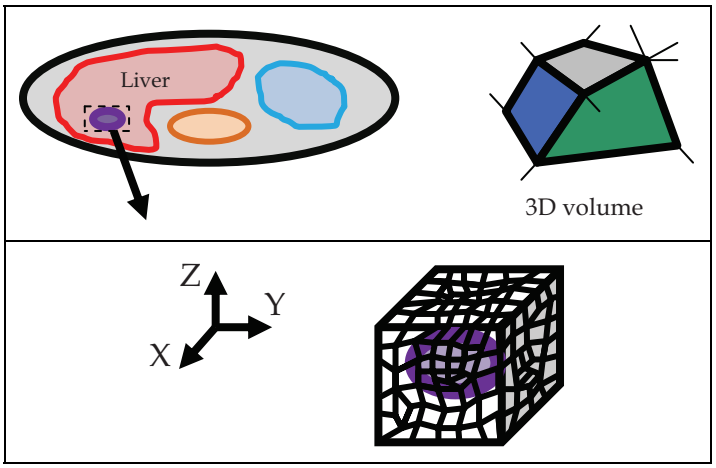


Fig. 3. Schematic representation of the grid cell system using a finite volume scheme

Then the governing equation is applied over each control volume in the mesh. So the volume integrals of Pennes equation can be evaluated over the control volume surrounding node *i* as

$$\oint_{\Omega i}\left[\rho c\frac{\partial T}{\partial t}-\nabla\bullet k\nabla T+w_b c_b(T-T_a)-Q\right]d\Omega=0 \quad (19)$$

By the use of the divergent theorem,

$$\oint_{\Omega i}\left[-\nabla \bullet k\nabla T\right]d\Omega = -\int_{\Gamma_i}\left(k\nabla T \bullet \hat{n}\right)d\Gamma = \int_{\Gamma_i} q_j n_j d\Gamma \tag{20}$$

where the heat flux $q = -k\nabla T$ and

$$\oint_{\Omega i}\left[\rho c\frac{\partial T}{\partial t}\right]d\Omega \cong \rho c\frac{\partial T_i}{\partial t}\bigcap_i,\ \oint_{\Omega i} w_b c_b T d\Omega \cong w_b c_b T_i \bigcap_i,\ \oint_{\Omega i}\left[Q + w_b c_b T_a\right]d\Omega \cong \left(Q_i + w_b c_b T_a\right)\bigcap_i$$

where $\bigcap_i$ is the volume of the control volume, T_i and Q_i represent the numerical calculated temperature and source term at node *i*, respectively. The boundary integral presented in equation (a) is computed over the boundary of the control volume, Ω_i, that surrounds node *i* using an edge-based representation of the mesh, i.e.

$$\int_{\Gamma_i} q_j n_j d\Gamma \cong \sum_{all\ \ edges} G_{ij} q_j + \sum_{all\ \ edges} H_{ij} q_j \tag{21}$$

where G_{ij} denotes the coefficients that must be applied to the edge value of the flux q_j in the x_j direction to obtain the contribution made by the edge to node *i* and H_{ij} represents the boundary edges coefficients that relate to the boundary edge flux q_j when the edge lies on the boundary, where H_{ij}=0 on all edges except on the domain boundaries. The approximation of q_j on edge is evaluated by different schemes based on the temperatures between nodes. For example,

$$q_j = \frac{T_j - T_i}{d_{ij}}$$

where d_{ij} is the distance between the center of the cells *i* and *j*.
The semi-discrete form of the transient bioheat heat transfer equation represents a coupled system of first order differential equations, which can be rewritten in a compact matrix notation as

$$P\frac{\partial T}{\partial t} + RT = S \tag{22}$$

with an initial condition. In equation (22), *P* represents the heat capacity matrix which is a diagonal matrix. *R* is the conductivity matrix including the contributions from the surface integral and perfusion terms. The vector *S* is formed by the independent terms, which arises from the thermal loads and boundary conditions. *T* is the vector of the nodal unknowns. Equation (22) can be further discretized in time to produce a system of algebraic equations. With the objective of validating the finite volume formulation described, one can use the simplest two-level explicit time step and rewrite equation (22) as the following expression

$$P\frac{T^{n+1} - T^n}{\Delta t} + RT^n = S^n \tag{23}$$

where $\Delta t = t_{n+1} - t_n$ is the length of the time interval and the superscripts represent the time levels. Such scheme is just first order accurate in time and the Δt must be chosen according to a stability condition (Lyra, 1994). Other alternatives, such as the generalized trapezoidal

method (Lyra, 1994; Zienkiewicz & Morgan, 1983), multi-stage Runge-Kutta scheme (Lyra, 1994) can be implemented if higher-order time accuracy is required.

4.4 Others

Other classes of methods have also been applied to the partial differential equations, such as boundary element method (Wrobel and Aliabadi, 2002), spectral method (Canuto et al, 2006), multigrid method (Briggs et al, 2000) ect.

5. Heating methods

Heating in bio-thermal systems that have many forms, they can be appeared in different power deposition calculations in PBHTE. They can be classified into three types which are invasive, minimal invasive and non-invasive methods. We introduced most clinical methods here.

5.1 Hyperthermia

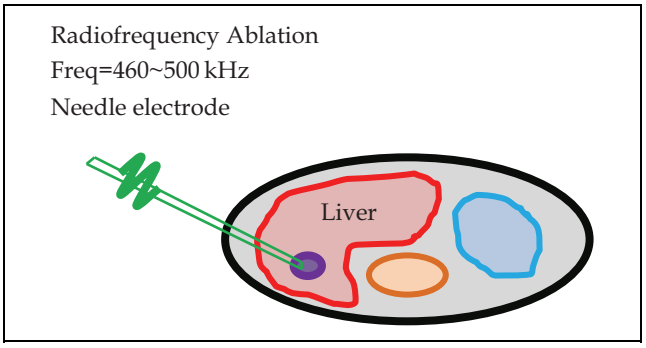
Hyperthermia is a heat treatment, and traditionally refers to raise tissue temperatures to therapeutic temperatures in the range of 41~45°C (significantly higher than the usual body-temperature) by external means. In history, the first known, more than 5000 years old, written medical report from the ancient Egypt mentions hyperthermia (Smith, 2002). Also, an ancient tradition in China, "Palm Healing", has used the healing properties of far infrared rays for 3000 years. As our bodies radiate far infrared energy through the skin at 3 to 50 microns, with a peak around 9.4 microns, these natural healers emit energy and heat radiating from their hands to heal. It could be applied in several various treatments: cure of common cold (Tyrrell et al, 1989), help in the rheumatic diseases (Robinson et al, 2002; Brosseau et al, 2003) or application in cosmetics (Narins & Narins, 2003) and for numerous other indicators.

5.2 Thermal ablation

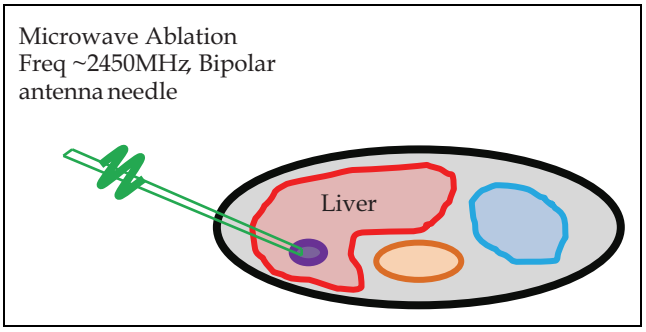
The differentiation between thermal ablation and hyperthermia relates to the treatment temperature and times. Thermal ablation usually refers to heat treatments delivered at temperatures above 55°C for short periods of time (i.e. few seconds to 1 min.). Hyperthermia usually refers to treatments delivered at temperatures around 41-45°C for 30~60 minutes. The goal of thermal ablation is to destroy entire tumors, killing the malignant cells using heat with only minimal damage to surrounding normal tissues. The principle of operation of the thermal ablation techniques is that to produces a concentrated thermal energy (heating or freezing), creating a hyperthermic/hypothermic injury, for example, by a needle-like applicator placed directly into the tumor or using focused ultrasound beams. Thermal ablation comprises several distinct techniques as shown in Figure 1: radiofrequency (RF) ablation, microwave ablation, laser ablation, cryoablation, and high-intensity focused ultrasound ablation. To have a good treatment, it is also crucial to destroy a thin layer of tissue surrounding the tumor because of the uncertainty of tumor margin and the possibility of microscopic disease (Dodd et al, 2000).

When it is not applicable for patients to surgery, one of alternative therapies for malignant tumors is thermal ablation. It is a technique that provides clinicians and patients a repeatable, effective, low cost, and safe treatment to effectively alleviate, and in some cases cure, both primary and metastatic malignancies. However, the common procedures for each thermal ablation technique are not yet clearly defined because the decision to use ablation,

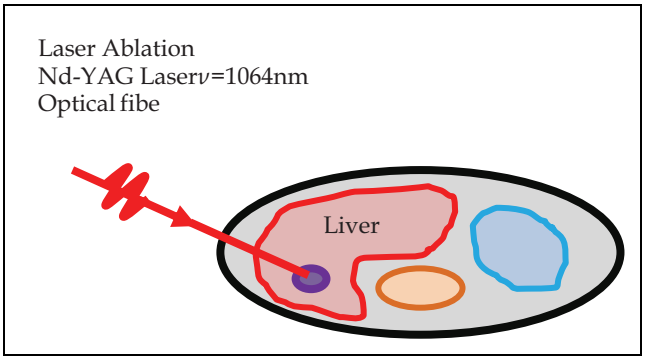
and which ablation technique to use, depends on several factors. In practice, the decision of whether to use thermal ablation depends on the training and preference of the physician in charge and the equipment resources available at his/her medical center. Moreover, physical characteristics of the treatment zone using ablation are also needed to concern, including the zone shape, uniformity, and its location. Up to now clinical results have been indicated that the different techniques of thermal ablation have roughly equivalent effectiveness for treating various tumors.



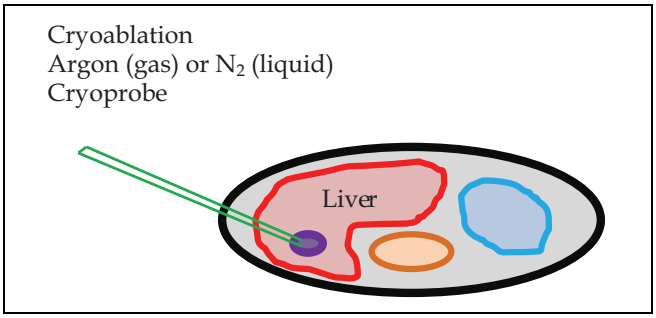
(a)



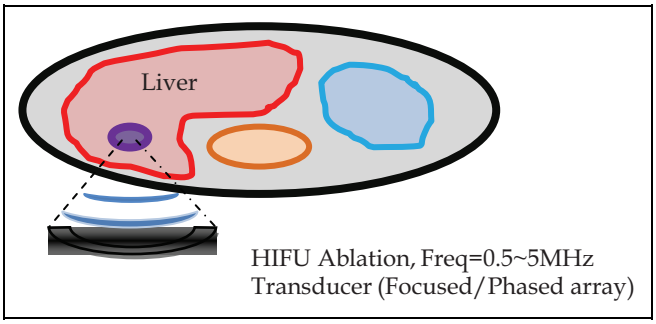
(b)



(c)



(d)



(e)

Fig. 4. Schematics of different thermal ablation techniques. (a) RF ablation (b) Microwave ablation (c) Laser ablation (d) Cryoablation (e) HIFU ablation

Patients referred for thermal ablation are initially evaluated in a clinic setting where the patient's history and pertinent imaging information are reviewed. Meanwhile, the applicability of ablation and the risks and benefits of the procedure are also discussed. Prior to ablation, the evaluation is very similar to a surgical evaluation that any possible risks of bleeding or serious cardiopulmonary issues are considered. Side effects from thermal ablation are also discussed, including postablation syndrome—for example, a short term fever, discomfort, and anorexia.

5.2.1 High-intensity focused ultrasound (HIFU)

HIFU is a non-invasive power deposition method via mechanical oscillation motion of object molecules. One of important features in the heating methods is non-invasiveness and it reduces external surgical operations on body object. Thus this method has become a promising tool for localized tumor therapy. Compared to hyperthermia which lasts long period of treating time, HIFU referred as thermal surgery, could heat the target region elevated temperature up to 50~55°C within a short period of time (i.e. few seconds to 1 min.). Another important feature is that this comparably higher temperature during treatment could cause thermal coagulation and thermal lesion. Therefore, precise location management and monitoring are required during clinic HIFU treatment to prevent irreversible heating process on tissues. Figure 1.e illustrated the method.

5.2.2 Radiofrequency (RF) ablation

Radiofrequency ablation is a "minimally invasive" treatment method mostly for primary and metastatic liver tumors. It is becoming a promising treating method to replace surgical resection. A study (Solbiati et al, 2001) in 2001 of RF ablation in 117 patients has shown 1-, 2-, and 3-year survival rates of 93%, 62%, and 41%, respectively. As compared to traditionally only low or 10-20 % of patients, those will have disease amenable to surgical resection due to limited hepatic reserve, high surgical risk, or unfavorable tumor location.

The mechanics of RF ablation uses the electromagnetic energy which is converted to heat by ionic friction. Tissue damage can occur at temperatures above 43°C with long heating times of several hours (Sapateto and Dewey, 1984). Elevated tissue temperature to 50°C near the probe required 3-min of heating time. Traditional and commercial design of the probe uses 17-gauge needles with active tip exposures of 1, 2 and 3 cm and the remainder of the needle is electrically insulated. Within the probe, water is circulated during the ablation procedure to cool tissue next to the probe and prevent tissue charring. Figure 1.a illustrated the method.

5.2.3 Microwave (MW) ablation

Microwave tumor ablation is also a "minimally invasive" treatment method. In contrast, while RF employs radio-frequency current to generate heat, MW ablation produces an electromagnetic wave that is emitted from a 14.5 gauge (standard) microwave antenna placed directly within the treatment site. The electromagnetic wave produces 60 W of power at a frequency ranging from 900 to 2450 MHz, which generate frictional heat from the agitation of polar water molecules (McTaggart and Dupuy, 2007; Liang and Wang, 2007; Simon et al, 2005). In principle the electromagnetic wave passes through the tissues, it causes polar water molecules to rapidly change their orientation in accordance with the magnetic field. Additionally, the design of MW antenna contributes significantly to the efficiency of MW therapy. Figure 1.b illustrated the method.

5.2.4 Others

Another interesting method to kill tumor cells is cryo-ablation, as shown in Figure 1.d. In contrast with other methods, cryo-ablation use lower temperature to ablate tumors. The procedure can be performed either by a laparoscopic or percutaneous approach under MRI, US or CT guidance. Cryoablation involves a number of freeze-thaw-freeze cycles with argon and helium gas (McTaggart and Dupuy, 2007). Gases are used to remove heat and induce thawing. It is used to treat lesions of the prostate, kidney, liver, lung, bone, and breast (Hayek et al, 2008; Orlacchio et al, 2005). As the tissue freezes, osmolarity increases and causes an imbalance of solutes between the intracellular and extracellular environments. Cellular death initially occurs through cellular dehydration and protein denaturization.

6. Adjuvant to other tumor treatment modalities

Although the effectiveness of hyperthermia alone as a cancer treatment may be not so promising, significant improvements in clinical trials using combined therapies with hyperthermia are observed. Recently, hyperthermia has been applied as an adjunctive therapy with various established cancer treatments such as radiotherapy, chemotherapy, and nano-particle drug treatments, etc. The combination therapies seem to be safe and effective approaches even when other treatments have failed. The rationale of combining

chemotherapy or other therapies with hyperthermia is that the available armamenterium for tumor heating has been substantially improved. The potential to control power distributions in clinic has been significantly improved lately by the development of advanced imaging techniques (particularly, online magnetic resonance tomography), planning systems and other modeling tools.

6.1 Radiotherapy

The efficacy of standard radiotherapy for patients with different tumor sites, for example, cervical, gastrointestinal, and genitourinary tumors, might become poor because the local-control rates after locoregional treatment are disappointingly low. To compensate this defect the combinations of radiotherapy with other therapies have been used. It has been known that hyperthermia probably is the strongest radiosensitizer known, with an enhancement factor of up to 5 (Kampinga and Dikomey, 2001). Although the exact mechanism why heat can cause cells more sensitive to radiation is not known, clinical results reveal that heat primarily interferes with the cells' ability to deal with radiation-induced DNA damage (Kampinga and Dikomey, 2001; Roti, 2004).

Clinical studies have shown that the combination of radiotherapy with hyperthermia increases cytotoxic effects and higher locoregional control rates. In the Netherlands 358 patients with tumors of the bladder, cervix, or rectum were treated with radiotherapy alone (n=176) or radiotherapy plus hyperthermia (n=182) from 1990 to 1996. Results showed the complete-response rates were 39% after radiotherapy and 55% after radiotherapy plus hyperthermia (Van der Zee et al, 2000). Radiotherapy plus hyperthermia was superior to radiotherapy alone and improved tumor response and survival.

Moreover, other clinical results of the combination of radiotherapy with hyperthermia are summarized in some recent studies (Wust et al, 2002; Van der Zee, 2002). The supplementary values of this combined therapy are from 41% to 61% in 3-year local control rate and from 27% to 51% in 3-year overall survival in cervix cancer, from 24% to 69% in 5-year local control rate in lymph nodes of head-and-neck tumors, and from 24% to 42% in 3-year overall survival in esophageal cancer. The differences reported for the other radiosensitizing agents (Horsman et al, 2006), insofar as there are clinical results, are in the range of 10% to 20%. Significant improvements in clinical outcomes by additional treatment with hyperthermia were also shown for cancer of the breast, brain, rectum, bladder, and lung, and for melanoma.

Whether the combination of radiation and heat is given in a simultaneous or sequential schedule, the thermal enhancement will be dependent on the heating time and temperature of both tumors and normal tissues (Horsman and Overgaard, 2002 & 2007).

Besides, hyperthermia has a direct cell-killing effect, specifically in insufficiently perfused parts of the tumor. Several randomized clinical trials have shown that the beneficial effect of hyperthermia, when added to radiotherapy, can be substantial, even while the temperature of 43°C that was thought to be necessary was not achieved in the whole tumor volume.

The improvements in clinical outcomes, despite the inadequacy to heat the whole tumor volume to temperatures of 43°C, can be explained by the more recent findings that hyperthermia has more effects than just that of direct cell kill and radiosensitization. Several additional effects that become apparent at different temperatures between 39° and 45°C have been described: vascular damage resulting in secondary cell death; improvement f perfusion and oxygenation, which results in a better effect of radiation; and stimulation of

the immune system (Dewhirst et al, 2007). All these effects may contribute o the desired eventual effect, which (certainly when combined with RT) is he achievement of local control. Several phase III trials comparing radiotherapy alone or with hyperthermia have shown a beneficial effect of hyperthermia (with existing standard equipment) in terms of local control (eg, recurrent breast cancer and malignant melanoma) and survival (eg, head and neck lymph-node metastases, glioblastoma, cervical carcinoma). Therefore, further development of existing technology and elucidation of molecular mechanisms are justified.

6.2 Chemotherapy

The combination of hyperthermia and chemotherapy has demonstrated several advantages over chemotherapy alone. The architecture of the vasculature in solid tumors is often insufficient due to the rapid growth of tumor tissue compared to normal tissue and/or chaotic, resulting in regions with hypoxia and low pH levels, which is not found in normal tissue. When using a mild hyperthermia (temperatures < 42 C), heat results in vasodilatation which improves the oxygenation of tissue (Iwata et al, 1996). Results reveal that the changes in tumor oxygenation are temperature dependent. This relationship could possibly influence treatment outcome of thermo-chemotherapy when the activity of chemotherapeutic agents is known to be oxygen dependent. This improvement of the blood supply can increase the cell metabolism which allows a greater effect of the chemotherapeutic agent on the tumor cells. Besides, heat also improves the cellular permeability which leads to the increase of the drug uptake by the tumor cells and intracellular spaces, the reaction of chemotherapy with DNA, and the prevention of DNA repair (Herman et al, 1988).

Moreover, the pathologic studies have shown that the enhanced drug cytotoxicity by heating induces both apoptosis and necrosis above a certain threshold temperature (Harmon et al, 1990; Yonezawa et al, 1996). In addition, several studies have also shown that some of the advantages of combining chemotherapy with hyperthermia are not only treating the primary cancers, but also reducing the risk of treatment-induced secondary cancers (Kampinga and Dikomey, 2001; Hurt et al, 2004; Hunt et al, 2007). These factors make cells more sensitive to heat especially in low perfused tissues. Therefore, in addition to direct cytotoxicity, hyperthermia leads in vivo to a selective destruction of tumor cells in hypoxic and, consequently, acidic environment within parts of malignant tumors (Vaupel et al, 1989; Vaupel, 2004).

More recent in vivo studies have demonstrated that the thermal enhancement of cytotoxicity of many chemotherapeutic agents is maximized with heat (Hahn, 1979; Marmor, 1979; Engelhardt, 1987; Dahl, 1988; Bull, 1984; Hildebrandt et al, 2002; Urano et al, 1999). The positive results of thermo-chemotherapy are observed that the rate at which cells are killed by the drug increases with temperatures. Besides, the efficacy of thermo-chemotherapy also depends on the treatment planning. In general, promising results indicate that patients need to take chemotherapeutic agents immediately before hyperthermia. However, some of agents like the antimetabolite gemcitabine, are taken prior to hyperthermia at least 24 h to achieve a synergistic effect in vitro and in vivo (Haveman et al, 1995; Van Bree et al, 1999).

Although the working mechanism of thermo-chemotherapy is not fully understood, with the promising results of clinical trials and the thermal enhancement of drug cytotoxicity from pathologic studies, hyperthermia combined with chemotherapy has demonstrated as one of effective modalities in the present cancer treatment.

6.3 Nano-particle drug therapy

The nanoparticles have been applied to facilitate drug delivery and to overcome some of the problems of drug delivery for cancer treatment. In the past, cancer therapies using anticancer drugs were dissatisfied and had major side effects. Because of their multifunctional character the nanoparticles can deliver larger and more effective doses of chemotherapeutic agents or therapeutic genes into malignant cells, minimize toxic effects on healthy tissues and then alleviate patients suffering from the side-effects of chemotherapy. Nanoparticles can be used to deliver hydrophilic drugs, hydrophobic drugs, proteins, vaccines, biological macromolecules, etc. Several nanoscale delivery devices, such as ceramic nanoparticles, virus, dendrimers (spherical, branched polymers), silica-coated micelles, cross linked liposomes, and carbon nanotubes (Portney and Ozkan, 2006) have been used to improve delivery of anticancer agents to tumor cells (Brigger el al, 2002). Some of the challenges in effectively delivering anticancer drugs have to be solved: how to ensure therapeutic drug molecules reach the targeted tumor, how to release them slowly over a longer period, and how to avoid the human immune system destroying them.

Normally, the structure of a nanoparticle drug carrier has four elements. The first of them is the targeted chemotherapy drug, for example, docetaxel or Taxotere. The second is a matrix made of a biodegradable polymer (polylactic acid), which contains the anticancer drug and breaks down slowly so that the drug is released gradually over several days. The third element is a coating layer of polyethylene glycol, which is used to prevent from attacking by antibodies and macrophage cells of the human immune system. The final element is a targeted tag, in the form of special enzymes attached to the outer coating, which can form electrostatic or covalent bonds with positively charged agents and biomolecules. This tag allows the nanoparticles to bind directly to desired tumor cells but to bypass healthy tissues and eventually to reduce the side effects caused by most chemotherapy drugs.

Several different drug delivery methods (Jain, 2005) have been shown their feasibility to treat human cancers. Lipid-based cationic nanoparticles (Cavalcanti et al, 2005), one of new promising tumor therapies, by loading suitable cytotoxic compounds can cause strong human immune responses and result in the destruction of tumor. Magnetic nanoparticles as the carrier have been used in cancer treatment avoiding side effects of conventional chemotherapy (Alexiou et al, 2006). Recent progress has been made in the application of nanoparticles to cancer treatment, including their use as delivery systems for potent anticancer drugs or genes, as well as agents for more advanced cancer treatment modalities, such as the combination treatments of radiotherapy, chemotherapy, and gene therapy with hyperthermia (Kong et al, 2000).

6.4 Others

Hyperthermia-regulated gene therapy

Major factors determining the effectiveness of gene therapy are the method of gene delivery and the details of the therapeutic gene expression in the targeted tissue. Some researchers have reported that heat can not only enhance the immunogenicity of tumor cells (Kubista et al, 2002), but also regulate the heat-sensitive promoters in the region of interest (Ito et al, 2003; Ito et al, 2006; Ito et al, 2004; Todryk et al, 2003). Heat shock proteins (HSPs) as sensitive promoters are recognized as significant participants in immune reactions (Kubista et al, 2002). Animal studies showed that the hyperthermia-regulated gene therapy using

hsp70 obtained strong prevention of tumor growth, complete regression of tumors, and the induction of systemic antitumor immunity in the cured mice (Ito et al, 2006; Ito et al, 2004; Todryk et al, 2003).

These studies suggest that the combination gene therapy with hyperthermia using hsp70 have great potential in cancer treatment. Nevertheless, results also suggested that inappropriate immune reactivity to hsp70 might lead to pro-inflammatory responses and the development of autoimmune disease. Moreover, endotoxin contamination has been reported to be responsible for the human hsp70 preparation (Gao & Tsan, 2003; Bausinger et al, 2002) and uncontrolled promoter activation by other than heat stressors for the HSP70B promoter system was found (Siddiqui et al, 2008). To have a safe and controllable gene therapy the unintentional activation of heat-responsive promoters should be avoided. Although some effects of heat shock proteins on the immunogenicity of tumor cells have been studied, more work is still needed before the hyperthermia-regulated gene therapy using hsp70 can applied into clinical cancer treatments.

Recently, a combination of gene therapy with magnetic resonance imaging (MRI), high-intensity focused ultrasound (HIFU) and a temperature-sensitive promoter is being evaluated in the cancer field (Moonen, 2007; Silcox et al, 2005; Plathow et al, 2005; Frenkel, 2006; Rome et al, 2005; Walther & Stein, 2009). With the help of advanced imaging techniques one can noninvasively monitor the temperature field induced by a high-intensity focused ultrasound system and simultaneously regulate the gene expression in the treatment region. Results indicated that although the application of MRI-guided HIFU in gene therapy is promising, further technical requirements of the heating and monitoring systems for precise control are still needed.

In recent molecular and biological investigations there have been novel applications such as gene therapy or immunotherapy (vaccination) with temperature acting as an enhancer, to trigger or to switch mechanisms on and off. However, for every particular temperature-dependent interaction exploited for clinical purposes, sophisticated control of temperature, spatially as well as temporally, in deep body regions will further improve the potential.

7. Conclusion

Thermal transport in bio-thermal systems signifies that temperature management in living systems can help us in curing and treatment of ill conditions. In analytic perspective, efforts on mathematical and numerical modelings have showed great progrssing in calculating temperature distributions. Advance in computer technology is one of critical contributing factors. In clinical perspective, many thermal energy related experiments and tests that are adjuvant to other tumor treatment modalities have identified effectiveness in treatments. In this regard, the well knowledge of heat transfer process revealed significant in optimal controling temperature in bio-thermal systems. Thus it shows us another great research and career opportunities in this field.

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Convection and Conduction Heat Transfer

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The convection and conduction heat transfer, thermal conductivity, and phase transformations are significant issues in a design of wide range of industrial processes and devices. This book includes 18 advanced and revised contributions, and it covers mainly (1) heat convection, (2) heat conduction, and (3) heat transfer analysis. The first section introduces mixed convection studies on inclined channels, double diffusive coupling, and on lid driven trapezoidal cavity, forced natural convection through a roof, convection on non-isothermal jet oscillations, unsteady pulsed flow, and hydromagnetic flow with thermal radiation. The second section covers heat conduction in capillary porous bodies and in structures made of functionally graded materials, integral transforms for heat conduction problems, non-linear radiative-conductive heat transfer, thermal conductivity of gas diffusion layers and multi-component natural systems, thermal behavior of the ink, primer and paint, heating in biothermal systems, and RBF finite difference approach in heat conduction. The third section includes heat transfer analysis of reinforced concrete beam, modeling of heat transfer and phase transformations, boundary conditions-surface heat flux and temperature, simulation of phase change materials, and finite element methods of factorial design. The advanced idea and information described here will be fruitful for the readers to find a sustainable solution in an industrialized society.

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