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Numerical study on the effects of blood perfusion and body metabolism on the temperature profile of human forearm in hyperthermia conditions

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ABSTRACT

The development of mathematical models for describing the thermal behavior of living tissues under normal or hyperthermia conditions is of increasing importance. In this research, a 3D forearm model based on anthropometric measurement of 25 samples in Tehran, Iran was developed. The tissue temperature distribution is obtained via the Finite Volume Method (FVM) by considering the appropriate boundary conditions, blood perfusion, body metabolism, and the application of hyperthermia conditions on the tissue. The Pennes Bioheat Transfer Equation (PBHTE) is considered in this regard. Also, various thermophysical properties are assumed for the model in order to clarify the effects of such parameters on the tissue temperature distribution. The results of this study indicate that it is possible to provide the desired conditions for many therapeutic processes by controlling the parameters such as blood perfusion, body metabolism and the type of external heat source applied on the tissue. Generally, by decreasing the body metabolism, increasing the blood perfusion rate in tissue and applying a fluctuating heat flux, instead of uniform heat flux on the surface of the forearm skin, it is possible to provide the hyperthermia conditions without causing damages such as burn injuries to the other parts of the tissue. By using the results of this study, the appropriate conditions of hyperthermia can be obtained.

1. Introduction

Learning the details of the human body organ structure is an essential factor in understanding the physiological activities and pathological changes of human body. A living tissue consists of cellular tissues and blood vessels, which together form a heterogeneous environment. In the human body, there are four basic types of tissues: muscle, epithelial, connective and nervous. Each is made of specialized cells that are grouped together according to their structure and function (Holmes, 2013).

Heat transfer in biological systems of living organisms plays a very important role in many physiological processes. The main difference between heat transfer in living tissues and other biological materials is the effect of blood perfusion on the temperature profile of the human body.

Hyperthermia is a condition where an individual's body temperature is elevated beyond normal and about 42 °C. High body temperatures typically results in illnesses such as fever or heat shocks, but a restricted rise in tissue temperature can treat many diseases (e.g. cancer). Most normal tissues are not damaged during hyperthermia if the temperature remains under 44 °C. However, due to regional differences in tissue characteristics, conditions such as burns, blisters, discomfort, or pain may occur in various spots due to tissue temperature elevation (van der Zee, 2002; Wust et al., 2002). The idea of using heat transfer for cancer treatment has been considered for a long time, and recent efforts have led to the implementation of this idea (Glazer and Curley, 2010; I.P. Soares et al., 2011; van der Zee, 2002).

Many researchers have studied various issues in the field of heat transfer in living tissues (Pennes, 1948). examined the tissue and blood temperature in the human arm in 1948 and presented a mathematical model for heat transfer in living tissues. His model is being used in many studies because of different advantages which will be described in subsequent parts (Wissler, 1964). developed a model to examine the physical parameters of the human body's thermal system in an unsteady state. He solved this equation by writing the first law of thermodynamics with different assumptions and also considering the effective parameters and boundary conditions, using the finite difference method (Shitzer, 1973). reviewed and classified the different models of bio-heat transfer. He explained the necessity of developing mathematical models in order to describe the phenomenon of heat transfer inside the human body and also the external thermal regulation device which controls the ambient temperature adjacent to the skin. He also presented some conclusions about the effect of some parameters, such as body metabolism and blood perfusion, on the temperature profile of human body

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(Weinbaum and Jiji, 2009). investigated the effect of blood flow on blood-tissue heat transfer and provided a simplified 3D bio-heat transfer model and named it WJ (abbreviation for Weinbaum and Jiji). They showed that the vascularization of tissue causes it to behave as an anisotropic heat transfer medium. It was also shown that blood perfusion between the countercurrent vessels can have a significant influence on heat transfer in regions where the vessels are under 70 μm in diameter (Charny et al., 1990). considered the WJ model with different assumptions and boundary conditions to extract the tissue temperature distribution under normal and hyperthermia conditions. They compared the predictions of the simplified (WJ) bioheat transfer equation in one dimension to those of the complete one-dimensional three-equation bioheat transfer model of Pennes (Zhong-Shan Deng and Jing Liu, 2004). solved the 3D Pennes bio-heat transfer equation (PBHTE), assuming an unsteady state and nonlinear boundary conditions. They used elliptical cylinders to adequately approximate a body geometry that accounts for heat transfer between large arteries and veins. They claimed that the results of their transient simulations are in excellent agreement with experimental data (Ferreira and Yanagihara, 2009). solved the general equation of heat transfer by dividing the body into 15 hypothetical cylindrical parts and considering the blood perfusion in the arteries and veins, and presented their mathematical model for the 3D transient heat transfer. They derived an analytical solution given by Bessel series to the transient one-dimensional bioheat transfer equation of Pennes in a multi-layer region. They studied two different heat source terms to simulate the therapeutic heating of a tumor during a cancer treatment technique called Magnetic Fluid Hyperthermia. Additionally, they investigated the potential of their model to study the effect of different environmental conditions in a multi-layered human head model including brain, bone and scalp. They further compared their analytical results with a numerical solution obtained by the Finite Element Method.

(Karaa et al., 2005) developed numerical methods for the modeling of a three dimensional heat transfer problem in biological bodies. Their technique was intended for the temperature predications and parameter measurements in thermal medical practices and for the studies of thermomechanical interaction of biological bodies at high temperature. They developed a mathematical model based on the PBHTE for heat transfer in biological bodies using the finite difference discretization scheme to solve the governing partial differential equation. They obtained numerical results to demonstrate the efficacy of their proposed numerical methods. They claimed that, numerical approaches presented in their study can be used to predict the increase of the tissue temperature during bioheat transfer processes, allowing the introduction of complicated source behaviors, boundary conditions, or nonlinearities into the analysis (Askarizadeh and Ahmadikia, 2015). conducted an exact analytical analysis of the 2D Fourier and non-Fourier bioheat transfer equations of Pennes, Dual Phase Lag (DPL) model and Thermal Wave (TW) model in a skin tissue exposed to instantaneous heating conditions by considering the effects of blood perfusion and metabolic heat generation on tissue thermal behavior. They concluded that by letting the relaxation constants $\tau_q = \tau_T$ or $\tau_q = \tau_T = 0$ within the DPL model and $\tau_q = 0$ in the TW model, the skin tissue temperatures can be obtained as equivalent to the prediction of the Pennes model (Shi et al., 2014). presented a new mathematical model for of cancerous tumors diagnosis, particularly breast cancer, and validated their model with real clinical cases. They started their solution by considering the Pennes bioheat transfer equation and developed their model so as to find out the relation between this disease and heat distribution in human body (Wang et al., 2015). investigated the effect of radio frequencies on the heat transfer system of human body by assuming a porous medium. They derived an analytical solution for the blood and tissue temperature distributions as well as an overall heat exchange correlation in cylindrical coordinates. The effects of various physiological parameters, such as metabolic heat generation, different biological media and the rate of heat transfer is investigated in their study, too. The results of this study enable the clinicians to predict the temperature distribution in a biological medium with a real time feedback mechanism (Łapka et al., 2016). compared two different heat transfer models in terms of skin burn injuries by considering different parameters: 1) the classical Pennes model, and 2) a more realistic two-equation model which takes into account the blood vessel structure in the skin. Also the heat transfer in the tissue and arterial blood is coupled with heat and mass transfer model, while an external layer of garment is considered, too. Both of these models are employed to predict the skin temperature distributions and possibility of skin burn injury infliction by applying different radiative heat fluxes on the surface of the geometrical model. Their results showed that heat transfer in the skin influenced by high heat flux is independent of the blood vessel structure (Talaee and Kabiri, 2017). considered the PBHTE under a strong and moving heat flux applied to the skin surface. They obtained the exact solution for kidney, liver and skin tissues by using analytical methods. They parametrically studied the behavior of tissue temperature distribution caused by the different moving speeds of the external heat source (Kumar et al., 2017). solved a nonlinear Dual Phase Lag (DPL) bioheat transfer equation under periodic heat flux boundary condition for skin geometry. They assumed blood perfusion to be temperature-dependent which results in a nonlinear DPL bioheat transfer model in order to predict a more accurate temperature distribution. They showed that the nonlinear DPL model with exponential variation of blood perfusion rate is closest to the experimental data. Also, the author describes the absence of phase-lag phenomena in Pennes bioheat transfer model as a disadvantage of PBHTE. In fact, the PBHTE achieves steady state more quickly and always predicts higher temperatures than TW and DPL nonlinear models.

Scientists have always emphasized that the temperature of cancerous tissues is higher than healthy tissues. The DPL bioheat transfer equation is more investigated by (Ziaei Poor et al., 2014) for different conditions of heating applied to the skin surface. They developed an analytical solution for dual phase lag bioheat transfer equation with constant, periodic, and pulse train heat flux conditions on skin surface. They showed that there is major discrepancy between the predicted temperature of Pennes, TW, and DPL bioheat transfer models when a short-time strong thermal flux is applied to the skin surface. In fact, by increasing the heating duration, the deviation between the results of mentioned approaches will decrease. Also (Liu et al., 2012) have studied the DPL model and present the same conclusions as well as the mentioned articles. They developed a bioheat transfer equation based on the DPL model for considering the effect of micro-structural interaction. By paying careful attention to the results of their study, the disparity between the temperature responses of the Pennes, DPL, and TW bioheat models will vanish by increasing the therapeutic heating duration.

High metabolic heat generations and the growth of the arterial regions of the cancerous area cause higher temperature around the cancerous cells compared to normal cells (Hatamieh et al., 2016). In fact, the metabolism of cancerous cells is higher than normal cells. On the other hand, cancerous tumors, due to their nature, require more nutrients which increases the blood perfusion in these areas. Also, normal vessels are wider in these areas due to the higher blood perfusion rates (Bronzino, 2018); therefore, thermography is used to detect various types of cancer.

Since tissue structure is heterogeneous and is affected by various parameters, the heat transfer phenomenon and the prediction of temperature distribution in living tissues are very complicated if all effective parameters are considered. The widespread use of the PBHT model is due to the simplicity of the analytical and numerical solutions.

Considering the importance of temperature distribution in living tissues, it can be said that obtaining a suitable simulation method the results of which are guaranteed to be valid can greatly help to improve various therapeutic methods, including hyperthermia techniques. Therefore, in this article, an attempt has been made to solve the 3D

PBHTE while considering blood perfusion and body metabolism in tissues by numerical methods. The simulation method of this study can be used to improve the actual prediction methods of hyperthermia.

2. Mathematical model

The reasons why the PBHT model is used to investigate the hyperthermia are its mathematical simplicity and ability of temperature distribution prediction in different geometries. The Pennes equation is based on many assumptions in order to simplify the bioheat transfer analysis. Prominent among these simplifications are not accounting for the effect of blood flow direction and the influence of the tissue thermophysical coefficients on temperature. Also PBHTE does not consider the phase lag phenomenon. These assumptions will also preserve the essential features of the subject while simplifying heat transfer analysis. The second order Pennes equation, considering blood perfusion and body metabolism, is written as follow:

$$\frac{\partial(\rho C_p T)}{\partial t} = \nabla\cdot(k\nabla T) + S_T; \quad T = T(x.\ y.\ z.\ t) \tag{1}$$

where k, ρ, and C_p are different for each layer.

Also, S_T is different for various layers of the tissue and is defined as:

$$\begin{matrix}\text{Layer 1: Epidermis}\\ \text{Layer 2: Dermis}\\ \text{Layer 3: Subcutaneous Layer}\\ \text{Layer 4: Inner Tissue}\\ \text{Layer 5: Bone}\end{matrix} \quad S_T = \begin{cases} 0 \\ \omega_{b2}\rho_b C_b(T_{b2} - T) + q_{2m} \\ \omega_{b3}\rho_b C_b(T_{b3} - T) + q_{3m} \\ \omega_{b3}\rho_b C_b(T_{b4} - T) + q_{4m} \\ 0 \end{cases} \tag{2}$$

where ρ is the tissue density, Cp is the specific heat capacity of the tissue, T is the tissue temperature, t is time and k is the thermal conductivity of the tissue. S_T is the heat source term in which $\omega_b\rho_b C_b(T_b - T)$ is related to blood perfusion and q_m is the volumetric density of metabolic heat. Also, ω_b is the volume of blood perfusion per unit volume of tissue, ρ_b is the density of blood, C_b is specific heat capacity of blood, and T_b is blood temperature. Pennes assumed that all of the heat transfer between the tissue and the blood is carried out in the capillaries; which means that blood perfusion and heat transfer are assumed to be uniform (Shih et al., 2007). As said before, blood perfusion direction is not taken into account in this model. Therefore, blood perfusion rate in the tissue is kept steady and constant. It should be noted that, the assumption of a constant blood perfusion rate will affect the results; but, as the range of temperature variation in the present study is not very high and also many of researchers assume that blood perfusion is constant and does not vary with temperature, this parameter is considered to be constant in the current study. Also, referring to (Barcroft and Edholm, 1943), blood perfusion rate is supposed to vary with the fluctuations in tissue temperature; but, considering the temperature variation range and other conditions in the current study, this parameter can be assumed constant on average and the deviation in results can be neglected.

The finite volume method is a numerical technique for solving Partial Differential Equations (PDE) that computes the values of the conserved variables averaged through the volume. Not unlike the finite difference or finite element methods, values are intended at discrete places on a meshed geometry. The small volumes surrounding each node point on a mesh are called “Finite volume”. The FVM does not require a structured mesh nothing like the other finite difference methods. Furthermore, the FVM is desirable to other methods because of the fact that, since the conserved variables are not located at nodes or surfaces and are located inside the volume element; therefore, the BCs can be applied noninvasively. These terms are assumed as fluxes at the surfaces of each small volume. As the flux enters a given volume and leaves the adjacent volume, mentioned techniques are conservative. Another advantage of the FVM is that it is easily formulated to allow for unstructured meshes (LeVeque, 2002).

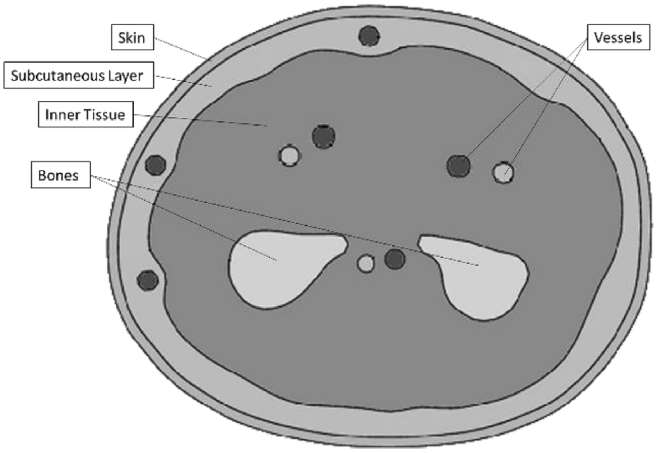

Fig. 1. Human forearm cross section (Gosling et al., 2008; Logan, 2018; Netter, 2018).

Over the years, researchers have come to the conclusion that changes in blood perfusion rate in tissues have a great influence on heat transfer from the surrounding environment to the skin (Charny, 1992).

3. Numerical analysis

3.1. Developing the geometrical model

In the present study, considering the scope of the subject and the complexity of studying the entirety of body, all analyses are conducted on the human forearm as a model area. The forearm consists of about twenty different muscles and has two distinct muscle parts: the flexor group on the palm side and the extensor on the back side of the arm. This body part consists of two bones named Ulna and Radius and a lower elbow, which are arranged together and interconnected in three regions. The Ulna is a long bone found in the forearm that stretches from the elbow to the smallest finger. The Ulna is the larger and longer of the two. (Gosling et al., 2008; Logan, 2018; Netter, 2018). The forearm details are visible in Fig. 1.

The human forearm model consists of three main parts: 1) the Ulna and Radius bones in the forearm are considered as a **single bone**, 2) muscles, fats, and veins are considered as **inner tissues**, and 3) the three layers of skin which are called epidermis, dermis and subcutaneous layer are considered as **skin** sections. These parts each contain a lot of details that can be ignored to simplify the solution.

3.2. Anthropometric measurements of the forearm

Since the environmental conditions and geographical zone directly affect the physiology of individuals, in this study the appropriate dimensions for the designed model are chosen by examining the dimensions of different human forearms in Tehran, Iran (Fishman and Berger, 1955; Laila et al., 1970). For this purpose, 25 different samples of men are selected and the dimensions of their forearms are measured in various sections. The dimensions of the final designed model are shown in Table 1 and Fig. 2. Also, the dimensions of the different layers of tissue are selected based on the information available in similar works (Ahmadikia et al., 2012; Dutta and Kundu, 2018; Jiang et al., 2002; Karmani, 2006; Ostrowski et al., 2015; Poppendiek et al., 1967), and are presented in Table 2.

3.3. Thermophysical properties of the forearm

The heat transfer in 3D model of the human forearm is analyzed by considering appropriate thermophysical properties (Table 3) and

Table 1
The geometrical dimensions of the forearm measured in this study.

L_{avg}	Cross sectional diameters (cm), Fig. 2				Gender
	$d_{1\ avg}$ at $x_1 = 0$	$d_{2\ avg}$ at $x_2 = 18$ cm	$d_{3\ avg}$ at $x_3 = 27$ cm	$d_{4\ avg}$ at $x_4 = 28.9$ cm	
28.9	9.4	8.8	6.9	6	Male

boundary conditions. The tissue geometry and the applied boundary conditions are shown in Fig. 3. The boundary conditions of the elbow and the wrist are considered to be symmetric and zero heat flux, which implies the absence of a thermal source in these locations. As shown in Fig. 3, a part of the model is considered as a therapeutic heating zone, where the heat sources are applied through in the following forms: constant temperature, uniform heat flux, and sinusoidal heat flux. The other parts of the forearm surface are considered to be exposed to ambient temperature. Blood temperature is 37.1 °C and the ambient temperature is assumed to be 28 °C (Jiang et al., 2002).

For the meshing of the selected model, tetrahedral elements are used. In order to study the effect of meshing on the results, different values for the maximum side size of the element (from 0.25 to 8 mm) were selected and the temperature of one arbitrary point of the tissue was obtained. This arbitrary point is exactly located at the upper surface of the dermis layer of the skin at the middle point of the forearm on the X-axis, which is observable in Figs. 2 and 3.

As predicted, the element size will directly affect the results. By decreasing the side size of elements from 8 to 0.25 mm, the temperature of the middle point of tissue will decrease until the size reaches 2 mm, at which point the temperature variation starts to vanish, as shown in Fig. 4. Therefore, the optimal size of 2 mm is chosen as the maximum side size of the element. For the meshing of the areas where the dimensions of the model are reduced, considering suitable number of elements on the edges of the model, the size of the elements is smaller; therefore, the heat distribution in the tissue is more accurately resolved.

In order to evaluate the accuracy of the results in this research (Dutta and Kundu, 2018), is considered as the reference. This study determines a 2D analytical solution for a single layer living tissue under a therapeutic condition by means of Fourier and non-Fourier heat transfer approaches. Both the PBHE and TW models are utilized for this analysis. As shown in Fig. 5, the conductive-convective boundary condition at the top surface of the skin tissue is assumed and zero temperature gradient is placed in both sides of the skin tissue due to the symmetric boundary effect for heat transfer. A high therapeutic temperature on the top of the skin surface is considered as the external heat

Table 2
Dimensions of different layers of the forearm model (Ahmadikia et al., 2012; Dutta and Kundu, 2018; Jiang et al., 2002; Karmani, 2006; Ostrowski et al., 2015; Poppendiek et al., 1967).

Based on sections in Fig. 2 (cm)				Layer
X1	X2	X3	X4	
0.3	0.3	0.35	0.37	t_1:Skin
0.4	0.4	0.45	0.48	t_2: Subcutaneous Layer
3	2.5	1.25	0.7	t_3: Inner Tissue
1	1.2	1.4	1.45	t_4: Bone

Table 3
Thermophysical properties of blood, tissue, and bone used in the present model (Ahmadikia et al., 2012; Dutta and Kundu, 2018; Jiang et al., 2002; Karmani, 2006; Ostrowski et al., 2015; Poppendiek et al., 1967).

ρ (kg/m^3)[a]	C_P (J/kg.°C)[a]	K (W/m.°C)[a]	Section
1200	3590	0.24	Epidermis
1200	3300	0.45	Dermis
1000	2500	0.19	Subcutaneous layer of skin
1000	4000	0.5	Inner tissue
1150	1254	0.56	Bone
1050	4200	0.53	Blood

[a] As said before, k, C_p and ρ are considered as thermal conductivity, specific heat capacity, and density of the material.

source. Tissue dimension of the verification model of this study is 10 × 10 mm, as the same as (Dutta and Kundu, 2018). The accuracy of the present numerical solution has been assessed by comparing the PBHTE solution with the results presented in (Dutta and Kundu, 2018). A point located at (0.005,0.005) in Cartesian coordinates is selected and the temperature distribution is extracted for the indicated point. Also, the other dependent parameters considered for this validation are shown in Fig. 6.

The graphical result of Fig. 6 confirms the suitability of the present numerical approach as well as the accuracy of the current analysis. The trend of temperature curve almost matches with the results of (Dutta and Kundu, 2018) with a maximum deviation of 1.2%. This deviation is almost certainly a result of the application of the present numerical method.

4. Numerical analysis results

In this section, the effect of different parameters on the tissue

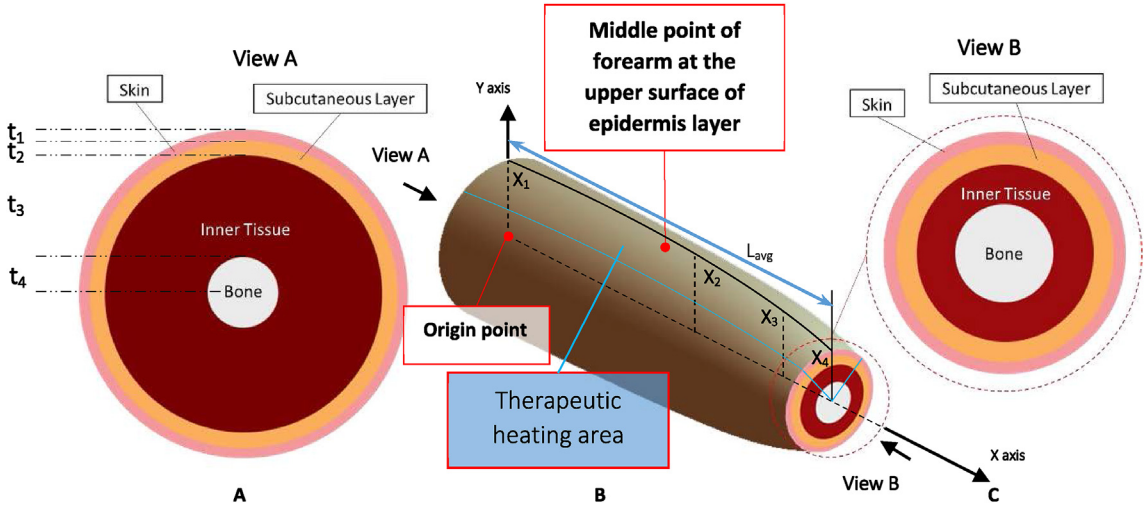

Fig. 2. Simulated model. A) Cross section of the forearm in the elbow joint section. B) Isometric view of the model. C) Cross section of the forearm in the wrist bond.

$$1: T_{Skin\ Surface}(t) = Constant = 44℃$$
$$2: q''(t) = Constant = 100; 200; 300; 400; 500\ Wm^{-2}$$
$$3: q''(t) = q''_0 \cdot \sin(\omega t)\ ;\ q''_0 = 200; 300; 400; 500\ Wm^{-2}$$

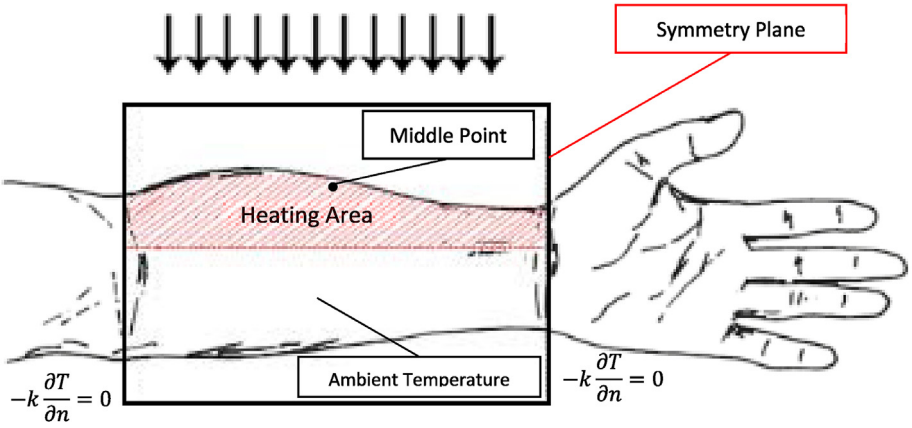

Fig. 3. Schematic of the forearm geometry and the boundary conditions in the present study.

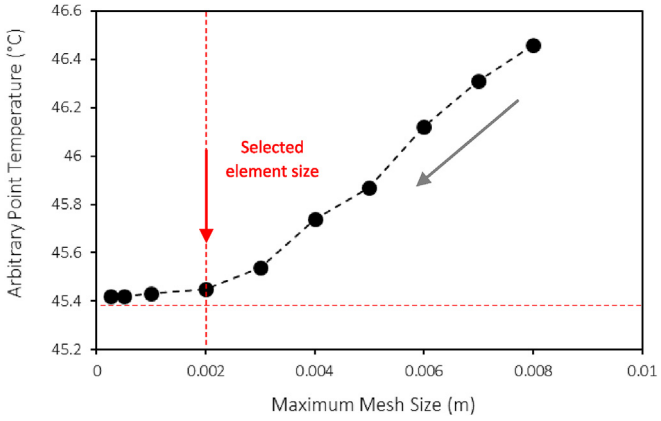

Fig. 4. Choosing the appropriate side size of elements.

temperature distribution is studied. In heat transfer of living tissues and from the tissue physiology point of view, there are a number of general facts; for example, blood perfusion exists in the inner tissue, dermis, and the subcutaneous layer of the skin. Also in all parts except the bone, the metabolic heat generation should be considered. The heat source applied to the therapeutic area on the skin is assumed to be a constant temperature of 44 °C, in the first stage. Then, a uniform and constant heat flux is applied to the heating area for 30 min. Finally, a sinusoidal heat flux which varies with time is considered for 30 min on the heating area. Different values considered for the body metabolism and blood perfusion rates are presented in Table 4.

The general coordinate system of this study is assumed to be cylindrical, but as all the investigations are conducted in different cross sectional areas of the model, the results are presented in the Cartesian coordinate system. In this regard, X-axis is supposed to pass through the primary axis of the cylinder and Y-axis is assumed to be perpendicular to the center point of the therapeutic heating area. The centroid of the cross section of the forearm model at the elbow area is considered as the origin point of the Cartesian coordinate system, as shown in Fig. 2. The parameter τ is assumed to be the total duration of therapeutic heating. There is some parallel horizontal dotted lines in each figure which define the different layers of tissue in the forearm. A better view of these lines can be seen in Fig. 7.

4.1. External heat application: constant surface temperature (T = 44 °C)

The presented model is examined, considering the metabolic heat transfer and blood perfusion in the tissue under the influence of an external constant temperature heat source. Different values for ω_b and q_m are assumed which are shown in Table 4. It should be noted that all the results are extracted for the point at X = 0, which shows the elbow section. As a reminder, by considering X = 0, the origin point of the coordinate system which is the intersection of Y-axis and Z-axis, will be the centroid of elbow section.

As can be seen in Fig. 7, the temperature of tissue varies with different slopes in different layers of the model, including skin, inner tissue and bone. This difference is a consequence of the different thermophysical properties which are assumed for the mentioned zones. By changing the value of q_m, an attempt has been made to examine the effect of this parameter on tissue temperature along the tissue depth. The point (0,0,0) is considered for this purpose, as the boundary condition at the elbow side is assumed to be symmetric and also the heat source is applied to the therapeutic zone symmetrically. The value of ω_b is assumed to be 0.0002 S^{-1}. According to Fig. 7, tissue temperature is directly related to body metabolism, where any growth in q_m will result in an increase in tissue temperature. Actually, a rise of 50% in q_m, will increase tissue temperature in all layers about 0.5%, excluding the skin layer. As the therapeutic temperature is considered to be constant at the surface of the skin, all the curves reach a fixed point (T = 44 °C) on the skin surface. Since the skin layer is exposed to the therapeutic heating instantly, the temperature of this part is supposed to be higher than the other layers. From Fig. 7, it can be concluded that, the effect of q_m on the temperature of tissue will decrease in higher temperatures. Taking a look at the temperature distribution of lower layers of the tissue further clarifies this point. Also it can be determined from Fig. 7, by assuming q_m = 0, 368.1, 500, and 1200 Wm^{-3}, the temperature of tissue in the zero-point of Y-axis is 41.62, 41.8, 41.87, and 42.2 °C, respectively. It seems that the relation between temperature variance and the volumetric density of metabolic heat can be assumed to be linear for the stated circumstances of analysis. Consequently, while applying hyperthermia in real-world cases, the effects of therapeutic heating on the deep tissue layers can be controlled.

Fig. 8 presents the effect of blood perfusion on the temperature distribution of forearm. As an assumption, q_m is considered to be fixed and equal to 368.1 Wm^{-3}. As presented in Fig. 8, tissue temperature is decreased with an increase in ω_b. In fact, while blood is perfused in the tissue, the existing heat is absorbed by the blood stream and

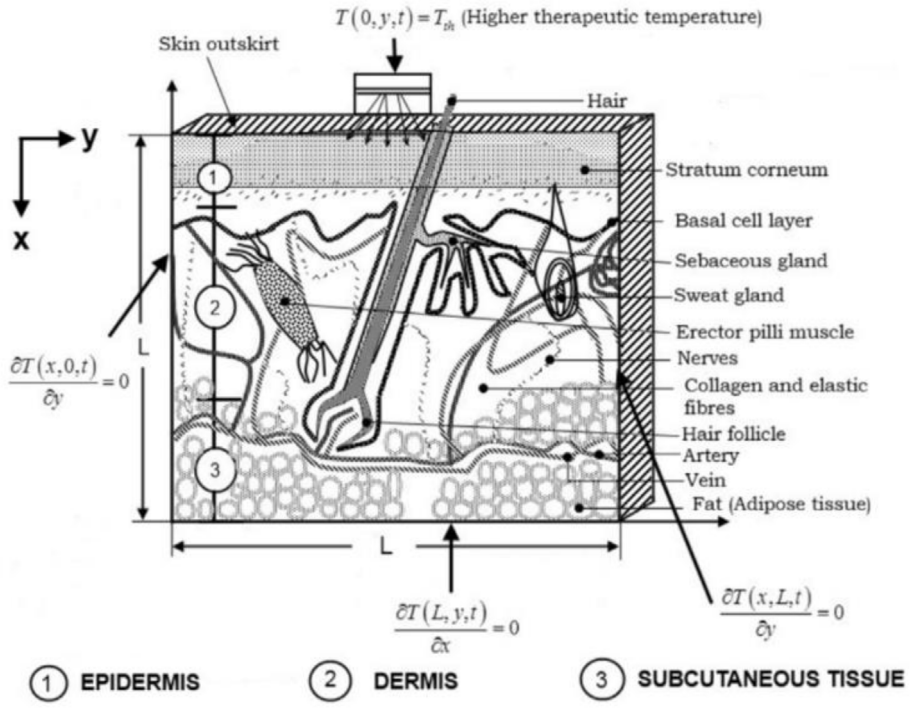

Fig. 5. Boundary condition of article (Dutta and Kundu, 2018), used to verify the accuracy of the results of the present study.

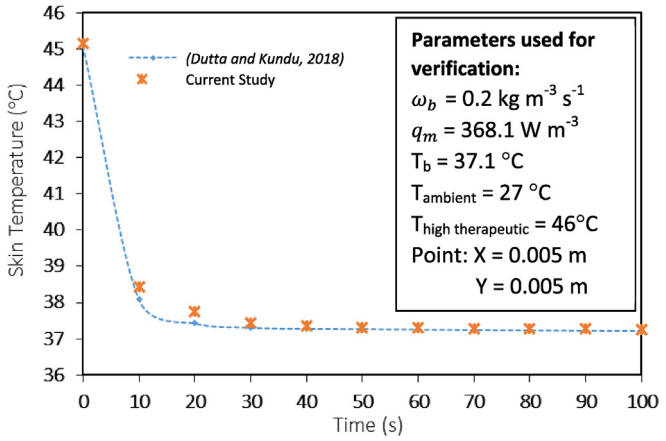

Fig. 6. Verification of present study by comparing the temperature change profile along the depth of the tissue with the results of reference (Dutta and Kundu, 2018).

Table 4
Various values of ω_b and q_m.

Value	Parameter
0.0002 0.0004 0.0008 0.002 0.001	$\omega_b(s^{-1})$ Blood perfusion rate
0 368.1 500 800 1200	$q_m(Wm^{-3})$ Volumetric density of metabolic heat

transported to the other parts of the tissue; thereby a balance in the tissue temperature will be created. Moreover, the amount of blood perfusion rate has a significant effect on the heat transfer to the underlying layers of the tissue. The bloodstream prevents the transfer of heat to the deep parts of the forearm tissue, which can be described as a preventive parameter in hyperthermia implementation. For example, if the blood perfusion rate is assumed to be 0.002 S^{-1}, the applied heat flux does not reach the deeper parts of the tissue and will rapidly get transferred by the bloodstream. Consequently, in this case, not only does applying heat on the tissue not lead to hyperthermia's primary purpose, but it will also cause some burn injuries to the upper layers of the tissue. Therefore, by changing the quantity of blood perfusion rate in the tissue, the amount of heat transfer to the deeper parts of the tissue can be controlled. For the point X = 0 on the elbow cross section, which is situated at the center of the computational area, the temperature of the tissue can be calculated as 37.2, 38.6, 40.2, and 41.8 for blood perfusion rates of 0.002, 0.0008, 0.0004, and 0.0002 s^{-1}, respectively. These values will reveal the inability to consider a linear relationship between the tissue temperature and the blood perfusion rate. Possibly, the indicated relation can be defined by polynomial or exponential functions. Certainly, this relationship can help in estimating the temperature distribution in order to achieve the desired conditions of hyperthermia.

4.2. External heat application: constant and uniform heat flux (q" = CTE)

A constant heat flux is applied to the therapeutic heating area with the intention of obtaining the temperature distribution of the tissue. Different values are considered for heat flux and the effect of this parameter on the tissue temperature distribution is predicted.

As shown in Fig. 9, tissue temperature is directly related to the amount of applied heat flux. Also, notwithstanding blood perfusion and metabolism, by increasing the heat flux, the temperature of the tissue will rise; but the amount of this growth in higher levels of the tissue is more than the increase of temperature in the lower levels. At the lower half of the forearm, this effect reaches zero, approximately. By applying a heat flux on the skin surface, bone temperature will be affected as well. The slope of these variations is dissimilar in different layers of the model, including skin, inner tissue or bone, which are attributable to the different thermophysical properties of each layer. In fact, the

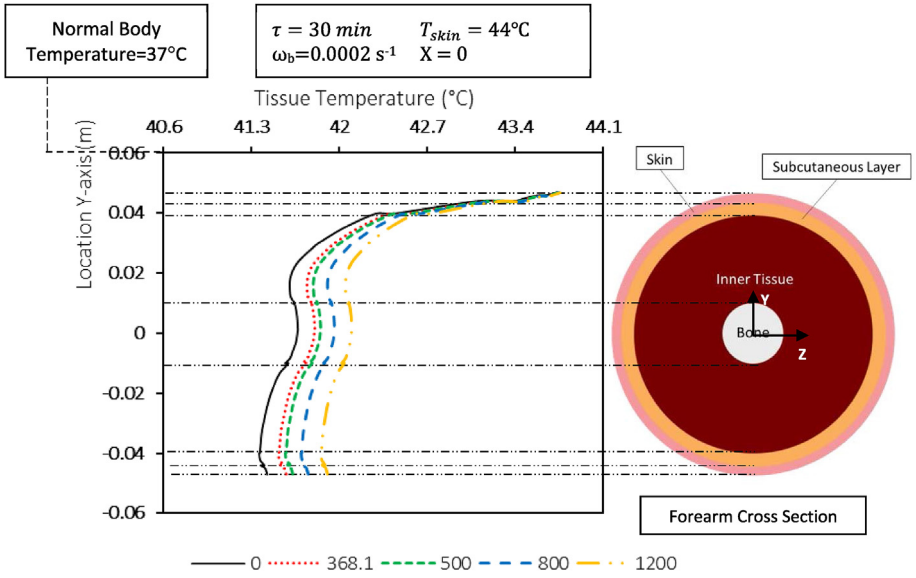

Fig. 7. The temperature variation along the forearm depth affected by different values of q_m under the influence of constant temperature heat source.

external heat source has a significant influence on the temperature of the upper half of the forearm, which is directly exposed to the therapeutic heat flux; but the temperature of the lower half of the forearm is almost constant for different values of heat flux. This means that, by increasing the amount of therapeutic heat flux, not only will the main aim of hyperthermia not be achieved, but also this rise in temperature will cause skin burn injuries. However, the rational action in case of the necessity of applying therapeutic flux on the lower half of the forearm, is to change the location of external heat source. On the other hand, while implementing the hyperthermia treatment by the stated method, it is guaranteed that the lower parts of the forearm, which are healthy, will not be affected thermally. By applying a uniform heat flux on the geometry, the tissue temperature, which is initially assumed to be 37 °C, will rise to a minimum of 42 °C. Although there is an upsurge of 5 °C in the minimum temperature of the tissue, still the condition for the tissue is safe and no injuries will be caused.

In Fig. 9, if the temperatures of skin surface for different values of heat flux is considered, a relationship between these temperatures can be seen. Actually, these temperatures depend on the value of therapeutic heat flux with an approximate linear relation. This relationship between the parameters mentioned above, can improve the approach of hyperthermia.

Referring to Fig. 10, for the constant heat flux boundary condition, the value of parameters ω_b and q" is assumed to be 0.0002 S^{-1} and 200 Wm^{-2}, respectively. The internal temperature of the tissue is directly related to the value of q_m. In fact, the relation between these two parameters is linear. Therefore, the amount of temperature variation in the depth of the tissue can be controlled by changing the amount of metabolism in order to attain the desired conditions of hyperthermia.

Similarly to Fig. 7, any growth in q_m will cause an increase in tissue temperature. As the skin layer is instantly exposed to the therapeutic heat flux, the temperature of the skin surface is higher than the other layers. According to Fig. 10, it can be determined that, the effect of q_m on the tissue temperature will decrease in higher temperatures. Taking

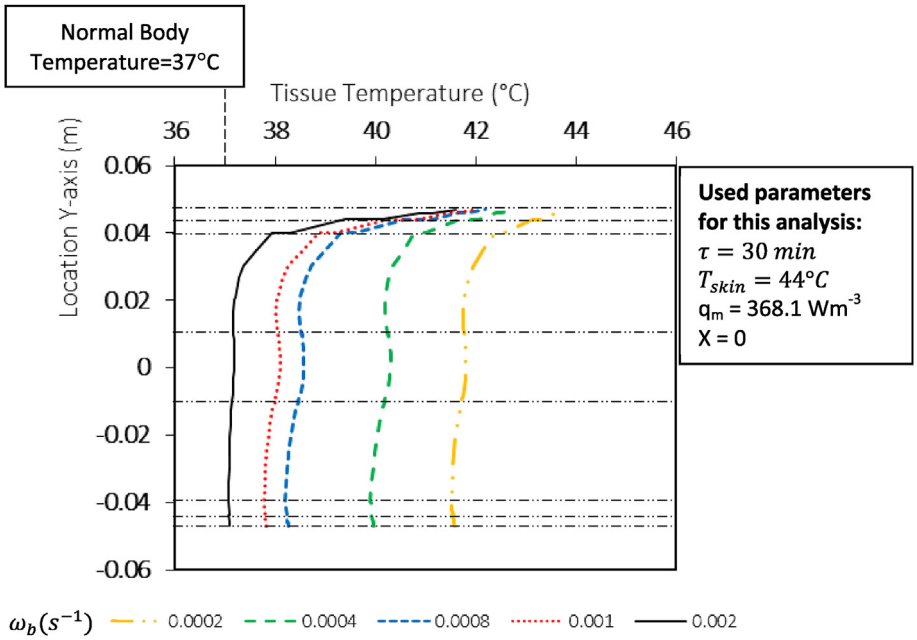

Fig. 8. Temperature variation along forearm's depth under the influence of different values of ω_b with a constant temperature heat source.

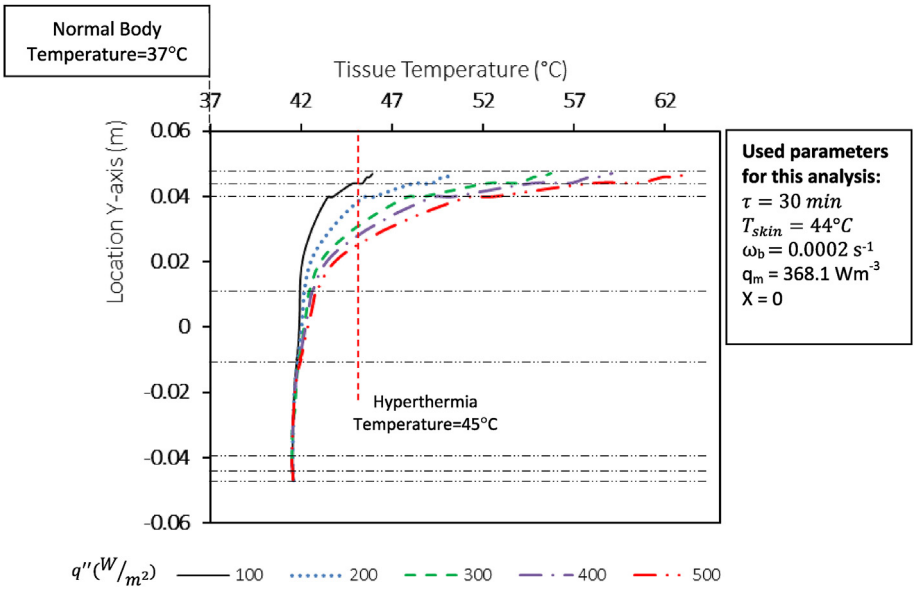

Fig. 9. Temperature variation along forearm depth affected by different values of heat flux under the influence of uniform heat flux.

a look at the temperature distribution of lower layers of the tissue helps clarify this. By changing the value of q_m from 0 to 1200 Wm^{-3}, the temperature of the tissue will increase about 0.5 °C. In fact, the maximum range of variation in tissue temperature is about 0.5 °C, which does not have a significant effect on the attainment of hyperthermia.

In Fig. 11, the effect of blood perfusion on the temperature distribution of living tissue is presented. Two parameters of external heat flux and body metabolism are assumed equal to 200 Wm^{-2} and 368.1 Wm^{-3}, respectively.

As shown in Fig. 11, by increasing the value of ω_b, the temperature of the tissue will decrease. Blood perfusion rate has a significant effect on the amount of heat transfer to the underlying layers of the tissue. Blood perfusion prevents the heat from reaching the deep parts of the forearm, which can be described as a preventive parameter in hyperthermia application. The blood absorbs the existing heat and transfers it to the other parts of the tissue by passing through various channels, which will cause a reduction in tissue temperature. The most important thing is the amount of heat transfer to the deeper parts of the tissue which can be controlled by changing the value of ω_b.

As depicted in Fig. 8, a nonlinear relationship exists between tissue temperature and the blood perfusion rate which can likely be defined by polynomial or exponential functions. This relationship helps to accurately estimate the temperature distribution of tissue in order to achieve the desired conditions of hyperthermia.

4.3. External heat application: sinusoidal heat flux, variable with time ($q'' = q''_o.sin(\omega.t)$)

In this section, a sinusoidal heat flux is applied to the skin surface. It should be noted that this heat flux is chosen according to the studies carried out in (Shih et al., 2007). With the intention of determining the exact effect of sinusoidal heat flux on the temperature distribution of

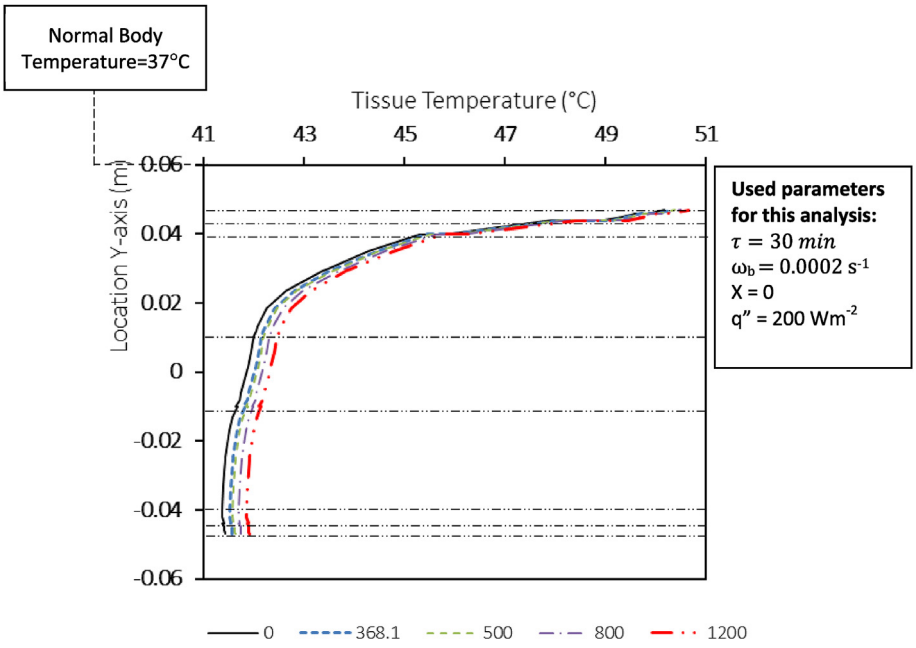

Fig. 10. Temperature variation along forearm depth affected by different amounts of q_m under the influence of uniform heat flux.

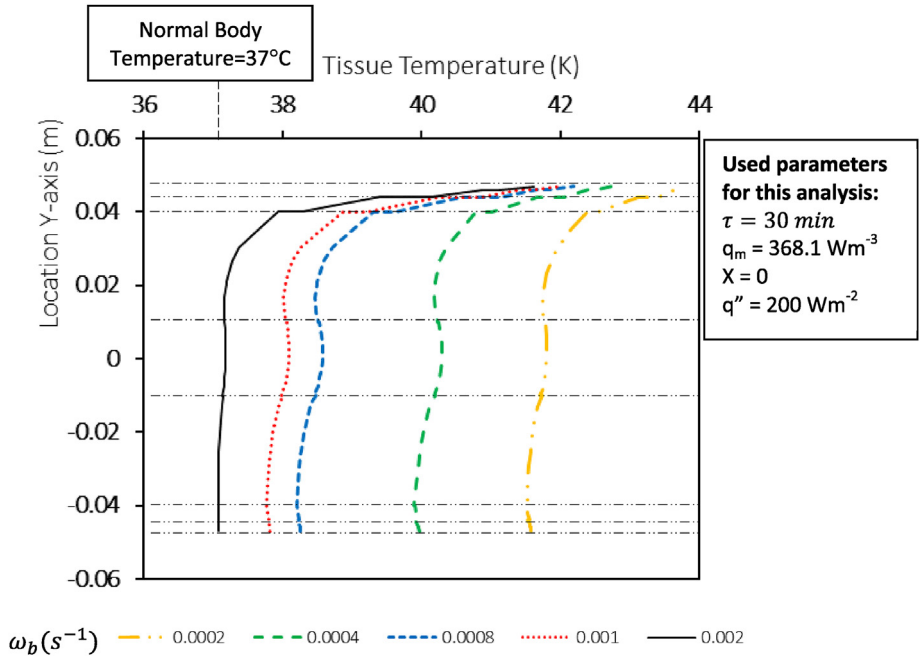

Fig. 11. Temperature variation along forearm depth affected by different values of ω_b under the influence of uniform heat flux.

living tissues, the heat flux is defined by the following equation (Shih et al., 2007):

$$q'' = q''_0 \sin(\omega t) \quad (3)$$

where q''_0 is the maximum value of heat flux and ω is the angular frequency of the function. In order to determine the effect of different thermal fluxes on the human forearm, different values of q_0 are considered, shown in Fig. 12. This sinusoidal heat flux is a half range of the entire sine function, which starts to rise from zero, reaches its peak in 15 min and then decreases and reaches 0 at the end of the period. For this analysis, the values of ω_b and q_m are assumed to be 0.0002 S^{-1} and 368.1 Wm^{-3}, respectively.

As shown in Fig. 12, the temperature of the tissue is directly related to the heat flux applied to the surface of the skin. By increasing the amount of thermal flux, the temperature at the upper levels of the tissue will increase. Due to the presence of blood flow in the tissue and metabolism of the body, in deeper parts, the effect of thermal flux on the tissue temperature is decreased and at the lowest level of the tissue, this effect reaches zero. For external sinusoidal heat flux, the temperature of different layers of the model, such as skin, inner tissue or bone, varies with different slopes, which can be attributed to the different thermophysical properties of these layers.

By applying a heat flux on the skin surface, bone temperature will be affected as well. The external heat flux has a major impact on the temperature of the upper half of the forearm, which is directly exposed to the therapeutic heat flux; but, the temperature of the lower layers of the forearm is almost constant for different values of heat flux. By applying a sinusoidal heat flux on the geometry, the tissue temperature, which is initially assumed to be 37 °C, will increase to a minimum of 41.5 °C. Although there is a rise of 4.5 °C in the minimum temperature

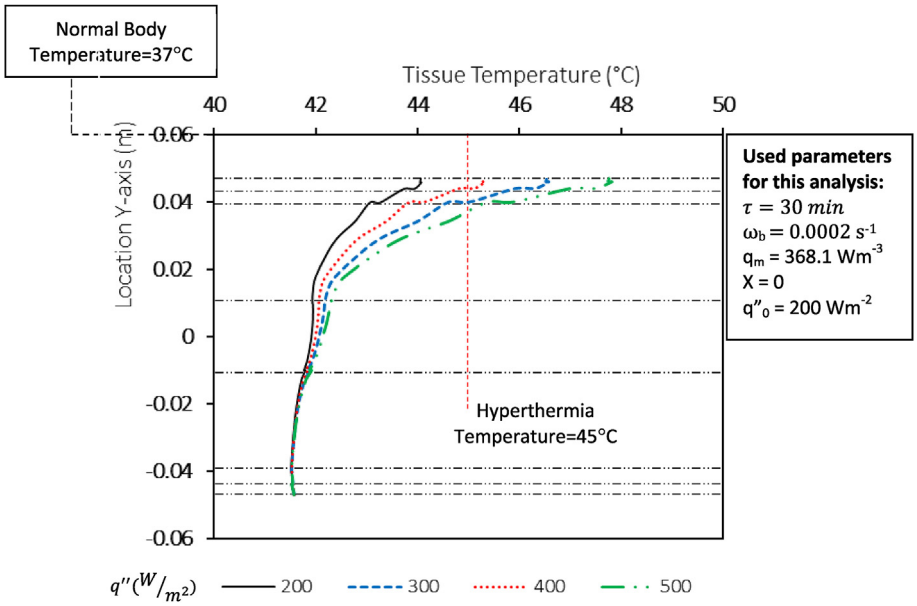

Fig. 12. Temperature variation along forearm depth affected by different values of sinusoidal heat flux under the influence of sinusoidal heat flux.

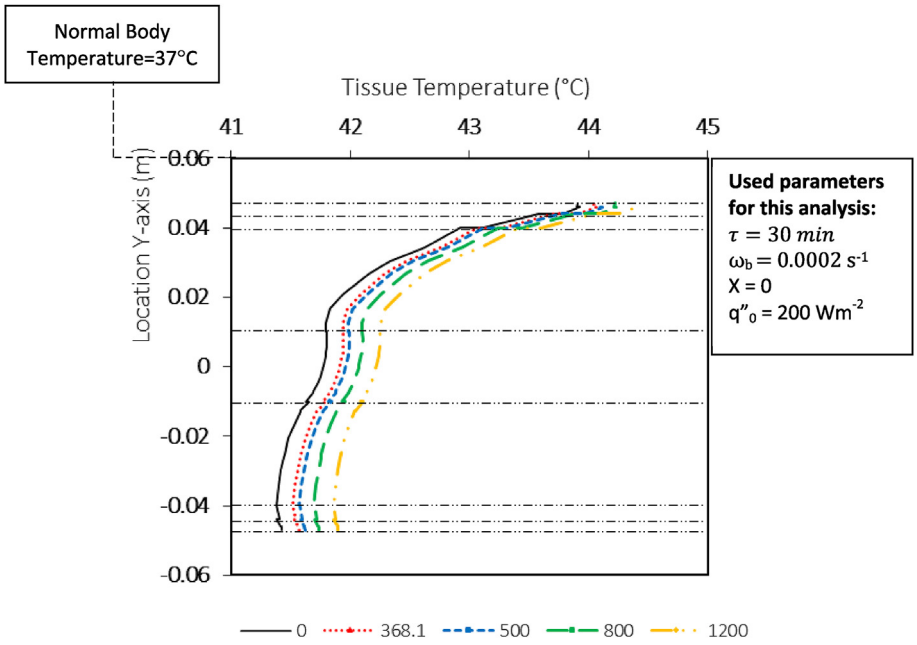

Fig. 13. Temperature variation along forearm depth at X = 0 affected by different values of q_m under the influence of sinusoidal heat flux.

of the tissue, the condition for the tissue is safe and no injuries will be inflicted.

Under the same conditions, it seems that the sinusoidal heat flux has a greater effect on the temperature variation of the underlying layers of the tissue, than constant temperature and the uniform heat flux. In fact, the average temperature of the middle parts of the forearm is higher than the one induced by constant temperature and uniform heat flux sources. Therefore, a greater effect on the temperature variation of the tissue depth than the constant temperature case can be obtained by the application of the sinusoidal thermal flux and control of other influential parameters.

According to Fig. 13, for the sinusoidal heat flux boundary condition, parameters ω_b and q" are assumed to be 0.0002 S^{-1} and 200 Wm^{-2}, respectively. The internal temperature of the tissue is directly related to the amount of q_m and there is a linear relationship between these two parameters. The amount of temperature variation in the depth of the tissue can be controlled by changing the amount of metabolism in order to reach the desired conditions of hyperthermia.

Similar to Figs. 7 and 10, any increase in q_m will cause an upsurge in tissue temperature. Since the skin layer is directly exposed to the therapeutic heat flux, the temperature of the skin surface is higher than the other layers. Consistent with Fig. 13, the effect of q_m on the temperature of the tissue will decrease in higher temperatures. This is clarified further by paying attention to the temperature distribution of the lower layers of the tissue. By changing the amount of q_m from 0 to 1200Wm^{-3}, tissue temperature will increase by about 0.5 °C. In fact, the maximum range of variation in tissue temperature is about 0.5 °C, which has a negligible effect on the attainment of hyperthermia. The effect of the sinusoidal heat flux on the temperature distribution of the upper layers of forearm is more considerable than that of the uniform heat flux. Actually, if certain layers are the target of hyperthermia, such as subcutaneous layer of skin, or the inner tissue, the temperature of these layers is more affected by the sinusoidal heat flux than the uniform heat flux. The uniform heat flux has a higher influence on the upper layers of the tissue, but the sinusoidal heat flux penetrates the tissue all the way to the middle layers and affects the temperature of these parts more than the uniform heat flux.

The difference between Figs. 7 and 13 lies in the fact that, due to the constant temperature of the skin surface in Fig. 7, all curves at the skin surface reach the same point; but in Fig. 13, due to the external sinusoidal flux, there is no limitation for the curves.

With careful attention to this difference between the two sources mentioned above and the value of temperature in different parts of the model, it seems that considering an external sinusoidal heat flux is more realistic in the implementation of therapeutic heating.

In this section, the effect of blood perfusion on the temperature distribution of living tissue under the influence of external sinusoidal heat flux is examined. Two parameters, maximum external heat flux and body metabolism, are considered as 200 Wm^{-2} and 368.1 Wm^{-3}, respectively.

As shown in Fig. 14, by increasing the value of ω_b, the temperature of the tissue will decrease. The quantity of blood perfusion rate has a major effect on heat transfer to the underlying layers of the tissue. Blood perfusion stops the heat from reaching the deep parts of the forearm, which can be described as a preventive parameter in hyperthermia implementation. The blood absorbs the existing heat and transfers it to the other parts of the tissue by passing through various channels, which will cause a reduction in tissue temperature.

Similar to Figs. 8 and 11, a nonlinear relationship exists between tissue temperature and the blood perfusion rate which can likely be defined by polynomial or exponential functions. This relationship helps to accurately estimate the temperature distribution in order to achieve the desired conditions of hyperthermia. The most important factor is the amount of heat transfer to the deeper parts of the tissue which can be controlled by changing the value of ω_b.

5. Summary of results

The primary purpose of the present study is to determine the effects of different influential parameters such as blood perfusion, body metabolism and external heat source on the temperature distribution of the human forearm during hyperthermia treatments. An attempt has been made to develop a numerical method for simulating heat transfer in living tissues which can estimate the temperature distribution accurately. This numerical approach can help to improve medical approaches such as hyperthermia treatments. In fact, by the presented method, it is possible to estimate the temperature profile of the tissue before implementing the therapeutic heating in real life situations. Utilizing the figures presented in the current study in the preceding sections, a better understanding of the thermal condition of living

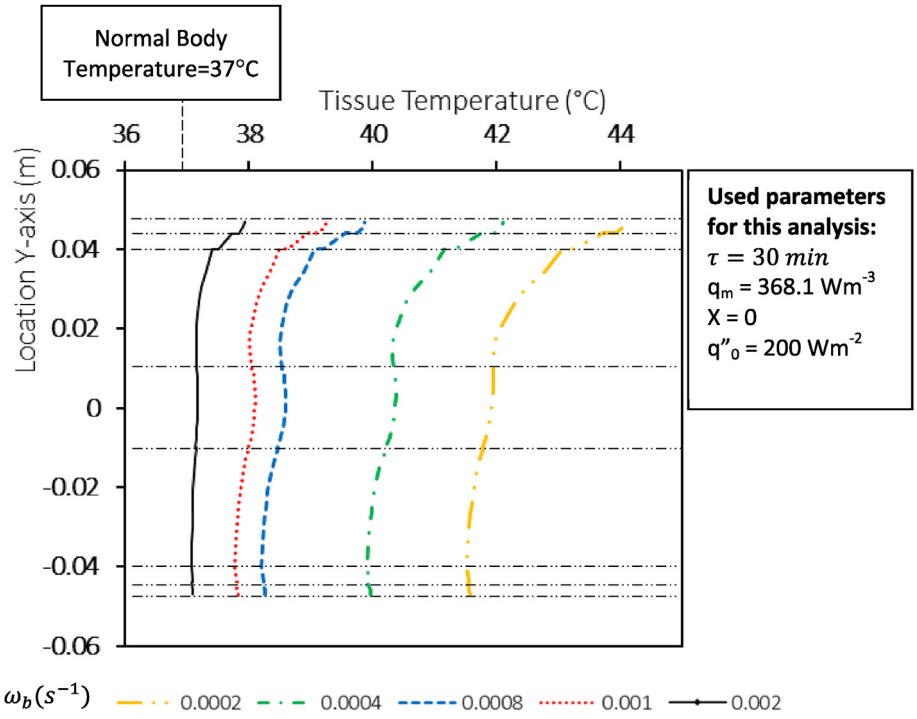

Fig. 14. Temperature variation along forearm depth at X = 0 affected by different values of ω_b under the influence of sinusoidal heat flux.

tissues during thermal therapies can be obtained.

After considering the suitable bioheat equation and developing the appropriate geometrical model, and using the following different heat sources, constant temperature, uniform heat flux and sinusoidal heat flux, the effect of stated parameters on the temperature distribution of the forearm is investigated. Generally, due to the symmetric and homogenous geometry of tissue and some simplifications applied to the stated bioheat equation, the temperature variation along the depth of the tissue is roughly similar for different sections along the main axis of the forearm cylinder. In fact, if a more realistic model of human forearm was taken into account, this similarity in the temperature distribution would be lost.

A summary of the results is presented as below:

1 As a general fact, the temperature of tissue varies with different slopes in different layers of the model, including skin, inner tissue and bone. This difference is a consequence of the dissimilar thermophysical properties which are assumed for the stated zones. In fact, the type of external heat source is not important in this case.
2 For all types of therapeutic heating, tissue temperature is directly related to the body metabolism. Any growth in qm will eventuate in an increase in tissue temperature. But this change in temperature is not similar for different kinds of external heat sources.
3 For a constant temperature heat source on the heating zone, a rise of 50% in qm will increase the temperature of the tissue in all layers about 0.5%, excluding the skin layer. As the therapeutic temperature is considered to be constant at the surface of the skin, the temperature of the skin surface is supposed to be fixed (T = 44 °C).
4 The effect of qm on the temperature of the tissue will decrease in higher temperatures. In fact, the temperature of the tissue is less affected by the variation of the volumetric density of metabolic heat (qm) in higher working temperatures.
5 In the case of a constant temperature heat source, the relation between temperature variation and qm can be assumed linear for the stated circumstances of analysis. This linear relation can improve the prediction of temperature distribution of living tissue before implementing hyperthermia treatments in clinical affairs.
6 While applying a uniform or sinusoidal heat flux on the skin surface, the maximum range of tissue temperature variation due to the change of qm from 0 to 1200 Wm-3, is about 0.5 °C, which does not have a significant effect on the attainment of hyperthermia.
7 While blood is perfused in the tissue, the existing heat is absorbed by blood stream and transported to the other parts of the tissue; thereby a balance in the tissue temperature will be created. Blood perfusion rate has a significant effect on heat transfer to the underlying layers of the tissue. The blood stream prevents the heat from being transferred to the deep parts of the forearm tissue, which can be described as a deterrent parameter in hyperthermia implementation.
8 Plotting the values of temperature against different blood perfusion rates, will reveal that it is impossible to consider a linear relationship between tissue temperature and the blood perfusion rate, regardless of the type of external heat source. Possibly, this relation can be defined by polynomial or exponential functions. This nonlinear relation can enhance the accuracy of temperature profile prediction of living tissue before fulfilling hyperthermia treatments in real conditions as well.
9 In the case of external uniform or sinusoidal heat fluxes application, tissue temperature is directly related to the quantity of applied heat flux. Notwithstanding blood perfusion and body metabolism, by increasing the amount of heat flux, the temperature of the tissue will rise. The amount of this growth in the upper levels of the tissue is more than that in the lower levels. At the lower half of the forearm, this effect reaches zero, roughly. This means that, by increasing the amount of therapeutic heat flux, not only the primary aim of hyperthermia will not be achieved, but also this rise will cause skin burn injuries.
10 By considering the presented approach of numerical modeling in the current study, if we consider the upper and middle layers of the forearm as our heating target, it is guaranteed that the lower parts of the forearm, which are assumed to be healthy, will not be thermally affected and no injuries will happen in these areas.
11 By applying a uniform and constant heat flux on the heating area of forearm, the tissue temperature, which is initially assumed to be

37 °C, will at a minimum rise to 42 °C in different locations. Although there is an upsurge of 5 °C in the minimum temperature of the tissue, still the condition for the tissue is safe and no injuries will be caused.

12 Actually, tissue temperature in different locations depends on the value of the therapeutic heat flux with an approximately linear correlation. This relationship between the parameters mentioned above, can improve the approach of hyperthermia implementation.

13 By applying a sinusoidal heat flux on the geometry, tissue temperature, initially assumed to be 37 °C, will increase to a minimum of 41.5 °C. Although there is a rise of 4.5 °C in the minimum temperature of the tissue, the condition for the tissue is safe and no injuries will be inflicted.

14 In the same conditions, it seems that the sinusoidal heat flux has a greater effect on the temperature variation of the underlying layers of the tissue, than the constant temperature and uniform heat flux. In fact, the average temperature of the middle parts of the forearm is higher than that induced by constant temperature or uniform heat flux sources. Therefore, a greater effect on the tissue temperature can be obtained by using the sinusoidal thermal flux and the control of other influential parameters.

15 Actually, if the target of hyperthermia is some certain layers, such as the subcutaneous layer of skin, or the inner tissue, the temperature of these layers is affected to a higher degree by the sinusoidal heat flux than the uniform heat flux or the constant temperature heat source.

16 Figures depicting temperature variation against different values of blood perfusion rate in the tissue are almost similar for the all types of external heat sources; consequently, the effect of blood perfusion on the tissue temperature distribution is not significantly affected by the type of external heat source.

In this research, many assumptions were made to simplify the problem solving process. These simplifications can be taken into account in other studies in order to achieve the most optimal and accurate estimation of hyperthermia treatment. The assumptions can be listed as follows: blood perfusion direction in the tissue, a more precise model of the forearm, porosity of living tissues, etc. The outcome of hyperthermia treatment can be predicted using the available diagrams in the present study and considering the differences in the tissue temperature distribution for different conditions.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtherbio.2019.07.023.

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