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A Short Review of Analytical Studies in Hyperthermia

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ABSTRACT

In planning hyperthermia treatments, it is desirable to predict the temperature of the tumour and the normal tissue so as to attain a therapeutic beneficial (desired) temperature of the tumour while avoiding the damage of the normal tissue. The desired temperature is attained by controlling both the heating power induced by microwave, laser and ultrasound etc [33] and surface cooling temperature. To attain this goal, improved version of mathematical models which include the effects of flow of blood through the vessels inside the tissue have been considered [2,3,4,5]. Recent developments of dual-phase-lag models in the biological tissue have been obtained on the aspects of hyperthermia treatment planning [8,9,10,11].

In Magnetic Fluid Hyperthermia (MFH), some recent analytical investigations on optimization problems to determine the optimum heating pattern, induced by multiple magnetic particle injections in tumour models, have been studied [12,13,14,15]. Some optimal control problems on temperature distribution of the tumour embedded inside the biological tissue in hyperthermia are investigated in few important articles [22,23,26,27,28,29,30,31,32].

1. Introduction

One of the important problems in clinical hyperthermia is the determination of the complete temperature field throughout both tumour and normal tissues. Since temperature are sampled at only limited number of locations during a clinical heating, the temperature in the majority of the tissue remain unknown and it is therefore difficult to asses the efficacy of the equipment and treatment protocol utilized [33]. Similarly, when planning hyperthermia treatments it is desirable to predict the temperature field in the tissue to be attained in case of a particular patient so that the treatment can be optimized.

In order to reach these goals, it is possible to use mathematical models, the power deposition pattern in the heated tissue and the thermal interactions in the tissue to calculate complete temperature fields in the heated tissue [33]. Thus, analytical investigations on the evaluation of abilities of different heating modalities, so as to optimize the proposed thermal treatment by determining the power deposition parameters, which maximize the therapeutic effects of the tumour temperature distribution while minimizing normal tissue damage, have been studied using standardized Pennes models [16,17,19,20,21,26,27,29,30,31].

More detailed models with further knowledge of variations in the arterial temperature, probably coupled with an improved version of the bio-heat transfer equation, which also includes flow directionality effects of blood through large vessels inside the tissue, have been investigated for realistic hyperthermia treatments [2,3,4,5,6]. Recent developments in dual-phase- lag model have focused a new outlook on the aspect of hyperthermia treatments [8,9,10,11].

In course of future developments, it is probable that an improved version of the Pennes bio-heat equation together with the concept of dual-phase- lag model will focus the guideline on the optimal distribution of the complete temperature field throughout both tumour and normal tissue.

2. Mathematical Modeling

Modeling and understanding heat transport and temperature variation within biological tissues and body organs are key issues in medical thermal therapeutic applications, such as hyperthermia cancer treatment. The biological media can be treated as a blood saturated tissue represented by porus matrix.

Heat transport through the biological tissues, represented by bio-heat models, involves thermal conduction in tissue and vascular system, blood-tissue convection and perfusion (through capillary tubes within tubes) and also metabolic heat generation. Assuming local thermal equilibrium between the blood and the tissue, Pennes bio-heat equation in a homogeneous tissue, can be written as [2,3,4,5],

$$\rho c\frac{\partial \chi}{\partial t} = k\left[\frac{\partial^2 \chi}{\partial x^2}+\frac{\partial^2 \chi}{\partial y^2}+\frac{\partial^2 \chi}{\partial z^2}\right] - w_b c_b(\chi - \chi_1) + Q_m + Q(x,y,z,t) \qquad \ldots (1)$$

Where $\chi(x,y,z,t)$ is the tissue temperature due to heating induced by electromagnetic wave, χ_1 is the arterial temperature, c_b is the specific heat of blood, ω_b is the blood perfusion rate, and $Q(x,y,z,t)$ is the volumetric heat due to spatial heating. Here, ρ, c and k denote the density of the tissue, specific heat of the tissue and thermal conductivity of the tissue respectively.

Modeling the hyperthermia –induced temperature distribution requires as accurate description of the mechanism of bio-heat transfer. It is well known that the blood flow affects the thermal response of the living tissue. The heat exchange between the living tissue and the blood network that passes through it depends on the geometry of the blood vessel, the blood flow through it, and the properties of the blood and the surrounding tissue [2,3]. The bio-heat transfer equations have focused on the distribution of the temperature in the tissue while assuming a steady state blood flow. The effect of blood velocity pulsations on bio-heat transfer equation is important to study the temperature distribution in living tissues as the actual blood flow velocity is periodically oscillating which has been investigated in [4,5,6] . Cooling effect of thermally significant blood vessels in perfused tumour tissue during thermal therapy was studied in [3]. Here, thermal modeling based on the Pennes bio-heat transfer equation describing heat transfer of perfused tumour tissue and the energy transport equation governing the heat convection and diffusion of the blood flow was investigated.

Considering the influence of blood flow of thermally significant blood vessel, a single blood vessel inside and throughout the perfused tissue in three-dimensional axis-symmetric geometric configuration of the tissue was studied in [3] . The energy transport equations of the tissue and blood were expressed by equations, given by [3],

$$\rho_t c_t \frac{\partial T}{\partial t} = k_t \left[\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial T}{\partial r} \right) + \frac{\partial^2 T}{\partial z^2} \right] - w_b c_b (T - T_a) + Q_t(r,z,t) \quad \text{... (2)}$$

$$\rho_b c_b \left[\frac{\partial T}{\partial t} + \omega \frac{\partial T}{\partial z} \right] = k_b \left[\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial T}{\partial r} \right) + \frac{\partial^2 T}{\partial z^2} \right] + Q_b(r,z,t) \quad \text{... (3)}$$

where c, k, Q, ρ designate specific heat, thermal conductivity, absorbed power deposition density and density with subscript b and t for blood and tissue respectively. T, T_a, w_b and ω signify the temperature of the tissue, arterial temperature, blood perfusion rate and average blood velocity along z-direction respectively.

Some of the effects of pulsatile blood flow on obvious change of the energy transport between the vessel wall and the blood flow within blood vessel, based on the assumption that the vessel wall was a perfect thermal sink , may be cited in [4,5,6] . A numerical study was carried out to determine the influence of pulsatile laminer flow and heating protocol on temperature distribution in a single blood vessel and tumour tissue in hyperthermia treatment by Khanfer et al.,[6].

Biological media usually consist of blood vessels, cells and interstitial space, which can be, categorized as vascular and extravascular region. As such, a biological structure can be modeled as a porax matrix, including cells and interstitial space, called tissue in which the blood infiltrates through [7]. Thus, the blood and tissue local heat exchange , while biological media is subjected to an imposed heat flux as in hyperthermia, should be analytically investigated incorporating the blood and tissue properties , arterial blood velocity, porocity and geometrical properties of the biological structure, internal heat generation within the tissue and heat penetration depth. In this respect, the anatomic structure was modeled as a porous medium consisting of the blood and tissue phases. The governing equations for the blood and tissues was given by [7],

Blood Phase:

$$K_{b,\ eff}\ \nabla^2 y(T_b)^b + h_{tb}a_{tb}\left\{(T_t)^t - (T_b)^b\right\} = \varepsilon\rho c_p (u)^b \frac{\partial (T_b)^b}{\partial x} \quad \text{... (4)}$$

Tissue phase:

$$K_{b,\ eff}\ \nabla^2 y(T_t)^t - h_{tb}a_{tb}\left\{(T_t)^t - (T_b)^b\right\} + (1-\varepsilon)q_{gen} = 0 \quad \text{... (5)}$$

where

$$k_{b,\ eff} = \varepsilon k_b + k_{b,\ dis}$$

$$k_{t,\ eff} = (1-\varepsilon)k_t$$

Where, the parameters $(T_b)^b$, $(T_t)^t$, $(u)^b$, $k_{b,\ eff}$, $k_{t,\ eff}$, $k_{b,}$ $k_{t,}$ $k_{b,\ dis}$, ε, ρ and c_p are intrinsic phase average blood and tissue temperatures, intrinsic blood phase average velocity, blood and tissue effective conductivities, blood and tissue thermal conductivities, blood dispersion thermal conductivity, porosity, blood density and specific heat respectively. The blood-tissue interfacial heat transfer coefficient is represented by h_{tb} and specific surface area by a_{tb} and q_{gen} is the heat generation within biological tissue.

Knowledge on heat transfer in living tissues has been widely studied in therapeutic applications, particularly in hyperthermia treatment in cancer. Due to simplicity and validity, the Pennes model is the most commonly used. The Pennes bio-heat equation describes the thermal behavior based on classical Fourier's Law. As is well known, Fourier's law depicts an infinitely fast propagation of thermal signal, obviously incompressible with physical reality. In this respect, a modified flux model for the transfer processes with a finite speed wave is important. This thermal wave theory introduces a relaxation time τ that is required for heat flux vector to respond to the thermal disturbances (i.e. temperature gradient) as, [8,9,10,11]

$$\vec{q} + \tau \frac{\partial \vec{q}}{\partial t} = -K\nabla T \quad \text{... (6)}$$

Where $\vec{q}$ is heat flux vector and K represents the thermal conductivity.

Energy conservation equation of bio-heat transfer described in Pennes model is,

$$-\nabla \vec{q} + w_b c_b (T_b - T) + q_m + Q = \rho c \frac{\partial T}{\partial t} \quad \text{… (7)}$$

where $\rho, c, T, c_b, w_b, q_{m,} Q$ and T_b are density of the tissue, specific heat of the tissue, temperature of the tissue , specific heat of blood, perfusion rate of blood, metabolic heat generation, spatial heat source and arterial temperature respectively.

To take account the finite heat propagation effect, the thermal wave model of bio-heat transfer can be derived from equations (6) and (7) as [10,11],

$$\nabla(K\nabla T) + w_b c_b (T_b - T) + q_m + Q + \tau\left(-w_b c_b \frac{\partial T}{\partial t} + \frac{\partial q_m}{\partial t} + \frac{\partial Q}{\partial t}\right) = \rho c\left(\tau \frac{\partial^2 T}{\partial t^2} + \frac{\partial T}{\partial t}\right) \quad \text{... (8)}$$

which is designated as the equation derived from the dual-phase-lag heat conduction model.

In Magnetic Fluid Hyperthermia (MFH) as a modality for cancer treatment, magnetic particles are localized in the diseased tissue. An alternating magnetic field is then applied to the tissue, which heats the magnetic particles by magnetic hysteresis losses. In this ideal hyperthermia treatment, the diseased cells should be selectively destroyed without damaging the surrounding healthy tissue. Among all hyperthermia modalities including microwave, laser and ultrasonic wave-based treatments, MPH has the maximum potential for such selective targeting [12,13] . In this respect, the analytical investigation on optimization problems to determine the optimum heating pattern induced by multiple magnetic particle injections in tumour models with irregular geometrics are very important. The injection site locations, thermal properties of tumour and tissue, and local blood perfusion rates can be used as inputs to determine the optimum parameters of heat sources for all particle injection sites [14,15].

3. Optimization problems

Optimal Control theory is the mathematical study of how to manipulate the parameters affecting the behavior of a system to produce the desired or optimal outcome [Butkovosky, 1969; Golub, 1969] . This theory is now undergoing rapid developments and much of this theory is being assimilated in the solution of enormous variety of bio-medical engineering, biological and social problems [23,24] . One of the most recent developments is that of optimal control in systems with distributed parameters which specially includes the heating of the biological tissues in course of cancer treatment by hyperthermia.

An important class of problem in biological processes with systems of distributed parameters are the problems of optimal heating of tissue in thermal therapeutic applications, such as hyperthermia treatment. Hyperthermia is potentially an effective method for the treatment of cancer, especially when combined with other treatment modalities such as radiotherapy or chemotherapy [25].

However, in case of spatial heating power $Q_1(x,t)$ induced by microwave, the important issue is to deal with the most typical one where the heat flux decays exponentially with the distance from the surface of the tissue [18,22]. Such heating power induced by microwave is, in fact, constructed from well known Beer's law. The spatial heating power $Q_1(x,t)$ can then be obtained as, $Q_1(x,t) = \beta e^{-\beta x} Q_2(t)$ where $Q_2(t)$ is time dependent heating power applied on the surface of the tissue and β signifies scattering coefficient. Thus, the heat distribution in the tissue can well be approximated by Beer's law [18,22].

Thus, in some cases, heating power applied on the surface of the tissue considered according to well known Beer's Law. In certain optimal control problems, both the heating power induced by microwave and surface cooling temperature are taken as input control variables as these are direct input accessible to direct control [17]. It has also been shown that surface cooling temperature can focus the microwave heating in deeper levels in the tissue [17,22].

In hyperthermia treatment, the tumour cells inside the tissue are heated to a beneficial therapeutic temperature so as to kill the tumour cells by avoiding the damage of the healthy tissue [26,27].

In the last two decades, the conjugate gradient method coupled with adjoint equation approach has been extensively used in the resolution of general inverse heat transform problems [34]. The conjugate gradient method devices the basis from the variational principle and transforms the original direct problem to the solution of two subproblems, namely, the direct problem in variation and the adjoint problem [26].

In this method, a system of adjoint function and the condition of optimality of the control variables are obtained with the aid of calculus of variation [26]. The optimal values of control variables, thus, can be obtained from the optimality condition of the controls by means of computer simulations [17, 26, 27, 29, 30].

In course of analytical investigation of optimal control problems in multi-layered biological tissue, the methodology generally adopted is the usual 'Maximal Principle' with a suitably constructed Hamiltonian followed by the use of a variant of finite difference method [16, 18, 28, 31, 32].

Some analytical investigations of optimal control problems on temperature distribution described by bio-heat transfer equation in multi-layered biological tissue have been carried out in different articles on the basis of Pennes bio-heat model [16,17,18,19,20,21] .

In order to raise the temperature of the tumour inside the tissue to it's beneficial therapeutic value, heat is generated in the tissue by microwave, laser and ultrasound which are most commonly used heating methods. Considering Pennes bio-heat model, analytical investigations on this aspect of temperature distribution in the tissue by controlling heating power have been studied in different articles [23,24,25,26,27,28,29,30,31,32,35,36].

4. Conclusion

On the background of dual-phase-lag heat conduction model, mentioned in equations 6,7 and 8, the optimal control problems can well be studied which may focus a modern guideline on the aspect of hyperthermia treatment.

Further, analytical and numerical studies on the optimization problems to determine the optimum heating pattern, induced by magnetic particle injections in the tumour models with irregular structures, can also be developed which will give a good insight on the strategy of modern hyperthermia treatment.

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