Analytical Study on Optimal Control Problems in Hyperthermia

synopsis

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by

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In hyperthermia treatment, the tumour cells inside the tissue are heated to a beneficial therapeutic temperature (desired temperature) so as to kill the tumour cells by avoiding the damage of the healthy tissue surrounding the tumour cells (Arora et al.[1], Butkovasky [2], Cheng et al.[3], Dhar and Sinha [5], Das et al. [6], Kowalski and Jin [8]) .

The chapter 1 is the 'Introduction'. This chapter deals with the concept of hyperthermia treatment together with methodologies adopted in course of analytical investigation of eight optimal control problems in single – layered (homogeneous) and multi – layered (non-homogeneous) biological tissues. This chapter also focuses the prospect of analytical study of those optimal control problems on further developments in future research work.

In this thesis, the optimal control problems are analytically investigated on the temperature distribution of the tissue described by Pennes bio-heat equation.

In the first four chapters (chapter 2 – 5), analytical investigations of four optimal control problems on the temperature distribution of single-layered (homogeneous) tissue, described by one-dimensional Pennes bio-heat equation, are carried out in order to attain therapeutic beneficial (desired) temperature at the tumour embedded inside the tissue. The desired temperature of the tumour is attained by controlling input control variables. The input control variables are taken as the heating power, unusually induced by microwave, and the surface cooling temperature.

As the structure of the biological tissue is multi-layered (non homogeneous), four optimal control problems on the temperature distribution for a system, described by one-dimensional Pennes bio-heat equation in a multi-layered tissue, consisting of skin, fat, muscle and tumour layers, are analytically investigated in the last four chapters (chapter 6 – 9). The therapeutic beneficial (desired) temperature at the tumour , embedded inside the tissue, is attained by controlling input variables.

In a system of distributed parameters, the distribution of temperature of the homogeneous tissue is described in space and time by Pennes bio-heat transfer equation given by (Deng and Liu[4]),

$$\rho c \frac{\partial \chi}{\partial t} = k \frac{\partial^2 \chi}{\partial x^2} + \omega(\chi_a - \chi) + Q(t)$$

Boundary condition : $k \frac{\partial \chi}{\partial x} = h\{\chi - u(t)\}$ $on\ x = 0,$

$$\chi = \chi_a \ on\, x = L$$

Initial Condition : $\chi(x, o) = \chi_0$

where $\rho, c, k, \chi(x,t), \chi_a, b, \ Q(t)$ h and u(t) represent the density of the tissue, specific heat of the tissue, thermal conductivity of the tissue, temperature of the tissue , arterial temperature , product of flow and heat capacity of blood time dependent heating power induced by microwave, heat transfer coefficient between skin and ambient air and surface cooling temperature respectively.

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 which is one of the most commonly used heating method. Thus, it is worthwhile to investigate analytically the distribution of temperature of the tissue so as to achieve the beneficial therapeutic temperature of the tumour inside the tissue by controlling microwave power level and surface cooling temperature which are accessible to direct controls (Wagter[12]).

Loulou and Scott [10] developed a method to optimize HIFU (High intensity focused ultrasound) treatments based on the resolution of an inverse heat conduction problem using 'Conjugate gradient method', where one-dimensional single layered Pennes bio-heat transfer equation was considered. They showed that conjugate gradient method provided an efficient, rapidly convergent and straightforward approach for solving a complex hyperthermia control problem .

On this viewpoint, in chapters 2, 4 and 5, the analytical investigations of optimal control problems on the distribution of temperature in the tissue, described by one-dimensional single-layered (homogeneous) Pennes bio-heat transfer equation, are carried out with the aid of Conjugate gradient method. Here the beneficial therapeutic (desired) temperature at the tumour inside the tissue is attained by controlling optimal heating power induced by microwave and surface cooling temperature

The conjugate gradient method devices the basis from the variational principle and transforms the original direct problem to the solution of two subnormal problems, namely, the direct problem in variation and the adjoint problem. (Loulou and Scott[10]).

In Chapters 2, an optimal control problem on the distribution of temperature in the tissue, described by one-dimensional Pennes bio-heat transfer equation in single-layered tissue (homogeneous), is analytically investigated such that a beneficial therapeutic (desired) temperature at a particular point of location of the tumour inside the tissue can be attained. The desired temperature of the tumour is attained during a specific time by controlling opitmal heating power induced by microwave $Q(t)$ when the surface cooling temperature is taken as constant throughout the fixed operation of the process.

In course of analytical investigation of this problem with the aid of conjugate gradient method under calculus of variation, it is found, from the condition for optimality of the control variable, that $Q(t)$ is a singular control. Thus, for the sake of simplicity, one specified discrete time instant is taken which is considered as a switching time t_1 (say).

The objective of this present problem is to find out the optimal values of control $Q(t)$ during the time intervals $(0,t_1)$ and (t_1,T), when T is the total time of operation of the process. The corresponding values of Q(t) are obtained by computer simulation from the condition for the optimality of control variable $Q(t)$.

It is observed that the temperature distributions of the tissue on the left side of the tumour at $x = 6$ mm, where the desired temperature $43^0 C$ is attained, are always less than $43^0 C$ of the tumour. Further, the temperature on the right side of the tumour decreases steadily to $37^0 C$ (artery temperature). This steady decrease of temperature may be accounted for as the effect of switching off the volumetric heat generation rate $Q(t)\ (Wm^{-3})$ in the second time segment of the operation of process (t_1,T) for switching time t_1. As the temperature of the healthy tissue on the both sides of the tumour stay below the desired temperature $43^0 C$ of the tumour, thus the damage of the healthy tissue is avoided when the temperature of the tumour rises to $43^0 C$ at the switching time. It requires mentioning that as the total time of operation increases from $T = 600s$ to $T = 1000s$, the time in the first segment of operation $(0,t_1)$ increases with the corresponding decrease of $Q(t)\ (Wm^{-3})$ in this segment.

In Chapter 3, a distributed optimal control problem on the temperature distribution, described by Pennes bio-heat equation in one-dimensional homogeneous tissue is analytically investigated such that a beneficial therapeutic desired temperature at a particular point of location of tumour inside the tissue can be achieved at the end of total time of operation of the process. The desired temperature of the tumour is attained by controlling both optimal time dependent heating power induced by microwave $Q_2(t)\ (Wm^{-2})$ and surface cooling temperature $u(t)\ (^0C)$. Here, the spatial heating power $Q_1(x,t)$ induced by microwave is constructed according to well known Beer's law, given by $Q_1(x,t) = \beta e^{-\beta x} Q_2(t)$, where $Q_2(t)$ (Wm^{-2}) signifies time dependent heating power, β is scattering coefficient and x is the distance of a point of the tissue from it's surface along x-axis.

As methodology, the ' Maximal Principle ' is applied on the time dependent ordinary differential equations which are obtained by discritizing the space derivatives, described by one-dimensional homogeneous Pennes bio-heat equation, with the aid of finite difference method.

Then, on the basis of 'Maximal Principle', a system of ordinary differential equations of adjoint functions together with the conditions for optimality of the control variables are obtained in the form of 'Hamiltonian function' (Golub [8], Lee and Markus [10]).

In course of analytical investigation of this problem, it is seen that the optimal control variables $Q_2(t)$ and $u(t)$ are singular controls. Thus, we have taken only two specified switching times t_1(say) and t_2(say), for the sake of simplicity, in the consideration of distributions of $Q_2(t)$ and $u(t)$ respectively.

It is observed that the temperature of tissue increases on the left side of the tumour, located at $x = 6$mm, till it attains the beneficial desired temperature 43^0C of the tumour at the end of operation of the process and then the temperature of the tissue on the right side of the tumour decreases steadily to 37^0C (arterial temperature). It is to note that as the total time of operation of the process increases from $T = 600s$ to $1000s$, the first time segment of operation of the process $(0, t_1)$ increases with the corresponding decrease of $Q(t)$ (Wm^{-2}) in this segment for the switching time t_1. The surface cooling temperature $u(t)$ (^0C) increases in the first time segment of operation of the process $(0, t_2)$ as the total time of operation increases from $T = 600s$ to $1000s$ for the switching time t_2.

It is seen that the value of the induced heating power Q(t) (Wm^{-2}) in the first time segment of operation of the process is much greater than it's value applied on the second time segment of operation of the process. In course of analytical observation on the distribution of the surface cooling temperature u(t) (^{0}C), it is found that the value of u(t) (^{0}C) is greater in the first time segment of operation (O, t_2) than it's value in the second time of operation of the process (t_2, T).

Further, it is to note that the decrease of temperature of the tissue on the right side of the tumour is rapid than the increase of temperature of the tissue on the left side of the tumour.

Again, it is seen that the temperature of the healthy tissue on the both sides of the tumour are less than desired rise of temperature 43^0C and thus the damage of the healthy tissue is avoided.

In chapter 4, we would like to investigate analytically an optimal control problem in a system described by one dimensional homogeneous Pennes bio-heat equation, so as to attain the desired temperature χ^* at the point of location of the tumour $x = x_1$. Inside the tissue. The desired temperature χ^* is attained during a specific time for fixed total time of operation of the process such that temperatures of the two neighbouring points, specified on the both sides of the point of tumour, can be achieved below the temperature of the tumor χ^* to avoid the damage of the healthy tissue at those points. Here, both optimal heating power Q(t), induced by conducting heating probe inserted at the tumour site at $x = x_1$, and surface cooling temperature $u(t)$ are taken as input controls.

The performance criterion can be written as

$$\frac{A}{2}\int_0^T\int_0^L \left\{\chi^* - \chi(x,t)\right\}^2 \delta(x - x_1)dxdt + \frac{1}{2}\int_0^T \int_0^L \left[\left\{\theta_1^* - \chi(x,t)\right\}^2 \delta(x - x_2) + \left\{\theta_2^* - \chi(x,t)\right\}^2 \delta(x - x_3)\right] dxdt$$

which is to be minimized where T is the total time of operaiton of the process.

Here, x_2, x_3 are two specified neighbouring points in normal tissue which lie on the left and right side of the location of the tumour respectively and θ_1^*, θ_2^* are the corresponding desired temperatures below the temperature of the tumour χ^*. A is the weighting factor to bias the rise of temperature of the tumour and $\delta(x-x_i)$ $(i=1,2,3)$ are the Dirac –delta functions.

In course of analytical investigation of this problem, it is seen that the optimal control variables $Q(t)$ and $u(t)$. are singular controls. For simplicity , we have taken two switching times t_1 and t_2 in consideration of the distribution of $Q(t)$ and $u(t)$ respectively.

Here, the tumour is located at the $x=.006m$ and the two neighbouring points $x=.005m$ and $x=.007m$ are specified on the left and right side of the tumour respectively. Here, 43^0C, 41.5^0C and 41^0C are the desired temperatures to be attained at the respective points $x=.005m$, $.006m$ and $.007m$.

It is observed that the temperature of the tumour at the point of location $x=.006m$ attains desired temperature 43^0C at times $t=300s, 400s$ and $700s$ respectively. These are the switching times of the heating power $Q(t)$ for the corresponding total time of operation of the process $T=600s, 800s$ and $1000s$.

In course of analytical observations, it is seen that the temperatures of the normal tissue, located at the neighbouring points $x=.005m$ and $x=.007m$ on both sides of the point of tumour , attain temperatures very close to the desired temperatures 41.5^0C and 41^0C respectively. It is also observed that temperature distributions of the tissue on the left side of the tumour at $x=.006m$ increases steadily till it attains the desired temperature 43^0C of the tumour and then decreases rapidly to the arterial temperature 37^0C.

It is also found that the heating power $Q(t)$ is applied in the first time segment of operation $(0,t_1)$ and then is switched off in the second time segment of operation (t_1,T) when t_1 is the switching time of $Q(t)$. The steady decrease of the temperature of the tissue on the right side of the tumour to 37^0C may be accounted for the effect of switching off the heating power $Q(t)$ in the second time of operation (t_1,T).

Further, it is to note, that values of the surface cooling temperature $u(t)$ applied in the first time segment of operation $(0,t_2)$ is always less than it's value in the second time segment of operation (t_2,T). Here t_2 signifies the switching time of the surface cooling temperature

$u(t)$. It requires mentioning that the switching time of $Q(t)$ is always less than the switching time of $u(t)$ for total time of operation of the process $T = 600s, 800s$ and $1000s$.

It is also observed that the position of the highest temperature of the tissue is attained at the point of location of the tumour, where the heating power is induced by inserting a conducting heating probe. Thus the highest temperature is attained at the position of the point heat source . This rise of highest temperature at the point of location of the heat source, obtained from the above observation, is in agreement with those found by (Deng and Liu [9]) in course of analytical investigation on the temperature distribution of the tissue due to the application of the heating power induced by inserting a conducting heating probe at the tumour site.

It is also observed that, as the total time of operation of the process increases from $T = 600s$ to $1000s$, the time in the first segment of operation $(0, t_1)$ increases with the corresponding decrease of $Q(t)$ in this segment.

It was found that a typical treatment with local hyperthermia consists of raising the temperature of the tumour to about $40 - 43^0 C$ (Deng and Liu[4], Cheng, et al. [3]). As there is a range of beneficial therapeutic (desired) temperature of the tumour to be raised in hyperthermia treatment, an optimal treatment goal may be assumed so that all temperatures of the tumours, located at some specific points along it's entire length, are to attain a specified beneficial temperature $43^0 C$ (say). This attempts to uniformize the temperature of all tumours, located at some specific points across the entire length of the tumour, to a desired temperature $43^0 C$ (Cheng, et al. [3]).

From this viewpoint, in chapter 5, we would like to investigate analytically an optimal control problem on the distribution of temperature in biological tissue , described by one-dimensional Pennes bio-heat equation in a single layered tissue, so as to attain the therapeutic beneficial (desired) temperature χ^* (say) on q number of tumours, located at specific points $x = x_1, x_2, ...x_q$ across the entire length of the tumour inside the tissue. The desired temperature χ^* is attained during a specific time by controlling optimal microwave induced heating power $Q(t)$ applied on the surface of the tissue when the surface cooling temperature is taken as constant throughout the fixed time of operation of the process

The objective function thus stands as [5]

$$\frac{1}{2}\left[\frac{1}{q}\int_0^T \int_0^L \sum_{i=1}^{q} \left\{\chi^* - \chi(x,t)\right\}\delta(x - x_i)dxdt\right]$$

which is to be minimized.

Here $\chi(x,t), T, L$ and $\delta\left(x - x_i\right)$ designate the temperature of the tissue, total time of operation of the process, length of the tissue and Dirac-delta function respectively.

In course of analytical investigation performed by conjugate gradient method for obtaining the condition for optimality of the control variable $Q(t)$ i.e., time dependent heating power induced by microwave, it is found that optimal control $Q(t)$ is a singular control.

For the sake of simplicity, we consider one switching time $t = t_1$ in case of control $Q(t)$. Thus $Q(t)$ assumes two extreme values within the intervals $(0, t_1)$ and (t_1, T) when T is the total time of operation of the process.

It is seen that the heating power $Q(t)$ induced by microwave is applied on the first time segment of operation of the process $(0, t_1)$ and is switched off in the second time segment of operation (t_1, T) where t_1 and T are switching time and total time of operation of the process respectively.

It is observed that distributions of temperature of the tissue on the left side of the tumour, lies between .005m-.006 m, are always less than $43^0 C$ of the temperature of the tumour. Further, the temperature on the right side of the tumour decreases steadily to $37^0 C$ (arterial temperature) which can be accounted for as the effect of cutting off the heating power Q(t) (Wm^{-3}) in the second time segment of operation of the process. Thus the damage of normal tissue is avoided as the temperature on the both sides of the length of the tumour stay below the temperature of the tumour $43^0 C$. Since the computations have been carried out for various values of the total time of operation of the process T, the optimal heating power $Q(t)$ as well as the switching time t_1 during which $Q(t)$ is operative have been changed. Considering this aspect, it is noteworthy to mention that as the total time of operation of the process increases from T = 600s to 1000s, the first time segment of operation $(0, t_1)$ increases with corresponding decrease of Q(t) (Wm^{-3}) in this segment.

In course of analytical investigations of last four chapters from chapter 6 – 9, four optimal control problems on the distribution of temperature in one-dimensional multi layered tissue, consisting of skin, fat, tumour and muscle layers, are carried out where each layer is assumed as homogeneous. The temperature distribution in multi-layered tissue is described in space and time by one-dimensional Pennes bio-heat equation with usual parameters k_i, b_i, c_i and ρ_i where k_i, b_i, c_i and ρ_i represent the thermal conductivity of the tissue , product of flow and heat capacity of blood, specific heat of tissue and density of the tissue in i^{th} layer respectively (Dhar and Sinha [5], Nachman and Turgeon [11], Wagter [12]).

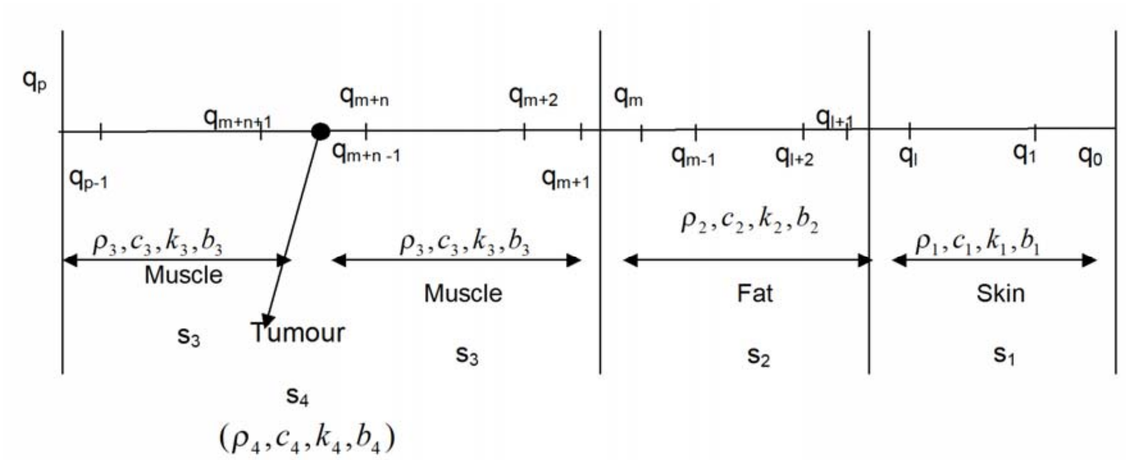

Fig – A

The objective of the optimal control problems presented in chapters 6 – 9 is to find out the optimal values of control variables in one dimensional multi-layered tissue where the methodology adopted is the usual 'Maximal Principle' with a suitably constructed 'Hamiltonian Function' followed by the use of a variant of finite difference method .

In this method, the space derivatives in Pennes bio-heat transfer equation with distributed parameters are discritized to a system of lumped parameters, described by time dependent ordinary differential equations, with the aid of finite difference method.
Then, on the basis of 'Maximal Principle' a system of ordinary differential equations of adjoint functions are obtained together with conditions for optimality of the control variables in the form of 'Hamiltonian function' where the calculus of variation and integrating by parts are used (Golub [7], Lee and Markus [9]).

We would like to present here, an as example, the methodology for obtaining the condition for optimality of control variable in a system described by time dependent ordinary differential equation given by (Golub [7] , Lee and Markus [9])

$$\frac{d\chi(t)}{dt} = f\{\chi(t), Q(t)\}, \quad 0 \le t \le T \qquad (1)$$

with initial condition $\chi(0) = \chi_0$ (2)

Here, $\chi(t)$ designates the temperature and $Q(t)$ is the control variable.

Let us choose an objective function $\int_0^T h\{\chi(t), Q(t)\}dt$ (Lee and Markus,[9]) as an optimization criterion which is to be minimized.
According to 'Maximal Principal' , we would like to formulate a functional J, given by

$$J = \int_0^T \left\{ H - \psi(t)\frac{d\chi}{dt} \right\} dt \qquad (3)$$

where $\psi(t)$ signifies adjoint function and the Hamiltonian function H is defined as $H = \psi(t) f\{\chi(t), Q(t)\} - h\{\chi(t), Q(t)\}$ (Golub [7]; Butkovosky [2], Lee and Markus [9]).

In order to obtain the condition for the optimality of the control variable $Q(t)$, we adopt the procedure to consider the stationary condition $\delta J = 0$ for any allowed functions $\delta\chi(t), \delta Q(t)$ and $\delta\chi(T)$ (Butkovosk [2], Golub [7]).

Here δJ represents a small variation of J due to small change $\delta\chi(t)$, where $\delta\chi(t)$ signifies a small change of $\chi(t)$ due to change of control variable $Q(t)$.
Thus, using calculus of variation and integration by parts, we obtain

$$\delta J = \int_0^T \left[\frac{\partial H}{\partial \chi(t)} \delta\chi(t) + \frac{\partial H}{\partial Q(t)} \delta Q(t) \right] dt - \left(\psi(t)\delta\chi(t)\right)_0^T + \int_0^T \frac{d\psi}{dt} \delta\chi(t) dt$$

From the condition $\delta J = 0$ (for $\delta\chi(0) = 0,$) we arrive to a system of equation of adjoint function $\psi(t)$ in terms of Hamiltonian function H, given by (Golub,[7]).

$$\frac{d}{dt}\psi(t) = -\frac{\partial H}{\partial \chi}, \ \psi(T) = 0 \tag{4}$$

The condition for the optimality of $Q(t)$ can be written as , $\frac{\partial H}{\partial Q(t)} = 0$. (5)

From the conditions of optimality of controls $Q(t)$, i.e. $\frac{\partial H}{\partial Q(t)} = 0$, one can obtain the optimal values of the control $Q(t)$ by solving equations (1) and (4).

In chapter 6, we have investigated analytically optimal distribution of time dependent heating power $Q_2(t)$ (Wm^{-2}) described by one dimensional Pennes bio-heat equation in a multi-layered tissue, consisting of skin, fat, muscle and tumour layer, so as to attain therapeutic beneficial desired temperature across the entire length of the tumour layer at the end of fixed time of operation of the process. The desired temperature across the entire length of the tumour, embedded inside the muscle layer, is achieved by controlling optimal time dependent heating power $Q_2(t)$ (Wm^{-2}) induced by microwave which is constructed according to Beer's law.

The methodology adopted here is the usual 'Maximal Principle' with a suitably constructed 'Hamiltonian' followed by the use of a variant of finite difference method .

In course of analytical observation on the numerical distribution of $Q_2(t)$ (Wm^{-2}), it is found that the value of $Q_2(t)$ (Wm^{-2}) is maximum at the beginning of the process and then

decreases steadily as time of the operation of the process increases. The value of $Q_2(t)$ (Wm^{-2}) ultimately approaches to zero at the end of operation of the process.
The distribution of temperature of the tissue due to the application of the calculated optimal distribution of heating power $Q_2(t)$ (Wm^{-2}) is then obtained numerically from which it is seen that the temperature across the entire length of the tumour attains near about beneficial therapeutic temperature $43^0 C$ at the end the time of operation of the process. Further, it is observed that the temperature on the left side of the length of the tumour steadily increases till it attains the beneficial desired temperature near about $43^0 C$ across it's entire length and then decreases to the arterial temperature $37^0 C$.

Thus, all together, it is found that the damage of the healthy tissue is avoided as it's temperature stays below the desired temperature $43^0 C$ of the tumour.

In chapter 7, an optimal control problem on the temperature distribution described by one-dimensional Pennes bio-heat equation in multi-layered tissue, consisting of skin, fat, tumour and muscle layers, is analytically investigated to achieve a therapeutic beneficial (desired) temperature across the entire length of the tumour inside the tissue. The desired temperature is attained during a specific time by controlling optimal time dependent heating power when surface cooling temperature is taken as constant throughout the fixed total time of operation of the process so that the temperature across the entire length of the first muscle layer (preceding tumour layer) attains temperature below the desired temperature of the tumour which attempts to avoid overheating of this muscle layer. Here the spatial heating power $Q(x,t)$ is constructed according to Beer's law.

The objective of this analytical investigation is to obtain the optimal values of the heating power $Q_2(t)$ (Wm^{-2}). It is found, from the optimal condition of $Q_2(t)$ (Wm^{-2}), that $Q_2(t)$ (Wm^{-2}) is a singular control.

For the sake of simplicity, one switching time $t = t_1$ (say) is taken during which the extreme values of the optimal heating power $Q_2(t)$ (induced by microwave) operates within the intervals $(0, t_1)$ and (t_1, T) where T signifies total time of operation of the process.

It is finally observed that 95% of the length of the tumour is being heated to 97.4% of it's therapeutic beneficial temperature $43^0 C$ at the switching time $t = t_1$ of the heating power $Q_2(t)$ (Wm^{-2}). Here the heating power is operative in the first time segment $(0, t_1)$ of total time of operation of the process T and then it is switched off in the second time segment of operation (t_1, T). Further, it is seen that the temperature of the tissue in the first muscle layer on the left side of the length of the tumour increases till it attains near about $43^0 C$ and then after attaining $43^0 C$ (desired temperature of the tumour) decreases steadily to approach arterial temperature $37^0 C$.

In Chapter 8, an analytical investigation of optimal control problem on the temperature distribution of the tissue, described by one-dimensional multi-layered Pennes bio-heat transfer equation, is performed in hyperthermia. A therapeutic beneficial desired rise of temperature at the point of location of the tumour embedded inside the muscle, consisting of skin, fat, muscle layers, is attained during a specific time by controlling both optimal heating power, induced by inserting a conducting heating probe at the tumor site, and surface cooling temperature when the total time of operation of the process is fixed. Here T is taken as total time of operation of the process.

In course of analytical investigation of this problem, it is found that the time dependent heating power $Q(t)$ (Wm^{-3}), induced by inserting a conducting heating probe at the tumour site, and surface cooling temperature $u(t)$ $({}^{0}C)$ are singular controls. We consider one specified switching time $t = t_1$ (say) of the heating power $Q(t)$ and another specified switching time $t = t_2$ (say) of the surface cooling temperature $u(t)$.

It is seen that the desired temperature $43^0 C$ is attained at the point of location of the tumour at the switching time $t = t_1$ of the heating power $Q(t)$, when $Q(t)$ is applied on the time segment $(0, t_1)$ and is switched off on the time segment (t_1, T). It is also observed that the temperature of the tissue on the left side of the point of location of the tumour increases steadily till it attains desired temperature $43^0 C$ whereas on the right side of the tumour the temperature of the tissue decreases rapidly to $37^0 C$ (arterial temperature) which can be accounted for due to cutting off the heating power $Q(t)$ in the time segment (t_1, T).

In chapter 9, an optimal control problem on temperature distribution described by one-dimensional Pennes bioheat equation in multi layered tissue, consisting of skin, fat and muscle layers, is analytically investigated so as to achieve beneficial therapeutic (desired) temperature at a particular point of location of the tumour imbedded inside the muscle layer. The desired temperature at the point of tumour is attained during a specific time by controlling optimal time dependent heating power $Q_2(x,t)$ (Wm^{-2}) induced by microwave when the surface cooling temperature is taken as constant throughout the fixed total time of operation of the process. Here the spatial heating power $Q_1(x,t)$ (Wm^{-3}) applied on the surface of the tissue is constructed according to Beer's law, given by $Q_1(x,t) = \beta e^{-\beta x} Q_2(t)$, where the control variable $Q_2(t)$ signifies time dependent heating power, β is the scattering coefficient and x is the distance of a point from the surface of the tissue.

Here, in course of investigating the optimal control problem on the temperature distribution in a multi-layered tissue, the space derivatives in one dimensional non-homogeneous Pennes bio-heat equation are discritized to a system of lumped parameters described by time dependent ordinary differential equations using finite difference method.

‘Maximal Principle’ is then applied on time dependent ordinary differential equations and a system of ordinary differential equations of adjoint functions are obtained together with condition for optimality of control variable in the form of ‘Hamiltonian Function’ where calculus of variation and integrating by parts are used .

In analytical observation, it is seen that the optimal heating power $Q_2(t)$ (Wm^{-2}) is a singular control. For the sake of simplicity , one switching $t = t_1$ is taken during which the extreme values of the microwave heating power $Q_2(t)$ operates within the intervals $(0, t_1)$ and (t_1, T) where T signifies total time of operation of the process.
It is finally observed that the temperature of the tumour located at particular point attains 98.7% of the therapeutic beneficial (desired) temperature $43^0 C$ at the switching time t_1 of the microwave induced heating power $Q_2(t)$ (Wm^{-2}). It is further seen that heating power operates in the first segment of operation $(0, t_1)$ and then the heating power is switched off in the second time segment of operation (t_1, T). The temperature of the tissue on the left side of the tumour increases till it attains near about $43^0 C$ and after attaining the desired temperature near about $43^0 C$, the temperature of the tissue on the right side of the tumour decreases steadily to arterial temperature $37^0 C$.

In Chapter 10, scope of future developments of research work on the aspect of optimal control problems in hyperthermia, analytically investigated in this thesis, are mentioned.

Pennes bio-heat equation describes the thermal behavior based on classical Fourier law which assumes the thermal disturbance that propagates with an infinite speed. However, due to the simplicity and validity, the Pennes bio-heat model is commonly used in optimal control problems for the distribution of temperature of the tissue in hyperthermia treatment.

As heat conduction in biological tissue is accomplished by interaction between the blood and the tissue, the propagation of the thermal disturbance is always at a finite speed. Thus, a dual-phase-lag (DPL) heat conduction model, which is based on the well-known two phase lags concept to interpret the non-Fourier heat conduction phenomena, was developed .

In Magnetic Fluid Hyperthermia (MPH) as a modality for cancer treatment, magnetic particles are localized in the diseased tissue. An alternating magnetic field is then applied in the tissue, which heats the magnetic particles by magnetic hysteresis losses. In this ideal hyperthermia treatments, the decreased cells (tumour) is selectively destroyed without damaging the surrounding healthy tissue. Among other hyperthermia modalities including microwave, laser and ultrasonic wave-based treatments, MPH has the maximum potentiality for heating selective targets .

Thus optimal control problems in hyperthermia treatment, analytically investigated in this thesis, may usually focus a good insight and useful guideline on the optimal distribution of temperature field throughout tie tissue (including tumour and healthy tissue) by incorporating the concept of dual-phase –lag (DPL) heat conduction model. Further, analytical investigation on optimization problems to determine the optimum heating patterns, induced by magnetic particle injections in the tumour, can also be studied on the background of optimal control problems analytically investigated in this thesis.

Bibliography

[1] Arora, D., Minor, M. A., Mikhail, S. and Roemer, R. B. Control of thermal therapies with moving power deposition field. Phys. Med. Biol. 51, 1201-1219 (2006).

[2] Butkovasky A.G., (1969) Distributed Control System, American Elsevier Publishing Company, New York.

[3] Cheng. K.S., Stakhursky. V., Cracinnesen. O.I., Stauffer. P., Dewhrist. M., Das. S.K.,(2008) Fast temperature optimization of multi-source hyperthermia applications with reduced –order modeling of 'virtual sources' , Phys. Med. Biol. Vol. 53, pp1619-1635.

[4] Deng Z.S., Liu J., (2002) Analytical study of bioheat transfer problems with spatial or transient heating on skin surface or inside biological bodies, ASME journal of Heat Transfer, Vol 124, pp 638-648.

[5] Dhar P.K., Sinha D.K., (1989) Optimal temperature control in hyperthermia treatment by artificial surface coling, Int. J. Systems. Sci, Vol 20, nr 11, pp 2275-2282.

[6] Das .S.K., Clegg. T.S., Samulski. T.V., (1999) Computational techniques for fast hyperthermia temperature optimization, Med. Phys., Vol 26, nr 2 pp 319-328.

[7] Golub N.N.,(1969) Optimum control of linear and non-linear distributed parameter systems, Aut. Remote Control, pp1378-1388 .

[8] Kowalski. M.E., Jin. J-M., (2003) A temperature-based feedback control System for electro-magnetic phased arrays hyperthermia : Theory and simulation, Phys. Med. Biol. Vol. 40, pp 633-651.

[9] Lee.E.B., Markus. L., (1967) Foundations of optimal control theory, The SIAM series in applied Mathematics, John Wiley & Sons.

[10] Loulou. T., Scott. E.P.,(2002) Thermal dose optimization in hyperthermia treatments by using the conjugate gradient method, Numerical Heat Transfer, Part A . Vol. 42, pp 661-683.

[11] Nachman, M. and Turgeon, G. (1984) Heating pattern in a multi-layered material exposed to microwave, IEEE Trans. Microwave Theory and Technique, Vol MTT 32, nr 5, pp 547-552.

[12] Wagter. C.G., (1985) Computer simulation for local temperature control during microwave-induced hyperthermia, J. Microwave Power, pp 31-45.