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ABSTRUCT

The present work focuses on the temperature distribution through the skin layer when the outer layer of the human skin surface is directly subjected to a sinusoidal heat flux to cure tumour cells located inside the body. The process of the treatment is known as local hyperthermia treatment. A mathematical model is developed to investigate the effect of phase lag due to thermal inertia and microstructural interaction. Spatial variation of temperature has numerically been calculated using Dual Phase Lag Model for Bio-Heat Transfer (DPLMBHT). Besides, blood perfusion rate, heat generation due to metabolism, and heat absorption in the skin layer has been analysed. Also, the effects of both phase lags are discussed, and the wave nature of heat propagation has been observed. It has been found that phase lag due to microstructural interaction has not much effect on the degree of slowness of heat propagation through the living tissue than the phase lag due to thermal inertia. Phase lag due to temperature gradient diffuses the heat ahead of the wave front of the heat propagation due to phase lag due to heat flux. It is also observed that the temperature variation decreases with the increase of frequency, which is essential for hyperthermia treatment to maintain a constant temperature at any particular position in the human body for a necessary period.

Keywords: *Thermal relaxation time, Thermal wave model, Dual-phase lag bioheat transfer, Temperature-dependent blood perfusion rate, Finite difference method.*

List of Symbols:

A.	*Greek Symbols*	
	ρ	Density, kg/m^3
	τ_q	Phase lag due to thermal inertia, s
	τ_t	Phase lag due to microstructural interaction, s
	ω	Frequency of the heat flux, Hz
B.	*General Symbols*	
	c	Specific heat, J/kg K
	G	Blood perfusion rate, m^3/s m^3
	k	Thermal conductivity, W/m K
	L	Thickness of the skin layer, m
	Q	Heat generation, W/m^3
	T	Temperature, K
	t	Time, s
	x	Space coordinate, m
C.	*Subscripts and Superscripts*	
	b	Blood
	cr	Body core
	exp	Exposure time
	ext	External heat source
	m	Metabolic production

1. Introduction

During hyperthermia treatment, heat transfer in the human skin layer is of great interest among researchers. It has vast application in the field of biotechnology and biothermomechanics. The human body behaves as a heterogeneous system with spatial and temporal temperature fluctuations; even within the same organ, it has non-uniform temperature distribution. So, the heat transfer in biological activities is an essential matter of concern. The skin has various vital roles in heat transfer as it is the largest single organ of the body (making up 14-16% approx.)[1]. Also, blood flow and metabolism rate take part in this regard by affecting the temperature distribution during different thermal treatments [1-4]. Nowadays, various thermal treatments treat diseases like cancer and injury involving skin (Dermatology), electromagnetic heating like microwave [5], radio frequency [6], and laser [7, 8] are the heat sources for this application. Most research in bioheat transfer has been done in a numerical or analytical approach, as in vivo experimental analysis is very expensive, risky, and challenging. In 1948, Penne's represented the following equation, built upon classical Fourier's law for heat transfer in biological tissues [9]:

$$\rho c \frac{\partial T}{\partial t} = k\nabla^2 T + (\rho c)_b G(T_{cr} - T) + Q_m + Q_{ext} \tag{1}$$

Where ρ, c, k signify density, specific heat, the thermal conductivity of the tissue respectively; G is the blood perfusion rate; T_{cr} is the body core temperature or arterial temperature of blood; Q_m and Q_{ext} are heat generation due to metabolism and external heat source, respectively. Most studies consider skin as a single-layer model for ease of analysis. The classical Fourier model's assumptions fail because most of the practical scenarios of heat conduction behave like a non-Fourier wave nature, as skin and biological tissue is an anisotropic system. So, Penne's equation has been modified by adding the concept of heat conduction with a finite speed, where an additional term has been added, known as phase lag or thermal relaxation time [10, 11]. The modified hyperbolic heat conduction equation looks like this:

$$Q(x,t) + \tau_q \frac{\partial Q(x,t)}{\partial t} = -k\left[\nabla T(x,t) + \tau_t \frac{\partial \nabla T(x,t)}{\partial t}\right] \tag{2}$$

Here τ_q is the phase lag due to 'thermal inertia' and τ_t is the phase lag due to 'microstructural interaction,' and to consider these two terms, the respective equation is known as the Dual-Phase-Lag (DPL) equation. Various experimental works have been conducted to evaluate the value of τ_q and τ_t in non-homogeneous biological tissues [12-14]. Penne's model can be obtained by taking τ_q and τ_t as zero. Although few researchers also did some analytical work to find temperature lag [15-17]. But till there is a lack of data for thermal phase lag, extensive studies are required to determine the exact values of both phase lag times in different situations.

In this present work, it has been shown that how temperature varies inside the skin layers during hyperthermia treatment to destroy cancer cells and the effect of phase lag in this regard. Here a sinusoidal heat flux is considered for the present study, which is used during hyperthermia treatment at the primary stage in the form of radio wave or high-frequency ultrasonic waves based on the position of the targeted bad cells. Analysis has been carried out by taking different values of metabolism rate according to age group and temperature-dependent blood perfusion rate. The main motive of this numerical study is to observe whether the attended highest temperature is in the required range or not (41^0 C – 46^0 C) at the targeted position to avoid unnecessary thermal damage of good cells [18].

2. Mathematical Model and Numerical Formulation

Hyperthermia treatment is the cancer-curing process in which the cancer cell is heated as high as 45^0 C (41^0 C – 46^0 C) with little or no damage to the good cells [18]. Present work assumes that cancer cells are located at the basal layer, the interface of the epidermis and dermis layer of human skin. So the target is to keep the basal layer temperature within the specified range for 1000s followed by a 500s cooling period. A sinusoidal heat source for transient heating on the skin surface is considered. Dual-Phase Lag bioheat transfer equation has been used to analyse the temporal variation of temperature throughout the different layers of skin. Also, considering heat generation due to metabolism and absorption, the following governing differential equation has been taken as:

$$\tau_q \rho C \frac{\partial^2 T}{\partial t^2} = \mathrm{k}[\nabla.(\nabla T) + \tau_t \frac{\partial(\nabla.(\nabla \mathrm{T}))}{\partial t}] + (\rho c)_b G(T_{cr} - T) - \left(\tau_q G(\rho c)_b + \rho C\right)\frac{\partial T}{\partial t} + Q_m + Q_{ext} + \tau_q \frac{\partial Q_m}{\partial t} + \tau_q \frac{\partial Q_{ext}}{\partial t} \tag{3}$$

As the thermoregulatory mechanism has an essential role in maintaining body temperature within some marginal limit, that's why a temperature-dependent blood perfusion rate has been taken in this work [1]. Other essential parameters like thermal conductivity, density, and other thermal properties of skin layers and blood are assumed

constant and given in Table 1. Heat generation due to absorption has taken according to Beer's law [2]. The following initial and boundary conditions have been considered in this study:

2.1. Initial Conditions:

i. $T(x, 0) = 307.15$ K; $(0 \le x < L)$ (4a)

ii. $\frac{\partial T(x,0)}{\partial t} = 0$; $(0 \le x < L)$ (4b)

2.2. Boundary Conditions:

i. $Q(0,t) = -k\frac{\partial T}{\partial t}$; $(0 \le t \le t_{exp})$ (4c)

Where, $Q(0,t) = 1000 + 500 \times \cos(\omega\, t)$;

ii. $T(L,t) = 310.65\, K$; (4d)

Body core temperature is assumed to be constant at $t \ge 0$

Here ω is the frequency of the supplied heat flux, L is the thickness of the skin layer, and t_{exp} is the exposure duration. The thermos-physical properties of the rectangular tumour cell are assumed as that of the dermis layer. Fig.1 shows that the schematic of the present model.

Table I. Thermo-physical Properties of Skin

Properties / Layers	*Density ρ (kg/m³)*	*Specific heat c (J/kg K)*	*Thermal conductivity k (W/m K)*	*Thickness L (m)*
Epidermis	1200	3590	0.24	8×10^{-5}
Dermis	1200	3300	0.45	0.002
Hypodermis	1000	2500	0.19	0.01
Blood	1060	3770	--	--

A numerical scheme, finite difference method with backward time and central in space scheme, has been used to discretize the transient partial difference equations. All discretized equations are solved using Thomas's Algorithm or Tri-Diagonal Matrix Algorithm (TDMA). A computer code has been developed in MATLAB R2016a with a uniform space grid size of 0.00001 and a time step size of 0.01.

To validate the present numerical model, current results are compared with the results obtained by Udayraj et al. It is found that the present results have excellent agreement with the obtained results by Udayraj et al.[1]. All the thermos-physical properties of skin and blood and a heat source are taken from Udayraj et al. [1]. Fig. 2 shows that the present results have less than 1% error with the obtained results of Udayraj et al [1].

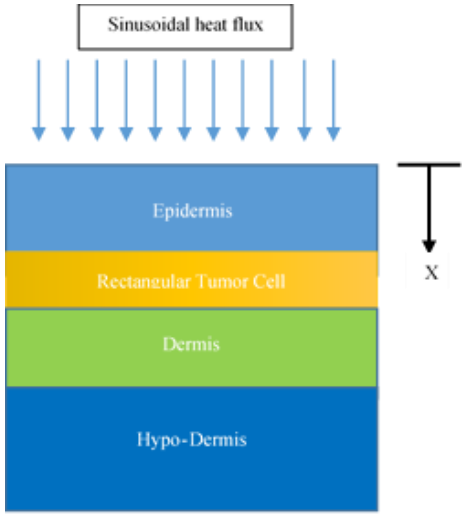

Figure 1. Schematic Diagram of Present Model

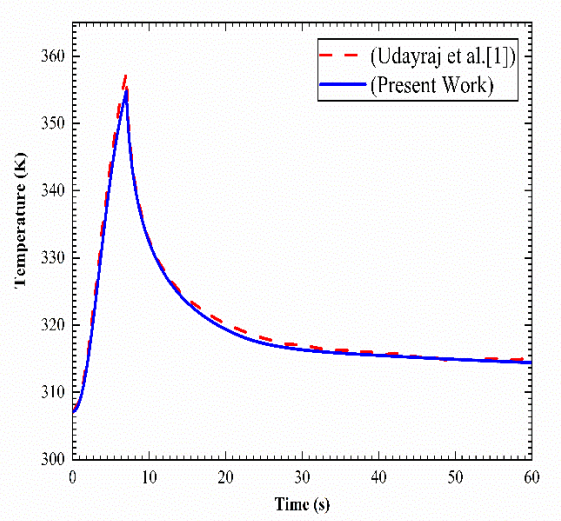

Figure 2. Comparison of Temperature Variation With The Results of Udayraj et al. [1]

3. Results and Discussions

The use of the phase lag phenomenon in heat transfer in biological tissue is inevitable for the analysis. Though, many researchers have used the phase lag in their calculations. But there is a lack of evitable value of τ_q and τ_t as in vivo experiment in tissue is very difficult. In the present work, few phase lag values have been taken from previous numerical work [19]. The phase lag depends on the blood vessel dimensions and properties of skin layers and the different locations of the human body. The effect of phase lag at the targeted cell has been shown in Fig. 3 at 20 Hz. It is noticeable that when the values of thermal relaxations are zero (Penne's Bio Heat Transfer Model), heat propagation is at an infinite speed, so a sudden increase of temperature can be observed before the graph has been flattened. However, the effect of thermal inertia is far more than the effect of microstructural interaction. It is also observable that if we incorporate thermal inertia and microstructural interaction (phase lag due to temperature gradient), both the degree of the slowness of heat propagation increases as the slope of the curve decreases (Fig.3). But if the value of τ_q (phase lag due to heat flux) decreases, the slope of the temperature

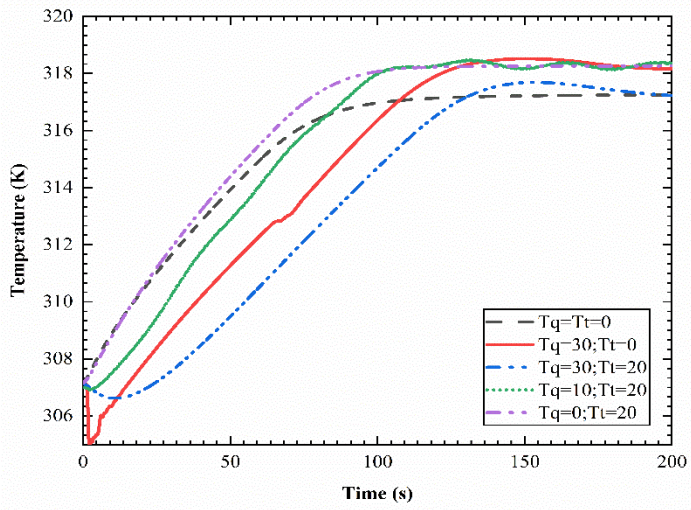

Figure 3. Variation of Temperature with Time up to 200s for better observation of Phase Lag Effect at the frequency of 20 Hz

curve increases, and it is close to Penne's Bio Heat Transfer Model. It signifies that heat transfer is dominated by diffusion over the wavy nature. So, thermal relaxation time plays an essential role in bioheat transfer in living tissues, for which Penne's model fails to approach a realistic scenario. In the case of hyperthermia treatment, the heat is supplied by using a microwave or laser with a high frequency (<Radio Frequency) for a minimum span of 20-30 minutes. Sometimes it goes even more than 1 hour, depending upon the type of hyperthermia. The temperature should be kept in a required range at the targeted cells [18]. In the present work, a sinusoidal heat flux has directly applied to the skin for 1000 seconds, followed by a cooling period of 500 seconds.

It is observed that the temperature fluctuation at the basal layer is significantly less at the frequency of 20 Hz (Fig.4). Also, it takes much time to attend to the highest temperature. By increasing the frequency of the supplied heat flux, the temporal variation of tissue temperature also decreases. This variation should not be high enough to exceed the limiting value up to which there is no dangerous damage of good tissues (41^0 C – 46^0 C). Fig.4 and Fig.5 show the temperature variation differences at the frequency of 0.02 Hz and 20 Hz, respectively. So the frequency of the heat supplied should be chosen based on the type of hyperthermia.

Moreover, it has been observed that the DPL model gives unrealistic results at a very high frequency for this particular case [20]. It has been found that temperature increases more in the case of Penne's model ($\tau_q = \tau_t = 0$) due to the infinite speed of heat propagation. Whereas, in the case of the Cattaneo Bio Heat Transfer Model ($\tau_q = 30; \tau_t = 0$) (TWMBHT), the temperature rise is less due to the thermal inertia. Due to microstructural interaction, the temperature rise is remarkable than TWMBHT but less than Penne's model ($\tau_q = 0; \tau_t = 20$). It signifies that the heat transfer is dominated by diffusion only. It is also observed from Fig. 3 that the DPL model results in the lowest temperature rise by considering relaxation time due to thermal inertia and microstructural interaction. Heat propagation with a finite speed (wave nature) can be observed while only phase lag due to thermal inertia is considered (Fig.6). However, microstructural interaction enlarges the penetration depth of the heat transfer. Hence, the wave nature disappears while the relaxation due to microstructural interaction has been considered (DPLMBHT), shown in Fig.6 and Fig.7. Fig.8 shows the wavy nature of the temperature distribution

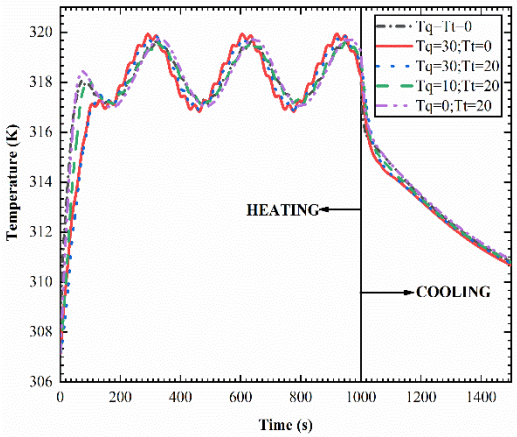

Figure 4. Temperature variation with time at the basal layer at the frequency of 0.02 Hz

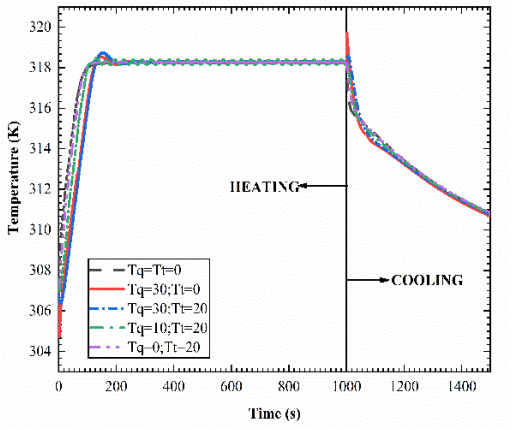

Figure 5. Temperature variation with time at the basal layer at the frequency of 20 Hz

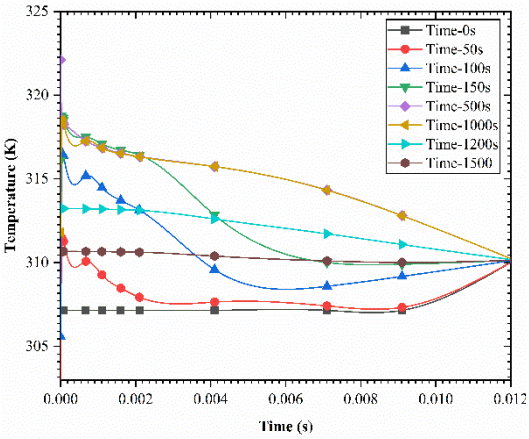

Figure 6. Spatial temperature variation at different times while τ_q=30 and τ_t=0 at the frequency of 20 Hz (TWMBHT)

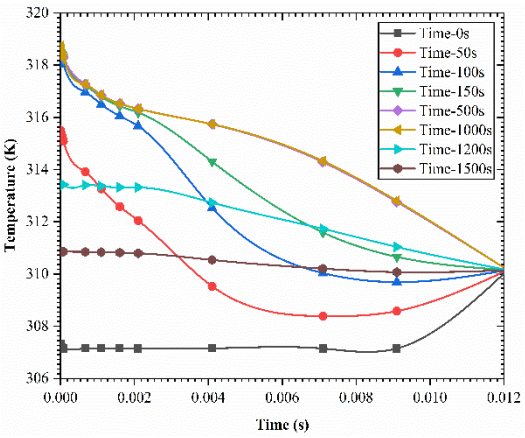

Figure 7. Spatial temperature variation at different times while τq=10 and τ_t=20 at the frequency of 20 Hz (DPLMBHT)

at different positions of the skin layers. According to the local thermal non-equilibrium approach, phase lag due to temperature gradient directly depends on the skin thermal conductivity [21]. Thus, increasing the value of phase lag due to microstructural interaction results in fast heat conduction ahead of the wave front of the propagating heat flux throughout the living tissue. Although, it has been observed that the temperature variation from all the models has converged with Penne's model after some time. It also results in the negligible effect of metabolism heat generation in temperature variation inside the skin layers. The heat generation due to absorption significantly impacts the temperature distribution throughout the skin layer during a prolonged heat exposure period.

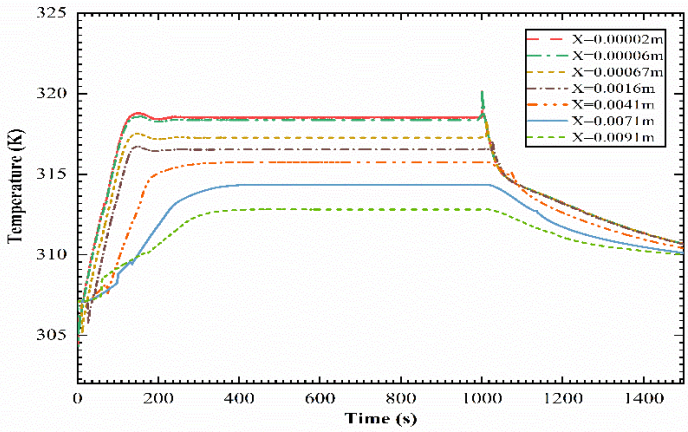

Figure 8. Temperature variation with time at different location of the skin using TWMBHT at 20 Hz

4. Conclusion

The present work is dedicated to analysing the skin layer's temperature variation during sinusoidal heating. It is found that both phase lag due to heat flux and temperature gradient results in less rate of temperature rise with time than Penne's bioheat transfer model. However, it has been found that the effect of phase lag due to thermal inertia is more than microstructural interaction in temperature distribution due to the wavy nature of the heat propagation when $\tau_t < \tau_q$. Also, the degree of the slowness of the heat propagation throughout the skin layer increase with increasing the value of phase lag time due to thermal inertia. But on the other hand, the rate of heat propagation increases with the value of phase lag time due to temperature gradient; as in this case, diffusive nature dominates over the wave front of the heat, and heat diffuses quickly. This particular effect can be more experienced while the analysis will be carried out by considering $\tau_t > \tau_q$. It is also found that heat generation due to metabolism does not create a noticeable variation in temperature distribution in resting or medical conditions. It can be concluded that sinusoidal heating directly on the skin surface is suitable for local or full-body external hyperthermia treatment as there is no sudden temperature rise. The cyclic order heating also helps to maintain minimal thermal damage for the long duration of the heating application.

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