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**Laser-Tissue Heating Model Modernization
Assessment**

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Contemporary methods used to model laser-tissue interactions most commonly employ Pennes' bioheat equation. Despite its successful implementation in many applications, Pennes' equation reflects some unrealistic assumptions, such as the condition of infinite thermal propagation speed. While in many applications the effect of this assumption may be negligible, evidence shows that this assumption may produce unrealistic temperature profiles in extreme cases (such as laser heating applications) depending on the complexity of the tissue structure. This report aims to introduce and discuss the advantages and disadvantages of alternate models to correct these assumptions. A detailed overview of modern alternatives to Pennes' equation, including a numerical comparison between a thermal relaxation time method, the classical Pennes' bioheat equation, and a fractional Pennes' equation, is provided.					
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1.0 SUMMARY

At the time of writing, contemporary methods used to model laser-tissue heating events primarily employ Pennes' bioheat equation; a heat equation modified to include additional source terms characterizing heat generation inherent to biological systems (e.g. blood perfusion and metabolic activity) [1]. The implementation of this equation has been generally successful in a multitude of applications of various systems and settings. However, laser-tissue interactions encompass the unique combination of exotic experimental parameters and boundary/initial conditions in the form of extreme energy deposition and heat generation over a brief period of time. This quality alone has been known to cause problems in traditional implementations of the heat equation and Pennes' bioheat equation alike [2]. Critiques of the traditional approach are discussed below, but include failure to correctly account for the scale of inhomogeneities in tissue.

Additionally, more recent works have shown the assumption of infinite thermal propagation speed within Fourier's law of heat conduction begins to break down under extreme conditions as well as when the problem setting contains complex structures [3]–[5]. In these instances, Fourier's law can be modified to account for this discrepancy through the inclusion of additional terms embodying thermal relaxation times.

While there are, of course, many other alternatives to Pennes' bioheat equation for modeling tissue heating, models and methods applying the thermal relaxation time modification to Fourier's law is the focus of this work due to its logical suitability for the problem parameters mentioned above. A comparison of computational performance and accuracy between the thermal relaxation time method, the classical Pennes' bioheat equation, and models leveraging non-local operators in the form of fractional derivatives previously identified as a suitable alternative [6] is also included.

2.0 INTRODUCTION

During the last century, the description of heat transfer in living tissue (known as bioheat transfer) and the mathematical modeling of temperature distribution under heating (or cooling) has been an active area of research due to its many potential applications. For example, this is an important problem in various medical applications where optimized hypothermia treatment and thermotherapy of tumors require precise control over the tissue temperature [7]–[9]. Furthermore, understanding heat transfer in tissue is critical in assessing damage thresholds. For example, exposure guidelines for radiofrequency (RF) energy (in the range of 3 kHz-300 GHz) have been established for many years; examples include limits enforced by the U.S. Federal Communications Commission (FCC 1997) and IEEE standards (Institute of Electrical and Electronics Engineers C95.1-2005 and C95.1a-2010). Investigating the thermal effects of electromagnetic waves on living tissue is difficult because of the complexity (and variety) of biological structures and the inherent complexity of quantifying the mechanisms of heat transfer for these structures. Furthermore, tissue interaction with electromagnetic waves varies based on frequency, intensity, and duration of exposure [10]. As an example, the dielectric constant relative to free space and conductivity are two electrical properties dependent on temperature and frequency. In fact, as the frequency increases from a few Hz to GHz, the dielectric constant decreases from several million to only a few units, while the conductivity increases from a few milliSiemens per cm to a few thousand [10]. A summary of the particular aspects of this problem contributing to its overall

complexity are as follows:

1. Mechanical behavior of skin tissue

Skin tissue is found to be heterogeneous, nonlinear, anisotropic, and viscoelastic in vivo due to the highly non-homogeneous structure and composition of living tissue. Factors which may affect these properties include age, gender, site, hydration, etc.

2. Thermal Behavior of skin tissue

Thermal behavior in skin is primarily a heat conduction process coupled with complicated physiological processes, such as blood circulation, metabolic heat generation, heat dissipation, etc. Furthermore, thermal properties not only vary by layer, but even within the same layer. There exists significant non-homogeneity and anisotropy due to the presence of blood vessels in the tissue. Physiological processes and thermal properties of living skin tissue are influenced by a number of factors, including temperature, damage, pressure, and age, etc. Thermoregulation due to blood circulation and perfusion is assumed to maintain the body core temperature at a constant value required for the normal physiological functions [11].

The problem of finding a mathematical model to predict thermal response is further complicated by the fact skin is an active system with self-regulating processes. For example, heat transfer through the skin can induce dramatic changes in the state of the skin; this triggers the redistribution of skin blood flow over the cutaneous vascular network and could influence the heat transfer in the skin. However, the blood circulation should maintain the body energy balance and therefore the tissue temperatures are results, not the causes for the thermoregulation process [12], [13]. For example, in a thermally neutral environment, the skin of a resting body received 5-10% of cardiac output, which can drastically increase to 50-70% during severe heat stress or even approach zero in a cold environment [14]. In fact, under thermal stress, skin blood flow can rise to levels more than 50 fold its thermoneutral value during thermoregulation [15] and, in this case, the local heat transfer in the skin may be dominated by convection of the perfused blood rather than tissue conduction [16].

3. Thermomechanical behavior in skin tissue

Thermally dependent mechanical properties of skin tissue are experimentally difficult to establish. Previous studies of the viscoelasticity of skin tissue reveal its stress-strain relationship depends on a variety of factors such as strain rate, loading rate and period, preconditioning stress history, and skin demonstrates considerable hysteresis in cyclic tests and stress relaxation under constant strain ([17]–[19]). For example, authors in [20] conducted an experimental study on the tensile behavior of pig skin tissue under different thermal loading conditions and different mechanical stretching rates. Their results indicated there is a significant variation among skin tensile behaviors under different temperatures and loading rates, which correlated with dermal collagen denaturation. Due to the thermal denaturation of collagen during heating, there appears to be thermally induced mechanical stress which corresponds to thermal shrinkage. Thermal shrinkage has been used as a continuum metric of thermal damage [17] and gross shrinkage has been shown to provide the same information on the kinetics of denaturation as other biochemical assays, however, it lacks detail on the underlying mechanisms at work [21]. Authors in [22] showed mechanical

load is functionally as important as the temperature level during shrinkage. Changes to the structure and hydration of collagen during denaturation further complicates the problem. In other words, thermal denaturation of a collagenous tissue can affect the mechanical, thermal, electrical, and optical properties.

3.0 SKIN STRUCTURE AND BLOOD FLOW

The skin is the largest organ in the human body comprising approximately 14-16% of the adult human body weight [23]. The skin performs a variety of functions, including thermoregulation, and consists of three layers: the epidermis, dermis, and subcutaneous tissue. The thickness and characteristics of each layer depends on the location of the skin. For example, the skin found on the palm of a human hand, known as glabrous skin, is characterized by a relatively thick epidermis and a lack of hair follicles. The presence of hair follicles has a notable influence on temperature profiles [24]. On the other hand, mucocutaneous skin borders the entrances to the interior of the body, such as the nose or mouth, and is characterized by being comprised of typical skin and mucous membrane. These observations are important in the bioheat context because tissue parameters (such as density and thermal conductivity) vary depending on skin location. Another complexity in applying bioheat models is the influence of skin appendages, such as hair follicles and sweat glands.

The epidermis is the outer-layer of skin containing both living and dead cells and is around 75-150 μm in thickness [25]. The dermis is approximately 1-4 mm [25] and is composed of fibrin proteins, blood vessels, nerves, lymph vessels, and the skin appendages. As discussed in the introduction, the collagen fibres in the dermis could influence temperature responses. In fact, collagen contributes 60-80% of the dry weight of fat-free skin and 18-30% of the volume of the dermis [26]. The hypodermis is the third layer of skin, or subcutaneous fat, which is composed of loose fatty connective tissue. While the hypodermis is not part of the skin, it holds the major blood vessels and nerves that supply the overlying skin. The thickness of these layers varies both over the surface of the body and also with age, sex, race, and health status of the individual. For details on the structure of the skin and its micro-structures, see [27].

4.0 BIOHEAT MODEL FORMALIZATION

Analysis of thermal energy balances in biological tissues are multifaceted due to the variation in tissue structure and functions. Heat transfer mechanisms, the relative time scale of the deposited energy, and differences in boundary and initial conditions affect the energy balance [28]. In order to model basic properties of the thermal state of living tissue, simplifying assumptions are necessary to reduce the complexity of the problem. Most models begin with the application of the energy balance law over a control volume V :

$$\frac{d}{dt}Q_{\text{gain}} = \frac{d}{dt}Q_{\text{storage}} + \frac{d}{dt}Q_{\text{loss}} + \frac{d}{dt}W. \quad (1)$$

Equation 1. Energy balance law

That is, the rate of heat gained is balanced by the heat stored, the heat loss (via conduction or heat exchange with advanced fluids), and the rate of work W performed by the tissue [28]. More

precisely, the heat gain due to heat generated by the unit tissue segment and heat energy storage can be expressed as integrals over the control volume:

$$\frac{d}{dt}Q_{storage} = \int_V \rho c \left[\frac{\partial}{\partial t} T(r, t) \right] dV. \quad (2)$$

Equation 2. Heat energy storage

As previously mentioned, continuum models regard the tissues of interest as a continuum in which the large number of vessels are accounted for collectively to simplify the system and by avoiding the microscopic anatomical structure. In this context, the governing equations represent the macroscopic temperature field with several source terms describing the thermal interaction between blood and surrounding tissues (e.g., blood convective heat transfer and blood perfusion) as well as the production and external supply of heat (e.g., metabolic heat generation and external heat supply during therapeutic procedures). This approach is consistent with our general interests (i.e. valid temperature predictions) in the macroscale rather than the microscale of heat transport for practical applications. However, as will be discussed in Section 4.2, research suggests in some instances (more specifically instances of high energy deposition over a short time period), microscopic response may have a notable influence on the temperature distribution [29], [30]. Using this treatment, most continuum bioheat models are based on the macroscale point equation of energy conservation:

$$\frac{\partial(\rho c T(\vec{r}, t))}{\partial t} = \nabla \cdot \vec{q}_{mac} + q_{m,mac} + q_{b,mac} + q_{c,mac} + q_{s,mac}, \quad (3)$$

Equation 3. bioheat energy conservation

where the subscript *mac* indicates a macroscale property. ρ and c represent the density and specific heat, respectively, and $T(\vec{r}, t)$ represents the temperature at position $\vec{r}$ and time t . $\vec{q}$ represents the heat flux density vector and q_m , q_b , q_c , and q_s are the volumetric rates of heat generation by the metabolic heating, blood perfusion, blood convective heat transfer, and an external heat supply (such as a laser), respectively. To apply this equation, two main considerations must be taken in to account:

- (i) The selection of the constitutive relation of heat flux density.
- (ii) Choosing accurate, yet feasible, expressions of the source terms to describe the interaction between blood and surrounding tissues.

Many models consider conduction and convection as the heat transfer mechanisms and the heat conduction mechanism is commonly modeled by Fourier's law when no inertia is taken into account. This is the main focus of this report and is the source of discussion in later sections. Bioheat models are often classified by the way in which the influence of blood flow in the vascular network is handled. Some examples with brief descriptions are listed below:

- Continuum models account for the blood perfusion using the effective conductivity of the tissue. These models typically account for blood perfusion using global parameters, such as blood flow rate. The general form of the bioheat equation of continuum models is

$$\rho c \frac{\partial T}{\partial t} = -\nabla \cdot q + q_s + q_b + q_m, \quad (4)$$

Equation 4. Bioheat equation

where ρ is density, c is specific heat, q represents the heat flux, q_s is the source term, q_b is the heat generation caused by blood perfusion, and q_m is the metabolic heat generation.

- Vascular models describe local heat transfer in the individual vessels and attempts to reproduce the real vascularity of the tissue. These models consider the vascular system as system of rigid tubes protruding through the tissue. Due to the complexity of the vascular system, often times larger vessels are considered while smaller ones are neglected thus reducing the order of complexity [31], [32]. Limitations of this approach are it requires detailed knowledge of the vascular geometry.
- Hybrid models combine different continuum and/or vascular models.
- Other models consider the matrix of tissue, arteries, veins, and capillary vessels as a porous medium with specific porosity variations, effective heat conductivities, and heat dispersion by blood flow [33]. The assumption that the blood flow and tissue are in thermal non-equilibrium is often described by two energy equations for the blood phase and solid phase [34].

The goal of this report is to address some known alternatives to Pennes' equation that may improve the overall accuracy of the model while considering the practical constraints of implementation. For this reason, energy balance-based continuum models are the primary area of focus of this report.

4.1 Fourier Models

The conduction component of the heat flux through the tissue (per unit area) is based on the classical Fourier's law which is

$$q(\vec{r}, t) = -\kappa \nabla T(\vec{r}, t), \quad (5)$$

Equation 5. Fourier conduction term

where κ is thermal conductivity and $\vec{r}$ represents the position vector. This equation implies an instantaneous thermal energy deposition in the medium.

4.1.1. Pennes' Bioheat Equation

Pennes' bioheat model was the first major effort in quantifying the heat transfer contribution of perfusion:

$$\rho c \frac{\partial T}{\partial t} = \nabla \cdot (\kappa \nabla T) + q_s + q_b + q_m. \quad (6)$$

Equation 6. Bioheat equation using Fourier heat conduction

The blood perfusion term is defined as

$$q_b = \omega \rho_b c_b (T_b - T)$$

where T_b , ρ_b , and c_b are the temperature, density, and specific heat of the perfused blood, respectively. ω is the blood perfusion rate coefficient. Substituting this expression for q_b in equation (6) produces Pennes' bioheat model:

$$\rho c \frac{\partial T}{\partial t} = \nabla \cdot (\kappa \nabla T) + q_s + \omega \rho_b c_b (T_b - T) + q_m, \quad (7)$$

Equation 7. Pennes' bioheat model

where ρ and c are the density and specific heat of the tissue. Radiative, convective, and evaporative thermal flux boundary conditions are imposed at the object surface:

$$\begin{aligned} q_{rad} &= \sigma \epsilon (T^4 - T_\infty^4) \\ q_{conv} &= h_{conv} (T - T_\infty) \\ q_{evap} &= h_{evap} (p_{sat}(T) - RH \cdot p_{sat}(T_\infty)), \end{aligned}$$

where σ is the Stefan-Boltzmann constant, ϵ is the surface emissivity, h_{conv} is the convective heat transfer coefficient, h_{evap} is the evaporative heat transfer coefficient, T_∞ is the air temperature surrounding the object, and RH is the relative humidity of air. The function $p_{sat}(T)$ is the temperature-dependent saturation pressure of water vapor. The model assumes infinite thermal propagation speed.

Pennes' model also assumes the effect of blood perfusion is homogeneous and isotropic (i.e. blood flow direction is not considered). Thermal equilibration is also assumed to occur in the microcirculatory capillary bed and the blood supplied to the tissue at the arterial temperature T_b which perfuses the tissue at a rate ω per unit volume and then attains thermal equilibrium with the surrounding tissue before passing to the veins. It is assumed blood vessels close to the capillary beds do not affect the heat exchange and the local vascular geometry is ignored. The convection (or perfusion) fluid-body term is

$$q_{conv} = h(T_w - T_f),$$

where the heat transfer coefficient (fluid-body surface) h [W/m²·K] is dependent on the fluid velocity. In biological tissue, the fluid related heat transfer should be attributed to the blood perfusion and flow distribution due to the heterogeneity of the living structures [35]. The heat flux is proportional to the difference between the blood temperature in the artery, T_a , and the venous level temperature, T_v . The pre-arteriole heat transfer and pre-venule heat transfers are neglected and it is often assumed in capillary beds the very slow blood flows attain complete thermal equilibria with the surrounding tissue ($T_v = T$). Furthermore, blood reaches capillary beds through the arterioles at deep body temperature (core temperature). The total energy exchange between the blood and the tissue is then represented as

$$q_b = \omega \rho_b c_b (T_b - T).$$

It is important to note thermal equilibration in the capillaries is a misconception since this process takes place in the pre-arteriole and post-venule vessels with diameters within the range of 70-500 μm [36]. The choice of this temperature difference is a distinction between continuum models and other types of models. Furthermore, these appear to be the only practically measurable temperatures. It should also be noted the previous result is conditional, despite the fact it is frequently used in model formulations. In larger arteries it would not hold due to strong blood mixing [28] and in these cases a hybrid or vascular model would be recommended. The metabolic heat generation, q_m , is assumed to be homogeneously distributed throughout the tissue of interest as a rate of energy deposition per unit volume.

The Pennes model assumes the arterial blood flow bathes the tissue at the same temperature everywhere in the limb cross sections (see the comments in [33], [34]). Some deficiencies from these assumptions are the perfusion term in Pennes' model assumes the tissue is bathed by the arterial flow, while the venous return from the distal part having an important effect on tissue temperature is neglected. In [37], [38], Shitzer et al. revealed the perfusion term may play a role of a sink in the warm core region of the tissue and as a source in the cooler peripheral area (also see [33], [34]). Charny [33] also showed with an increase in the arterial blood flow, or the perfusion rate, the perfusion term acts as a heat source in a large section of living tissue. Mathematically, this indicates the sign of the perfusion term should change (to represent a source or sink) depending on the location of the modeled tissue; a property not accounted for in Pennes' model. Pennes' model and other continuum models also do not account for the detailed structures of the vascular network. Failure to consider the vascular geometry also limits the model by not accounting for counter-current heat transfer between artery-vein pairs. Furthermore, the blood perfusion is overestimated in this model because the arterial temperature changes continuously from the deep body temperature of the aorta to the secondary arteries and further to all branches of the system [35]. As a result, the pre-arteriole temperature and returning vein temperature are not equal to core body temperature or average tissue temperature. Lastly, the flux term is expressed using Fourier's law which assumes an infinite thermal propagation speed. Alternative models which correct this assumption are discussed in section 4.2.

Currently SESE (Scalable Effects Simulation Environment) implements the Monte Carlo method for radiative energy transport determining the spatial distribution of applied radiation in the object space. The optical properties of the material dictate probabilistic interactions and SESE employs an implementation of the Monte Carlo radiative transport method (described in [39]). SESE solves the heat equation in a three-dimensional domain with a finite-volume voxel discretization by employing a Gauss-Seidel red-black successive over-relaxation method [40].

4.1.2. Wulff's Continuum Model

Many investigators have questioned the physical and physiological validity of the underlying assumptions in Pennes' bioheat model. In 1974, Wulff [41] examined the validity of the blood perfusion term in Pennes' bioheat equation (7). Wulff suggested the description of the thermal convection by blood is inconsistent in equation (7) and the perfusion term is a global (integral) term that does not correspond to the other terms which are local derivatives. Wulff's argument was since the blood is passing through the tissue, it may remove or derive heat by convection in any direction and not only in the direction defined by the local temperature gradient. With these

assumptions, Wulff proposed the following equation for the convective energy transport through tissue [41]

$$\rho_b \bar{h}_b v_h = \frac{1}{4\pi} \int_{\Omega} \rho_b \bar{h}_b v d\omega, \quad (8)$$

Equation 8. Convective energy transport by Wulff

where v represents the blood velocity in the capillaries and ω is a solid angle across the control surface of the blood vessel, while Ω is the entire solid angle, and v_h is the local mean apparent blood velocity. In equation (8), $\bar{h}_b$ is the blood specific enthalpy. Under these assumptions the energy flux at any point of the tissue is [41]

$$q = -\kappa \nabla T_t + \rho_b \bar{h}_b v_h. \quad (9)$$

Equation 9. Energy flux by Wulff

The simplified energy balance equation is

$$\rho c \frac{\partial T}{\partial t} = -\nabla \cdot q \quad (10)$$

Equation 10. Simplified energy balance equation

and with the previous energy flux term (and ignoring property variations and mechanical work) Wulff proposed the following bioheat equation [41]:

$$\rho c \frac{\partial T}{\partial t} = \kappa \nabla^2 T - \rho_b v_h \cdot (c_b \nabla T_b - \Delta H_f \nabla e) \quad (11a)$$

$$\rho c \frac{\partial T}{\partial t} = \kappa \nabla^2 T - \rho_b c_b v_h \cdot \nabla T - q_m, \quad (11b)$$

Equation 11. Bioheat transfer equation suggested by Wulff

where the metabolic reaction term $\rho_b \Delta H_f v_h \cdot \nabla T$ is q_m in equation (7) and, like in Pennes model, Wulff assumed the temperature gradient and the blood temperature gradient are equal permitting the assumption $T_b = T$. It should be noted equation (11) can be re-written in a more familiar form as the convection-diffusion equation of heat transfer.

Numerical examples completed by Wulff [41] compared the steady-state case of equations (7) and (11) without metabolic heat generation so the impact of blood perfusion could be more readily studied. For a one-dimensional heat transfer through a plane-parallel slab, Wulff showed there was convergence of solutions of the nondimensional equation (11) to the solution of (6). It was also shown equation 7 produced errors of the same order of magnitude as the effect of blood flow itself. However, the estimate of the local blood mass flux, $\rho_b v_h$, is complex and requires much more effort than using the simplified assumption of volumetric blood perfusion rate, ω_b , in equation

(7). Furthermore, equivalence of Pennes' bioheat equation and the Wulff continuum model has been shown for 1-D planar tissue [42]. The derived conditions of equivalence are specific to tissue without metabolic heat generation, but the analysis discovered the local mean blood velocity in a tissue is a function of the square root of the blood perfusion rate. The authors also demonstrated this dependence numerically.

4.1.3. Klinger's Continuum Model

The continuum model proposed by Klinger [43], [44] is similar to Wulff's model in it focuses on a correct description of experimental data from thermal clearance experiments. Klinger's model assumes the tissue temperature is related to the rate at which the deep temperature changed during point source heating [45], [46]. Taking into account the critique of Perl [45], [46] that the Pennes model postulated unidirectional blood flow and neglected nonunidirectional blood flow, Klinger identified a few problems in Pennes' model. First, the solution represents the local temperature at each point in the tissue, but measuring devices have finite dimensions and, in most cases, this is larger than the length scale of the tissue of interest. The consequence of this is the measured temperature should be viewed as an average value and not as a local one. Second, to correct the missing nonunidirectional blood flow in Pennes' model, Klinger introduced the concept of convection multipoles related to the in vivo vascular autonomy, therefore accounting for not only the magnitude of blood flow but also the direction [33], [43], [44]. Klinger's model is based on the assumption of constant tissue properties (κ, ρ, c) and the incompressibility of the blood flow. The model is expressed as

$$\rho c \frac{\partial T}{\partial t} + \rho c \vec{v}_b \cdot \nabla T = \kappa \nabla^2 T + q_s. \quad (12)$$

Equation 12. Bioheat model by Klinger

This equation appears similar to Wulff's model (11), except it is more general and applies to the case of a spatially and possibly temporally nonuniform velocity field $\vec{v}$ and heat source q_s . In its spacially dimensionless form this equation becomes [33], [43], [44]

$$\frac{\partial T}{\partial \tau} + Pe \vec{v}^* \cdot \bar{\nabla} T = \bar{\nabla}^2 T + \frac{q_s L^2}{\kappa}, \quad (13)$$

Equation 13. Dimensionless bioheat model by Klinger

where $\vec{v}^*$ denotes the fluid velocity relative to the characteristic velocity, Pe is the Peclet number for flow based upon the characteristic velocity, $\bar{\nabla}^2$ is a dimensionless Laplacian operator based upon the characteristic length L , and $\tau = \frac{L^2}{a_t}$ is the characteristic time (a_t is the tissue thermal diffusivity). To understand the main idea of the model, it should be mentioned Klinger introduced a dimensional velocity $\bar{\mathbf{v}} = Pe \vec{v}^*$ which allows the energy balance equation to be written as

$$\psi T + \frac{q_s L^2}{\kappa} = 0, \quad (14)$$

Equation 14. Energy balance equation by Klinger

where ψ is the dimensionless operator $\left[\bar{\nabla}^2 - (Pe\bar{v}^* \cdot \bar{\nabla}) - \frac{\partial}{\partial \tau}\right]$. Assuming point heat source heating the source term $\frac{q_s L^2}{\kappa}$ is replaced by a Dirac delta function $\delta_{\vec{r}_1}$ which vanishes everywhere except at the position $\vec{r}_1$, Klinger then used a Green's function formulation to solve equation (13) [31], [33], [43], [44]. In accordance with Klinger, the multiple moment was directly proportional to the total volumetric blood flow rate through the vessels with repeating tissue elements in all vascular arrangements studied. The effects of the multipole moments depend on the ratio $\frac{\lambda}{L}$, where L is the microscopic length scale and λ is the length of the side of the cube over which the average tissue temperature is being determined. Since $\frac{\lambda}{L} < 1$ Klinger's modeling experiments demonstrate the countercurrent flow effect on the tissue heat transfer is a second order effect. The results of Klinger's findings and the concept of averaging the temperature around a certain position can be summarized as follows [47]:

- The effects of blood convection on the average temperature can be represented as a superposition of terms, each mirroring a particular property of the local symmetry of the vascular system.
- The order of magnitude of the convection effect decreases with increasing the symmetry.
- The Peclet number used by Klinger in [43] is defined as a ratio of two characteristic times

$$Pe = \frac{t_{conv}^{char}}{t_{cond}^{char}} = \frac{v_0/L}{L^2/a_t},$$

Klinger's model is often applauded for addressing some important issues in bioheat modeling. Since $\epsilon_b \ll 1$ [33] it follows κ_{eff} , the effective thermal conductivity, is practically independent of the blood flow which implies it is reasonable to accept $\kappa_{eff} \approx \kappa_{solid\ tissue}$. Secondly, the Green's function solution permits quantifying the vessel number density, blood perfusion rate, and the vessel spatial construction. The outcome of this is the temperature field is strongly influenced by the spatial geometry of the blood carrying vessels [33], [34].

4.1.4. Chen-Holmes Continuum Model

In the Chen-Holmes (CH) model, blood vessels are grouped by size; large vessels are treated separately and smaller vessels which due to their size and large number are treated as part of a continuum. To do this, Chen and Holmes [31] evaluated the thermal equilibration length of individual vessels (l_e) defined as the length of the blood vessel for which the temperature difference between blood and tissue is reduced to $1/e$ of its initial value. l_e depends on the vessel dimensions, the local average blood velocity, and the overall heat transfer coefficient. Using a rough estimate of the heat transfer coefficient, Chen and Holmes [31] calculated l_e for vessels ranging in size from as large as the aorta to as small as capillaries. Their findings were consistent with the criticisms that the underlying assumptions of Pennes' bioheat model were incorrect. Chen and Holmes [31] found the thermal equilibration of the blood with the tissue occurs not in the capillaries, but in vessels with diameters in the range of 0.2-0.5 mm. Chato [48] also conducted a detailed analysis of the thermal relation between tissue and vessels with various geometrical configurations and concluded the magnitude of heat transfer between vessels and tissue strongly depends on vessel size; large

vessels exchange little energy with the surrounding tissue and their temperatures are unaffected by the thermal field in the tissue, while small vessels, such as precapillary arterioles, venules and capillaries, are nearly in complete thermal equilibration with tissue. However, the results in Chato's paper regarding the heat exchange efficiency of intermediate vessels were inconclusive and Chen and Holmes [31] pointed out the thermal significance of these intermediate-sized vessels was the center of the criticism regarding Pennes' equation. Weinbaum et al [32] also evaluated l_e for several specific vessel configurations and their analysis of the vessel size at which most of the thermal equilibration occurs confirmed the findings of Chen and Holmes. Baish et al. [49] analyzed hypothetical vascular geometries in order to explain the relation between l_e and the contribution of blood to heat transfer in tissue. For cases when $l_e \approx l$ (where l is the physical length of the vessel), Baish et al. [50] recommended using a full model that couples equations for heat exchange between blood vessels with that of the adjacent tissue.

In the CH model, the distinction by size is determined by the ratio between the actual length of the particular blood vessel and the calculated value of its l_e . The heat transfer between the small blood vessels and tissue was separated into three modes. The first mode captures the equilibration of blood temperature, initially at that of the larger vessel, with tissue temperature. Blood exits the control volume at essentially the average temperature of the confined tissue. Hence the thermal contribution due to the temperature difference between the entering blood and the tissue within the control volume is

$$q_p = \omega^* \rho_b c_b (T_a^* - T), \quad (15)$$

Equation 15. Blood perfusion term introduced by Chen and Holmes

where the perfusion parameter ω^* in equation (15) refers to the blood flow within the vessels in the control volume and T_a^* represents only the temperature of the blood within the largest vessels, which is typically between the temperatures of the major supply vessel and the tissue. Note the similarities between (15) and the perfusion term in Pennes' equation (7). Another mode of heat transfer occurs due to convection between thermally equilibrated vessels and the tissue gradient. Because of thermal equilibrium, the blood temperature is basically equal to that of the tissue T , yielding a contribution of

$$q_c = \rho_b c_b \vec{u} \cdot \nabla T, \quad (16)$$

Equation 16. Contribution of thermally equilibrated vessels by Chen and Holmes

where $\vec{u}$ represents the net volume flux vector of the blood permeating a unit area of the control surface. However, in biological tissues, the arteries and veins frequently occur in countercurrent pairs with blood flowing in opposing directions. Therefore, the mass conservation principle imposes that the net flux vector is practically zero, hence the effect of the term in equation (16) is negligible except for tissue regions close to the blood vessel pair. The third and last mode describes the thermal contribution due to the small fluctuations in temperature of nearly equilibrated blood along the tissue temperature gradient. To accommodate the time lag between the temperatures of the tissue and of the closely following blood, the mode of heat transfer is assumed to be

proportional to the tissue temperature gradient and dependent on the microvascular structure. This gave rise to a tensor, κ_p , denoted as the *perfusion conductivity*. This mode of heat transfer is described by the following conduction equation:

$$q_{pc} = -\nabla \cdot \kappa_p \nabla T. \quad (17)$$

Equation 17. Thermal contribution of nearly-equilibrated blood by Chen and Holmes

The perfusion conductivity depends on the local blood flow velocity within the vessel, the relative angle between the directions of the blood vessel, and the local tissue temperature gradient on the number of vessels included in the control volume [31]. Chen and Holmes evaluated the conductivity tensor by representing the small temperature fluctuations of nearly equilibrated blood vessels by a Fourier integral which allowed them to calculate the conductivity tensor for a single vessel with one spectral component. In one dimension, the tensor perfusion conductivity becomes a scalar parameter. However, Chen and Holmes did not provide a clear definition of the nearly-thermally equilibrated vessel as compared to modes one and two (that is, the contributions of blood perfusion and the thermally equilibrated vessels) and the relative contribution of this term is an open discussion at the time of writing [35].

The Chen-Holmes model of bioheat transfer is obtained by replacing the single perfusion term in Pennes' model (7) with the terms in equations (15, 16, 17):

$$\rho c \frac{\partial T}{\partial t} = \nabla \cdot \kappa \nabla T + \rho_b c_b \omega^* (T_a^* - T) - \rho_b c_b \vec{u} \cdot \nabla T + \nabla \cdot \kappa_p \nabla T + q_m. \quad (18)$$

Equation 18. Bioheat transfer equation by Chen and Holmes

In comparison to Pennes' equation (7), the Chen-Holmes model (18) replaces the original blood perfusion term with the three modes outlined above. The practical application of this model is difficult (in comparison to Pennes' model) because it requires knowledge of the local vascular geometry. However, there is evidence the predictions from Pennes' equation are similar to those from the Chen-Holmes equation [51], but due to simplicity, Pennes' equation is usually preferred.

Table 1. Summary of source terms in Pennes, Wulff, Klinger, and Chen & Holmes models

Model	$q_{m,mac}$	$q_{b,mac}$	$q_{c,mac}$
Pennes	$q_{m,mac}$	$(\rho c)_{b,mac} \omega (T_{b,mac} - T_{mac})$	0
Wulff	$\rho_{b,mac} \Delta H_f v_h \nabla T$	0	$(\rho c)_{b,mac} v_h \nabla T_{mac}$
Klinger	$q_{m,mac}$	0	$(\rho c)_{b,mac} \vec{v}_{b,mac} \cdot \nabla T_{mac}$
Chen & Holmes	$q_{m,mac}$	$(\rho c)_{b,mac} \omega^* (T_{a,mac}^* - T_{mac})$	$-(\rho c)_{b,mac} \vec{u} \cdot \nabla T_{mac}$

4.2 Non-Fourier Models

The various models for heat conduction discussed up to this point were all based on Fourier's law (5). This is a reliable model confirmed by experiments but there are serious limitations to its applications. Equation (5) gives an adequate description of the microscopic phenomenon of heat diffusion in cases when the length scales are much greater than the mean free path and the time scales are much greater than the thermal relaxation time [52]. However, there are nonphysical consequences of assuming (5), with the most significant being the assumption the heat flux has no dampening. Put simply, this assumes an infinite thermal propagation speed that is unrealistic since temperature distribution is due to motion of particle carriers (such as electrons or photons/quanta) [52]. As such, it is reasonable to expect thermal disturbances to propagate with finite speed.

Research to establish a connection between heat conduction and the underlying microscopic dynamics has produced some controversial examples [53]–[55]. In [56], Li et al. investigated the microscopic origin of the anomalous heat conduction observed in many 1D models. The main result can be summarized as ballistic transport leading to an anomalous heat conduction with a divergent thermal conductivity, $\kappa \propto L$. A normal diffusion means a normal heat conduction obeying the Fourier law. A superdiffusion leads to an anomalous heat conduction with a divergent thermal conductivity and a subdiffusion means a zero thermal conductivity in the thermodynamic limit. The authors compared their results with the existing analytical and numerical results with success.

Though heat transfer in biological tissues is generally solved by Pennes' equation, as mentioned, assuming infinite thermal propagation speed could have unrealistic implications for certain thermal applications. Temperature oscillation in living tissue has been observed by Richardson et al. [4] and later by Roemer et al. [5], who subjected canine thigh muscle to an abrupt application of microwave heating at different power levels. Mitra et al. [3] also performed four different experiments with processed meat for different boundary conditions and also observed wave-light behavior. Davydov et al. [57] experimentally observed heat transfer in a muscle tissue under local strong heating exhibits substantial anisotropy, which cannot be explained by the standard Fourier-theory based heat diffusion model. This has led to the formulation of thermal wave bioheat models based on two main approaches:

- Dampening of the heat flux by introducing a time lag, also known as the Single-Phase Lag approach, or the Maxwell-Cattaneo approach.
- Introducing relaxation constants in both the heat flux and the temperature gradient propagation. This approach is known as the Double-Phase Lag approach.

It should be mentioned fractional or nonlocal models also address the concern of infinite thermal propagation speed, as is discussed in section 5, but this section specifically focuses on models derived by considering phase modifications to the flux term. The models of Pennes, Wulff, Klinger, and Chen-Holmes are based on Fourier's law with infinite speed of heat flux and lead to parabolic equations. The non-Fourier approaches mentioned above lead to hyperbolic equations. Parabolic equations are often used to describe problems with diffusion and one characteristic of these equations is changes in a solution effect only the solution at a later point in time. On the other

hand, hyperbolic equations describe time-dependent scenarios with little dissipation. Hyperbolic equations also have two characteristic paths, as opposed to only one in the parabolic case.

In the 1950s, the Italian mathematician Carlo Cattaneo [58] tried to overcome the problem of infinite speed of heat propagation by deriving a new equation to relate the heat flux q and the temperature T , and hence replace Fourier's law. Cattaneo introduced the thermal relaxation characteristic time τ_q , which is interpreted as "the time lag required to establish steady heat conduction in a volume element once a temperature gradient has been imposed across it" [59]. In other words, τ_q is the time needed to reach thermodynamic stability. Therefore, the relaxation time introduces the idea of finite speed of heat propagation. The equation proposed by Cattaneo [58] (and separately by Vernott [60]) is

$$q(\vec{r}, t) + \tau_q \frac{\partial q(\vec{r}, t)}{\partial t} = -\kappa \nabla T(\vec{r}, t), \quad \tau_q > 0, \quad (19)$$

Equation 19. Modified unsteady heat conduction term

where the new term is called *thermal inertia* [61]. $\tau_q = \frac{\alpha}{C_t^2}$ is often referred to as the *thermal relaxation time*, where α is the thermal diffusivity and C_t is the speed of the thermal wave in the medium [3], [62]. The reciprocal of the relaxation time, $\frac{1}{\tau_q} = f$ is the critical frequency dictating the activation of thermal wave behavior [63]. Both τ_q and α are intrinsic thermal properties of the medium and, hence, the thermal wave speed C_t is also an intrinsic property [64]. This equation can be viewed as the first Taylor approximation of

$$q(\vec{r}, t + \tau_q) = -\kappa \nabla T(\vec{r}, t). \quad (20)$$

Equation 20. Single phase lag flux

Equations (19) and (1) form the Maxwell-Cattaneo equations, sometimes also referred to as Maxwell-Cattaneo-Vernotte equations. Maxwell's name was attached to the equation because he derived a similar expression when providing a mathematical basis kinetic theory of gases [65]. Due to its similarity with an acoustic wave, the proposed wave-like propagation of thermal signals is sometimes referred to as the *second sound wave* [63], [66]. Equation (19) has also been used by Lord and Shulman [67] to derive the equation of the generalized theory of thermoelasticity with one relaxation time.

Kaminski [68] proposed τ_q represents the interaction of different inner structural elements of material during heat transfer and postulated τ_q ranges from $10^{-8} - 10^{-14}$ s in homogeneous substances. Many heating processes are much longer than this time scale and this supports the success of Fourier's law in some heat conduction applications. In nonhomogeneous materials, the structural heat transfer interaction takes place at a different level and τ_q may take on much larger values of $10^{-3} - 10^3$ s [69]. Biological systems are largely comprised of porous capillary bodies and cells that are heterogeneous and multiphase. In these highly nonhomogeneous structures, τ_q can have a different meaning from the commonly referred thermal relaxation. In this case, it is defined as the characteristic time needed for accumulating the thermal energy required for

propagative transfer to the nearest element within the nonhomogeneous inner structures [68]. It reflects energy interaction at the structural level rather than at the molecular or crystal lattice level as in the case of homogeneous materials and it therefore may take on a much greater value. The characteristic time can be attributed to the non-equilibrium between fluids and solids, as well as the effect of the cell membrane acting as the energy storage and conversion element in biological systems [70]. The value of τ in biological systems has been predicted by [68] and [71] to be 20 – 30 s. Mitra *et al.* [3] recorded experimental measurements on processed meat and $\tau \approx 16$ s was obtained. However, Roetzel *et al.* found the value of τ_q to be closer to 1.77 s [72].

Estimation on in vivo characteristic time can possibly be realized through observing the temperature delay (or jump) inside the tissue heated by an external power [3], however, this warrants further investigation. A detailed development of the concept of transmission of heat by waves is reviewed and interpreted in [73] and [74]. This heat flux relaxation (or dampening) postulates the temperature gradient established at position $\vec{r}$ at time t gives rise to a heat flux vector at a later time $t + \tau_q$. This time-shift τ_q is called a phase-lag parameter and has been interpreted from different points of view which can be summarized as [23]:

- From the framework of the second law of irreversible thermodynamics [64].
- τ_q comes from the phase-lag shift between the heat flux vector and the temperature gradient in high-rate responses.
- τ_q is a constant representative for the interaction of different inner structural elements of a material with heat flux [68] and may take large values within the range ($10^{-3} - 10^3$ s) [75].

Fabrizio and Franchi investigated the thermodynamic compatibility of this constitutive equation (20) for a rigid medium. They found that while this constitutive equation is generally not in agreement with the laws of thermodynamics, compatibility of the first-order Taylor expansion of the single-phase lag equation was demonstrated [76]. Furthermore, some researchers have pointed out some physical defects of the hyperbolic heat conduction equation [77]. More specifically, Korner *et al.* showed the hyperbolic heat conduction equation (with conduction term based on equation 19) predicts physically impossible solutions, particularly negative thermal energies [77].

Equation (19) can be solved using the integrating factor method to yield

$$q(\vec{r}, t) = q(\vec{r}, 0)e^{-t/\tau_q} - \frac{k}{\tau_q} e^{-\frac{t}{\tau_q}} \int_0^t e^{\frac{\xi}{\tau_q}} \nabla T(\vec{r}, \xi) d\xi. \quad (21)$$

Equation 21. Phase lag heat flux

This equation suggests the heat flux $q(\vec{r}, t)$ at time t depends on the entire history of the temperature gradient on the entire interval $[0, t]$ and motivates the use of fractional models as discussed in section 5. In other words, the heat flux can be thought of as having “memory” that keeps track of the time-history of the temperature gradient. The thermal wave theory shows a strong path dependency of the temperature gradient rather than the point value of ∇T at t depicted by Fourier’s

law [68], [78]. Alternatively, by applying the translation $t' = t + \tau_q$, equation 19 can be rewritten in the following “delayed” form:

$$q(\vec{r}, t) = -\kappa \nabla T(\vec{r}, t' - \tau_q), \quad t' > \tau_q. \quad (22)$$

Equation 22. Phase lag heat flux - delayed form

Equations (21) and (22) are the forward and backward forms of the single phase lag (SPL) model [76]. As mentioned, the first-order Taylor expansion is typically used and has been shown to be consistent with the second law of thermodynamics [76], [79], [80].

However, using higher order expansions of the heat flux is possible. For example, with the second-order Taylor expansion of (20), one has

$$q + \tau_q \frac{\partial q}{\partial t} + \frac{\tau_q^2}{2} \frac{\partial^2 q}{\partial t^2} + O(\tau_q) = -\kappa \nabla T. \quad (23)$$

Equation 23. Second order single phase lag

As briefly mentioned, the second-order Taylor expansion of the SPL model is not compatible with the second law of thermodynamics [76] and therefore will not be considered in this report.

Combining the simplified energy balance equation (10) and the Maxwell-Cattaneo equation (19) yields a hyperbolic heat equation. However, the method of applying this idea can yield slightly different results depending on how the phase lag is treated in the energy balance equation (10) [35].

In an effort to unify the theory for heat conduction, Tzou [29] adapted the relaxation concept hypothesized by [58] and [60] to attempt to answer the following question: Is it possible to provide a *macroscopic* description that can also capture the *microscopic* effect of phonon-electron interactions? Tzou proposed to lump the microstructural effects into the delayed response in *time* in the macroscopic formulation. A macroscopic lagging response between the temperature gradient and the heat flux vector was proposed to account for phonon-electron interactions which dominate the short-time heat transfer before diffusion occurs [29]. Mathematically, this was expressed as

$$\vec{q}(\vec{r}, t + \tau_q) = -k \nabla T(\vec{r}, t + \tau_T), \quad (24)$$

Equation 24. Dual phase lag flux

where τ_q is the phase lag time for the heat flux vector, and τ_T is the phase lag time for the temperature gradient. This model introduces a phase lag of heat flux which is the time delay due to the fast transient effect of thermal inertia and it is believed to be suitable for high flux heating over very small time scales.

The equation shows that the temperature gradient established across a material volume located at a position $\vec{r}$ at time $t + \tau_T$ results in a heat flux to flow at a different instant of time $t + \tau_q$. The phase

lags τ_q and τ_T are both positive and assumed to be intrinsic properties of the medium. It should be noted equation (24) reduces to the single phase lag equation (20) by setting $\tau_T = 0$ and reduces to Fourier's law by also setting $\tau_q = 0$. The theory of this model is based on the cause-effect concept. That is, the quantity with the higher relaxation time is the effect caused by another quantity. When $\tau_q < \tau_T$, heat flow initially occurs and subsequently causes the temperature gradient. On the other hand, when $\tau_q > \tau_T$, heat flow is induced by the temperature gradient established at an earlier time [81]. Also, if one considers the change of variable $t' = t + \tau_T$, the previous equation reduces to a single phase heat flux term, $\vec{q}(\vec{r}, t' + \tau_d) = -k\nabla T(\vec{r}, t')$, where $\tau_d = \tau_q - \tau_T$. Furthermore, if $\tau_q = \tau_T$, then the change of variables yields Fourier's law.

4.2.1. Thermal Wave Model for Bioheat Transfer (TWMBT)

To motivate the development of the Thermal Wave Model (TWMBT), one must first consider the simplified energy balance equation (10). With equation (19), we get (a 1-dimensional) hyperbolic version of Pennes' model [82] where both the blood perfusion term and the metabolic heat source are not affected by the thermal relaxation:

$$\tau_q \frac{\partial^2 T}{\partial t^2} + \left(1 + \omega_b \frac{\rho_b c_b}{\rho_t c_t}\right) \frac{\partial T}{\partial t} + \omega_b \frac{\rho_b c_b}{\rho_t c_t} (T_t - T_b) = a \frac{\partial^2 T}{\partial x^2} + \frac{q_m}{\rho_t c_t}. \quad (25)$$

Equation 25. Hyperbolic bioheat model

Based on equation (19) for the heat flux including the characteristic time τ_q as well as the general bioheat equation, a general form of the thermal wave model of bioheat transfer (TWMBT) in living tissues was initially introduced by Liu *et al.* [83]:

$$\begin{aligned} \nabla \cdot [\kappa \nabla T(\vec{r}, t)] + \omega_b c_b (T_b - T) + q_m + q_s + \tau_q \left(-\omega_b c_b \frac{\partial T}{\partial t} + \frac{\partial q_m}{\partial t} + \frac{\partial q_s}{\partial t} \right) \\ = \rho c \left[\tau_q \frac{\partial^2 T}{\partial t^2} + \frac{\partial T}{\partial t} \right], \end{aligned} \quad (26)$$

Equation 26. Thermal wave model for bioheat transfer (TWMBT)

where T_b, ρ, c , and κ are the same as above. c_b is the specific heat of blood and ω_b is the blood perfusion rate, and q_m and q_s are volumetric heat due to metabolism and spatial heating, respectively. As previously mentioned, the main assumption is the heat flux and temperature gradient occur at different moments for a specific position. Since τ_q is speculated to be within 16 – 30 s in biological materials, for short heating with its duration comparable to this value, the TWMBT (which accounts for finite speed of heat propagation) could provide more realistic predictions than that from the traditional Pennes' bioheat equation.

Mitra *et al.* [3] conducted experiments on processed meat (bologna) to find the corresponding thermal characteristic time, which was found to be $\tau = 16$ s. The experiments demonstrated wave behavior (including superposition phenomenon) in the conduction mechanism of processed meat and are often cited as motivation for considering non-Fourier heat flux. In [30], the one-dimensional TWMBT in a finite medium was solved using separation of variables. A finite

difference method was then used to simulate practical problems involved in burn injuries in which skin was stratified as three layers with various thermal physical properties. The authors compared the thermal wave model to Pennes' equation and deduced the magnitude of the characteristic time had an important effect on the temperature prediction and, hence, burn evaluation. They concluded if the change rate of heat flux is very high, consideration of the thermal wave effect was necessary. Comparison between the Pennes' bioheat equation and the TWMBT equation showed that, at the initial stage, the Pennes' equation gives higher predictions (due to infinite speed of heat propagation). Since the TWMBT equation accounts for heat propagation in living tissues at a finite speed, a period of time is needed for the surface heating to travel to a particular point inside the body. When the surface heat flux becomes zero (after a short heating period) the elevated tissue temperature from Pennes' equation quickly decreases while a time lag exists for the disappearance of heat flow from the TWMBT equation. Ma et al. [84] analyzed the non-Fourier effect of laser irradiation in human skin and found similar results. They concluded the rates of temperature rise at different depths of skin were comparatively slow due to the non-Fourier effect. Ozen et al. [2] conducted a thermal analysis of biological tissues exposed to microwaves using the TWMBT and also conducted a comparative study on the traditional Pennes' equation. The authors concluded the TWMBT equation initially gives a lower heat rise prediction than that of Pennes' equation, but it overlaps with Pennes' equation when it approaches to steady state. A comparison of the TWMBT with the traditional Pennes' equation and experimental data is discussed in section 7.

4.2.2. Dual Phase Lag

In 2008, Xu et al. [85] applied the Dual-Phase-Lag (DPL) model to study bioheat transfer in skin tissue. They proposed three DPL models for bioheat, two of which are included below.

- **Type 1 DPL Model of Bioheat Transfer (DPL1MBT)**

Using the first order expansions for both q and T ,

$$q(\vec{r}, t) + \tau_q \frac{\partial q(\vec{r}, t)}{\partial t} = -k \left[\nabla T(\vec{r}, t) + \tau_T \frac{\partial \nabla T(\vec{r}, t)}{\partial t} \right]. \quad (27)$$

Equation 27. Type 1 DPL flux approximation

Then, substituting the bioheat conduction equation (4) into this equation, one obtains the so-called Type 1 DPL model of bioheat transfer:

$$\begin{aligned} \tau_q \rho c \frac{\partial^2 T}{\partial t^2} = & k \nabla^2 T + \tau_T \kappa \nabla^2 \frac{\partial T}{\partial t} - \omega \rho_b c_b T - (\tau_q \omega \rho_b c_b + \rho c) \frac{\partial T}{\partial t} \\ & + \left(\omega \rho_b c_b T_b + q_m + q_s + \tau_q \frac{\partial q_m}{\partial t} + \tau_q \frac{\partial q_s}{\partial t} \right). \end{aligned}$$

Equation 28. Type 1 DPL bioheat model

Antaki [86] pointed out the DPL model combines the wave features of hyperbolic conduction with a diffusion-like feature not captured by the hyperbolic case.

- **Type 2 DPL Model of Bioheat Trasfer (DPL2MBT)**

Applying first-order and second-order Taylor series expansion for q and T respectively, one has

$$q + \tau_q \frac{\partial q}{\partial t} = -k \left[\nabla T + \tau_T \frac{\partial \nabla T}{\partial t} + \frac{\tau_T^2}{2} \frac{\partial^2 \nabla T}{\partial t^2} \right]. \quad (29)$$

Equation 29. Type 2 DPL flux approximation

Using the bioheat conduction equation (4) as before:

$$\begin{aligned} \tau_q \rho c \frac{\partial^2 T}{\partial t^2} = & k \nabla^2 T + \tau_T \kappa \nabla^2 \frac{\partial T}{\partial t} + \kappa \frac{\tau_T^2}{2} \frac{\partial^2}{\partial t^2} \nabla^2 T - \omega \rho_b c_b T - (\tau_q \omega \rho_b c_b + \rho c) \frac{\partial T}{\partial t} \\ & + \left(\omega \rho_b c_b T_b + q_m + q_s + \tau_q \frac{\partial q_m}{\partial t} + \tau_q \frac{\partial q_s}{\partial t} \right). \end{aligned} \quad (30)$$

Equation 30. Type 2 DPL bioheat model

It should be mentioned the main idea of the DPL approach is to capture dampening and heat wave behavior, which is also the main idea in fractional bioheat models (see section 5).

Xu et al. [85] compared predictions of temperatures from five different models, including the classical Pennes' equation, the TWMBT, DPL1MBT, and DPL2MBT. Other types of DPL models were investigated, but are omitted from this technical report because the TWMBT is the primary phase lag model being investigated. In each case, $\tau_q = 10$ s and $\tau_T = 10$ s were used. Their study assumed skin is initially under the influence of environmental air ($T_e = 25^\circ\text{C}$) and at $t = 0$, the skin surface is placed in contact with a heat source of constant temperature at 100°C . Then the skin is cooled by use of water ice mixture at 0°C for 30 s. They compared predictions at the epidermis-dermis interface, as well as the dermis-fat interface, and distributions along skin depth for different moments in time. The results demonstrated the various models could deviate substantially under constant surface temperature heating. The DPL models systematically predicted lower temperature increases when compared to TWMBT and the classical Pennes' equation. With the TWMBT, the tissue temperature inside the body was undisturbed during the initial heating, before suddenly increasing. This can be viewed as the wave front emerging from the assumption of finite propagation, or the existence of τ_q . Unlike the TWMBT, no wave behavior is observed in the DPL models, but a non-Fourier diffusion-like behavior exists due to the second thermal relaxation time τ_T . The effect of τ_T is to weaken the thermal wave, thereby destroying the sharp wave front. A sudden temperature drop for heating or a step for cooling was noted by the authors and it was remarked that this is associated with DPL models [85]. The results showed the damage distribution along the skin depth was comparable for the classical Pennes' equation and the TWMBT, which was much larger in magnitude than those observed by DPL models.

As is expected, implementing DPL models of any type requires more complex methods. Depending on boundary conditions, solutions can be found using a Laplace transform technique where the inversion is evaluated using the Stehfest algorithm, a finite element Legendre wavelet Galerkin method (FELWGM) [87], and numerical methods based on finite difference and Runge-Kutta (4,5) schemes [88].

Furthermore, the connection between DPL models and the TWMBT is clear and a better understanding of the latter could potentially provide a better framework for understanding DPL models. For these reasons, no DPL numerical model simulations were completed as part of this technical report.

5.0 FRACTIONAL CALCULUS MODELING APPROACH

Fractional calculus has been used to improve model accuracy of many phenomena in natural science and fractional differential equations have shown promise in simulating the dynamics of anomalous processes whose analytical representations are continuous but strongly not differentiable (such as Weierstrass-type functions) [89]. This makes it possible to create new models for phenomena which traditional differential models cannot accurately represent. Specifically, nonlocal operators allow for an evolution of the system states which simultaneously depends on the system's current and prior states. However, nonlocal models are varied in their approach. For this reason, only the three models discussed in [6], [70], and [90] will be discussed in this section and one model [6] will be numerically tested for proof of concept in this technical report. For the sake of completeness, the principle directions in the formalization of fractional calculus heat conduction models are overviewed as follows:

1. Application of fractional Taylor series expansions concerning three primary examples:
 - (a) Heat flux dampening by application of the fractional first order Taylor series approximation (these models will be the primary focus of this section.)
 - (b) Both heat flux and thermal gradient dampening (usually) by application of the fractional first order Taylor series approximation.
 - (c) Thermal gradient damping (in a viscoelastic manner) by application of time-fractional derivatives.
2. The fading memory concept relates the flux $j(x, t)$ to its gradient using the Boltzmann linear superposition functional to express the flux history [91] through the influence of the memory kernel R . In the following equations, D_0 and D' are transport coefficients and $C(x, t)$ is a causal function (which vanishes for $t < 0$). Two popular uses of this concept in the bioheat application are:
 - (a) For simple fading memory (SFM) the heat flux is represented as

$$\nabla \cdot j(x, t) = -D' \int_0^t R(t - \tau) \Delta C(x, \tau) d\tau. \quad (31)$$

Equation 31. Simple fading memory concept

- (b) For extended fading memory (EFM) the heat flux is represented as

$$\nabla \cdot j(x, t) = -D_0 \nabla C(x, t) - D' \int_0^t R(t - \tau) \Delta C(x, \tau) d\tau. \quad (32)$$

Equation 32. Extended fading memory concept

Note that equation (31) comes from equation (32) for $D_0 = 0$.

As previously mentioned, Cattaneo [58] addressed the concern of a finite speed of heat diffusion by generalizing Fourier law. That is, considering a linear superposition of the heat flux and time history (with time-delay, s , by a “memory”, or “hereditary”, integral) or

$$q(x, t) = - \int_0^t R(x, t-s) \frac{\partial}{\partial x} T(x, s) ds. \quad (33)$$

Equation 33. General heat flux with fading memory

With this perspective, the main question then becomes: What function $R(x, t)$ is a suitable memory kernel? $R(x, t)$ depends on the response of the material and careful consideration of the physics is necessary. A sample of memory kernels that have been investigated in the literature is discussed below. For the sake of completeness, it should be mentioned the representation of flux in (33) is nothing more than a convolution integral. If $R(x, t)$ is assumed to be the Dirac delta function δ , where $\lim_{t \rightarrow 0^+} \int_0^t \delta(s) ds = \int_0^t \delta(s) ds = 1$, this immediately leads to the classical diffusion equation. This makes intuitive sense given there is no damping effect in the flux propagation in the Fourier model.

Fractional Taylor series techniques could be extended to considering space-fractional models, but this requires careful consideration of the non-homogeneity of the tissue and physical motivation. For convenience, basic definitions for common fractional operators are provided in Appendix A.

5.1 Fading Memory Concept

Various kernels have been the subject of investigation in literature and in this section, some examples currently being implemented in bioheat models are highlighted. For example, for homogeneous rigid heat conductors the memory function $R(x, t)$ is space-independent and has been represented by the Jeffrey kernel [73], [92] as

$$R(x, t) = e^{-t/\tau}, \quad (34)$$

Equation 34. Exponential kernel

where the relaxation time τ is a constant. To connect the fading memory concept to the Thermal Wave Model (26), one should note that with an exponential memory kernel (34), sometimes referred to as the Cattaneo kernel or the Jeffrey’s kernel, the energy balance equation yields the Cattaneo equation:

$$\frac{\partial T(x, t)}{\partial t} + \tau \frac{\partial}{\partial t} \left(\frac{\partial}{\partial t} \right) = a \frac{\partial}{\partial x} \left(\frac{\partial T(x, t)}{\partial x} \right). \quad (35)$$

Equation 35. Cattaneo equation

As $\tau \rightarrow 0$, the limit of the Cattaneo equation (35) gives the Fourier law [93]. Furthermore, this definition of $q(x, t)$ corresponds to the first order approximation of the modified Fourier law (as

discussed in Section 4.2) [93], [94] and continuing the integration and applying the energy balance law would yield the hyperbolic equation.

Joseph and Preziosi [73] considered a modified relaxation function consisting of two terms where the first term models the instantaneous (memory-less) reaction of the heat conductor and the second term captures the flux dampening effect and finite speed of propagation shown as

$$R_{JP}(x, t) = \kappa_1 \delta(t) + \frac{\kappa_2}{\tau} e^{-\frac{t}{\tau}}, \quad (36)$$

Equation 36. Joseph and Preziosi memory kernel

where κ_1 and κ_2 are the effective thermal conductivity and the elastic conductivity, respectively. Using this assumption in the conservation energy equation yields an integro-differential equation which contains both Fourier-like terms and non-Fourier terms [94]. The non-Fourier terms go to zero for large values of time since the memory function fades, however, the presence of the time variable in the second term is related to the assumption of finite heat flux speed [35]. This idea is an example of the extended fading memory concept using a simple exponential kernel.

To motivate the fractional model tested in this technical report 5.2.1, the fading memory concept with a simple power-law kernel is considered:

$$R(x, t) = \frac{t^{\alpha-1}}{\Gamma(\alpha)}, \quad 0 < \alpha < 1. \quad (37)$$

Equation 37. Simple power law kernel

Following this idea, Hristov noted some discrepancies in the constitutive equation proposed by Ferras' et al. [6], [35] and cautions readers further investigation is needed to apply these techniques in the specific case of bioheat models. However, adapting the approach of Joseph and Preziosi [73], Hristov proposed the following extended kernel:

$$R_{EPL}(x, t) = \kappa_1 \delta(t) + \kappa_2 \frac{t^{\alpha-1}}{\Gamma(\alpha)}, \quad 0 < \alpha < 1. \quad (38)$$

Equation 38. Extended power law kernel

Similar to (36), use of the extended power law kernel yields an integro-differential equation whose second term represents the Riemann-Liouville fractional integral [95] which is defined in the next section. This observation coincides with results obtained by the extended fading memory concept and simple power-law kernel [35].

5.2 Existing Fractional Models

Ezzat et al. [70] considered the non-Fourier construction of the heat flux in (19) or $q(\vec{r}, t + \tau_q) = -\kappa \nabla T(\vec{r}, t)$. As previously mentioned, the nonlocal time dependence between the heat flux vector and the temperature gradient with a memory kernel can be interpreted in terms of the fractional

calculus, but for the purpose of motivating the fractional order model tested in this technical report, the discussion in this section will reflect the treatment in [70].

Recall that a first order Taylor series approximation is used in the hyperbolic heat conduction equation (25) and Ezzat et al. used this idea to apply a fractional Taylor series expansion (of order α) with a modified Riemann-Liouville Junmmarie derivative [96]. More specifically, the modified heat-flux term proposed by Ezzat [70]

$$q + \frac{\tau^\alpha}{\Gamma(\alpha+1)} \frac{\partial^\alpha q}{\partial t^\alpha} = -\kappa \nabla T(\vec{r}, t), \quad 0 < \alpha \leq 1, \quad (39)$$

Equation 39. Fractional order heat flux

where

$$\frac{\partial^\alpha}{\partial t^\alpha} f(y, t) = \begin{cases} f(y, t) - f(y, 0), & \alpha \rightarrow 0 \\ I^{\alpha-1} \left[\frac{\partial f(y, t)}{\partial t} \right], & 0 < \alpha < 1 \\ \frac{\partial f(y, t)}{\partial t}, & \alpha = 1 \end{cases}$$

and I^α represents the Riemann–Liouville fractional integral (see equation (A-4)). As α tends to one, equation (39) reduces to Vernott-Cattaneo equation (19).

Considering the general bioheat equation (4) with no source term and taking the partial time derivative of fractional order α gives

$$\rho c \frac{\partial}{\partial t} \left(\frac{\partial^\alpha T}{\partial t^\alpha} \right) = -\kappa \nabla \left(\frac{\partial^\alpha q}{\partial t^\alpha} + \frac{\partial^\alpha Q}{\partial t^\alpha} \right), \quad 0 < \alpha \leq 1, \quad (40)$$

Equation 40. Fractional Time Derivative in bioheat Equation

where the source term $Q(\vec{r}, t) = \omega \rho_b c_b (T_b - T) + q_m$. Multiplying equation (40) by $\frac{\tau^\alpha}{\Gamma(\alpha+1)}$ and adding to equation (4) yields

$$\rho c \frac{\partial}{\partial t} \left(T + \frac{\tau^\alpha}{\Gamma(\alpha+1)} \frac{\partial^\alpha T}{\partial t^\alpha} \right) = \kappa \nabla^2 T + \left(Q + \frac{\tau^\alpha}{\Gamma(\alpha+1)} \frac{\partial^\alpha Q}{\partial t^\alpha} \right), \quad 0 < \alpha < 1, \quad (41)$$

Equation 41. Ezzat et al. fractional order model

where equation (39) was used to substitute the heat-flux term. This equation also inherits the assumption of Wulff’s model, i.e. that the reference temperature is equal to the arterial blood temperature. It should also be noted the pre-factor $\frac{\tau^\alpha}{\Gamma(\alpha+1)}$ on both sides of the equation is necessary for the model to be dimensionally consistent, but the explanation of why these pre-factors exist and what exactly they model are questions that remain largely unanswered. A counter point to this notion is that models based on Pennes’ equation use dynamic optical and thermal properties that

rely on available measurements. This often fails to account for physical changes in the material (such as volume, mass, and density). Carefully introduced parameters with proper motivation could be useful in accounting for the variability in tissue properties that occurs in heating applications.

In the context of fractional models, the model of Damor et al. [97] is also worth mentioning. This fractional order bioheat equation employs a Caputo derivative of order $\alpha \in (0, 1)$ with a power-law type kernel and a spatial Riesz-Feller fractional derivative of order $\beta \in (0, 2]$ which appears as

$$\rho c \frac{\partial^\alpha T}{\partial t^\alpha} = \kappa \frac{\partial^\beta T}{\partial x^\beta} + \omega \rho_b c_b (T_b - T) + q_m. \quad (42)$$

Equation 42. Damor et al. fractional order model

Since the Riesz-Feller fractional derivative is not a main focus of this report, the reader is referred to [97] for further information. Damor et al. also considered the case where $\alpha = 1$ and a Riemann-Liouville space derivative of order $\gamma \in (0, 2]$ was employed [98]. Damor et al. [97] used Laplace and Fourier transforms to obtain solutions to their model for particular cases. The authors also presented a method for the numerical solution of these equations, but did not provide proof of convergence or stability [90].

5.2.1. Fractional Pennes' Model by Ferras et al.

Ferras et al. [6] adapted Pennes' equation using a fractional order time derivative producing

$$\frac{\partial^\alpha T(x, t)}{\partial t^\alpha} = A \frac{\partial}{\partial x} \left(\kappa(x) \frac{\partial T(x, t)}{\partial x} \right) - BT(x, t) + C, \quad 0 < t < T^*, \quad 0 < x < L. \quad (43)$$

Equation 43. Ferras et al. bioheat model

In this case, $\frac{\partial^\alpha}{\partial t^\alpha}$ denotes the Caputo derivative (A-5) of order $0 < \alpha < 1$, and $A = \frac{1}{\rho c \tau^{\alpha-1}}$, $B = \frac{\omega \rho_b c_b}{\rho c \tau^{\alpha-1}}$, and $C = \frac{\omega \rho_b c_b T_b + q_m}{\rho c \tau^{\alpha-1}}$.

Ferras et al. noted the model (42) proposed in [90] by Damor et al. is not dimensionally consistent and the parameter $\tau[s]$ is introduced to overcome this obstacle.

In the context of fading memory, Ferras et al. assumed a memory kernel of power-law type which is equivalent to saying the heat flux is proportional to a Riemann-Liouville derivative of the temperature gradient. In this case, the nonlocality of the heat flux is expressed as a convolution integral [99]:

$$q = -\kappa \int_0^\infty R(t - \tau) \nabla T(x, \tau) d\tau. \quad (44)$$

Equation 44. Gurtin and Pipkin heat flux

Then Ferras et al. [6] obtain the following heat conduction equation with memory:

$$\frac{\partial T(x,t)}{\partial t} = a \int_0^t R(t-\tau) \Delta T(x,\tau) d\tau. \quad (45)$$

Equation 45. Ferras et al. heat conduction equation A

As observed by Hristov [35], equation (45) is incomplete because following the treatment of the fading memory approach by Gurtin and Pipkin [99] causes the right-hand side of this equation to represent only the elastic part of heat flux [73]. In this case, the heat flux is expressed as a Riemann-Liouville derivative (A-4) that leads to the time-fractional diffusion equation. However, with this assumption, Ferras et al. employed a power-law type memory kernel that results in an equation that is relatively simple to numerically implement and could provide valuable insight to understanding more complete fractional order models. More specifically, if the assumption that the dependence between the heat flux vector and the temperature gradient is given by a power-law type kernel yields

$$q = -\frac{\kappa}{\Gamma(\alpha)} \frac{\partial}{\partial t} \int_0^\infty (t-\tau)^{\alpha-1} \nabla T(x,\tau) d\tau, \quad 0 < \alpha \leq 1, \quad (46)$$

Equation 46. Ferras et al. heat flux equation

then the heat conduction equation becomes

$$\frac{\partial^\alpha T(x,t)}{\partial t^\alpha} = a \frac{\partial}{\partial x} \left(\frac{\partial T(x,t)}{\partial x} \right), \quad (47)$$

Equation 47. Ferras et al. heat conduction equation B

where a is the thermal diffusivity coefficient of suitable dimension [100]–[102]. As previously mentioned, choosing an exponential kernel yields the standard Cattaneo equation (35) [58], which is the simplest equation admitting finite speed of flux propagation and a root assumption in the TWMBT. The introduction of the parameter $\tau[s]$ in equation (43) requires careful investigation into what values should be used for τ . Furthermore, Ferras et al. provide no physical meaning for τ . The authors claim equation (46) suggests a new relationship between heat flux and the temperature gradient and instead of changing the density or specific heat, it can be assumed the change is occurring in the thermal conductivity κ . The “new” thermal conductivity κ_α is given by $\frac{\kappa}{\tau^{\alpha-1}}$, as has been observed in other fractional order models [103].

The authors [6] provide a numerical method for solving the fractional order bioheat model which is described in section 6, and used a variety of approaches to validate their method. The method was tested against particular examples where analytical solutions are known (see [6] and [104]) and numerical results for variations in α , maximum absolute errors, and experimental orders of convergence were provided. The numerical method was shown to be robust and verify the expected theoretical results. Three case studies were also performed: (a) assuming the tissue is formed of only one layer, (b) assuming the tissue has three layers (the epidermis, dermis, and subcutaneous layer), and (c) using the parameter τ to fit the experimental data. The results show the temperature initially increases with α , but then the opposite behavior occurs after a certain time period. It was

concluded the parameter τ has a small influence on the temperature variation, which was expected in the context a small change in τ can be interpreted as small changes in the density and/or specific heat. However, the authors [6] note the influence of τ on the temperature variation is expected to increase for smaller values of α . In one example, Ferras et al. demonstrated exceptional agreement of their numerical results with an analytical solution derived in [104] of the classical bioheat model. Because the classical model assumes $\alpha = 1$, the value $\alpha = .999$ was used in this comparison.

Case study (c) used experimental data provided by Barcroft and Edholme [105]. The experiment consisted of measuring the temperature decrease of the subcutaneous tissue (1 cm below the skin surface) when a human forearm is submerged in a 12°C water bath. Numerical testing assumed a 1-D model and the fractional model (with $\tau^{\alpha-1} = 0.5248$ and $\alpha = 0.96$) showed greater agreement with the experimental data than the classical bioheat model ($\alpha = 1$) (see Figure 8b in [6]). This suggests the proposed fractional bioheat model could be used to improve the accuracy of thermal predictions.

As briefly mentioned, the choice of the parameters α and τ require further investigation for practical use. Ferras et al. [6] demonstrated that for fixed $\alpha = 0.999$, comparing values of τ equal to 0.5, 1, and 2 created negligible temperature variations ($< .04^\circ\text{C}$ difference). However, using the same values of τ and letting $\alpha = 0.5$ produced greater variation (a difference of $\approx 2^\circ\text{C}$ at $t = 2$ s) in the temperature profile. Ferras et al. also showed for the fixed value of $\tau = 1$ s, varying α between the values 0.5, 0.8, and 0.999 showed significant changes in the temperature profile by changing the concavity of the graph.

6.0 NUMERICAL METHODS

This section presents a brief overview of the numerical methods used to simulate both the TWMBT (26) and the fractional Pennes' equation (43). Since the standard methods for solving hyperbolic equations are more widely known, the analysis begins with the TWMBT which uses the classical finite difference method. The goal is to contrast these equations with the classical Pennes' equation by generating analogous comparisons to figures 4 (a) and (b) in [24].

6.1 Thermal Wave Model for Bioheat Transfer (TWMBT)

The divergence of the gradient term in equation (26) in two dimensional cylindrical coordinates is represented as

$$\begin{aligned} \nabla \cdot (\kappa \nabla T(r, z, t)) &= \frac{1}{r} \frac{\partial}{\partial r} \left(\kappa r \frac{\partial T}{\partial r} \right) + \frac{\partial}{\partial z} \left(\kappa \frac{\partial T}{\partial z} \right) \\ &\approx \kappa_z \left(\frac{T_{r+1,z}^{l-1} - 2T_{r,z}^{l-1} + T_{r-1,z}^{l-1}}{(\Delta r)^2} \right) + \frac{\kappa_z}{r} \left(\frac{T_{r,z}^{l-1} - T_{r-1,z}^{l-1}}{\Delta r} \right) \\ &\quad + \kappa_z \left(\frac{T_{r,z+1}^{l-1} - 2T_{r,z}^{l-1} + T_{r,z-1}^{l-1}}{(\Delta z)^2} \right) + \left(\frac{\kappa_z - \kappa_{z-1}}{\Delta z} \right) \left(\frac{T_{r,z}^{l-1} - T_{r,z-1}^{l-1}}{\Delta z} \right), \end{aligned} \quad (48)$$

Equation 48. 2-D cylindrical coordinate representation of $\nabla(\kappa \nabla T)$

where κ is treated as a function of the depth z to accommodate for the thermal properties of different layers of skin. In the equation above, the usual notation is adopted where κ_z represents the heat conductivity at depth node z , and $T_{r,z}^{l-1}$ represents the temperature at node $(r, z, l-1)$. The discretized version of the TWMBT is thus written as

$$\begin{aligned}
& \rho c \left(\tau_q \frac{T_{r,z}^l - 2T_{r,z}^{l-1} + T_{r,z}^{l-2}}{(\Delta t)^2} + \frac{T_{r,z}^l - T_{r,z}^{l-1}}{\Delta t} \right) \\
&= \kappa_z \left(\frac{T_{r+1,z}^{l-1} - 2T_{r,z}^{l-1} + T_{r-1,z}^{l-1}}{(\Delta r)^2} \right) + \frac{\kappa_z}{r} \left(\frac{T_{r,z}^{l-1} - T_{r-1,z}^{l-1}}{\Delta r} \right) \\
&+ \kappa_z \left(\frac{T_{r,z+1}^{l-1} - 2T_{r,z}^{l-1} + T_{r,z-1}^{l-1}}{(\Delta z)^2} \right) + \left(\frac{\kappa_z - \kappa_{z-1}}{\Delta z} \right) \left(\frac{T_{r,z}^{l-1} - T_{r,z-1}^{l-1}}{\Delta z} \right) \\
&+ \omega_b c_b (T_b - T_{r,z}^{l-1}) + q_m + q_s + \tau_q \left(\omega_b c_b \frac{T_{r,z}^{l-1}}{\Delta t} + \frac{q_m^l - q_m^{l-1}}{\Delta t} + \frac{q_s^l - q_s^{l-1}}{\Delta t} \right).
\end{aligned} \tag{49}$$

Equation 49. Discrete TWMBT equation

To best match the boundary conditions in [24], radiative, convective, and evaporative boundary conditions are imposed as follows:

$$\kappa_z \frac{\partial T}{\partial z} \Big|_{z=0} = -h_{conv}(T_{r,0} - T_\infty), \tag{50}$$

Equation 50. Convective boundary condition

where h_{conv} (W/m²K) is the convective heat transfer coefficient and T_∞ is the air temperature.

$$\kappa_z \frac{\partial T}{\partial z} \Big|_{z=0} = \sigma \varepsilon (T_{r,0}^4 - T_\infty^4) \tag{51}$$

Equation 51. Radiative boundary condition

where σ is the Stefan-Boltzmann constant W/m²K⁴ and ε is the unitless surface emissivity.

$$\kappa_z \frac{\partial T}{\partial z} \Big|_{z=0} = -h_{evap}(p_{sat}(T_{r,0}) - p_{sat}(T_\infty)) \tag{52}$$

Equation 52. Evaporative boundary condition

where h_{evap} is the evaporative heat transfer coefficient (W/m²Pa) and $p_{sat}(T)$ is the temperature-dependent saturation pressure of water vapor. At the boundary, $z = z_{max}$ and $r = r_{max}$. The temperature is assumed to be set to body temperature $T_b = 37^\circ\text{C}$. The axial temperature can be found by solving the one-dimensional TWMBT:

$$\begin{aligned}
T_{0,z}^l = & \left(\frac{(\Delta t)^2}{\tau_q \rho c + \Delta t (\rho c + \tau_q \omega_b c_b)} \right) \left[\rho c \left(\tau_q \frac{2T_{0,z}^{l-1}}{(\Delta t)^2} + \frac{T_{0,z}^{l-1}}{\Delta t} - \tau_q \frac{T_{0,z}^{l-2}}{(\Delta t)^2} \right) \right. \\
& + \kappa_z \left(\frac{T_{0,z+1}^{l-1} - 2T_{0,z}^{l-1} + T_{0,z-1}^{l-1}}{(\Delta z)^2} \right) + \left(\frac{\kappa_z - \kappa_{z-1}}{\Delta z} \right) \left(\frac{T_{0,z}^{l-1} - T_{0,z-1}^{l-1}}{\Delta z} \right) \\
& \left. + \omega_b c_b (T_b - T_{0,z}^{l-1}) + q_m + q_s + \tau_q \left(\omega_b c_b \frac{T_{0,z}^{l-1}}{\Delta t} + \frac{q_m^l - q_m^{l-1}}{\Delta t} + \frac{q_s^l - q_s^{l-1}}{\Delta t} \right) \right].
\end{aligned} \tag{53}$$

Equation 53. Localized axial temperature (TWMBT)

6.2 Fractional Pennes' Model

The numerical method for obtaining an approximate solution of (43) described by Ferras et al. [6] is outlined below. Note the original equation assumes no heat source, so some modifications will be noted below so the method can be adapted for testing purposes. The equation with the addition of the heat source q_s appears as:

$$\frac{\partial^\alpha T(x,t)}{\partial t^\alpha} = A \frac{\partial}{\partial x} \left(\kappa(x) \frac{\partial T(x,t)}{\partial x} \right) - BT(x,t) + C, \quad 0 < t < T^*, \quad 0 < x < L, \tag{54}$$

Equation 54. Modified Ferras et al. bioheat model

where $\frac{\partial^\alpha}{\partial t^\alpha}$ again denotes the Caputo derivative (A-5) of order $0 < \alpha < 1$, and $A = \frac{1}{\rho c \tau^{\alpha-1}}$, $B = \frac{\omega \rho_b c_b}{\rho c \tau^{\alpha-1}}$, and our modified term $C = \frac{\omega \rho_b c_b T_b + q_m + q_s}{\rho c \tau^{\alpha-1}}$.

Meshes of uniform space and time are applied on the interval $[0, L]$ defined by grid points $x_i = i\Delta x$ for $i = 0, 1, \dots, N$ with $\Delta x = \frac{L}{N}$. The time mesh uses a step size $\Delta t = \frac{T^*}{R}$, where T^* represents the entire time interval, and grid points $t_l = l\Delta t$ for $l = 0, 1, \dots, R$. The spatial derivative is then approximated using a second order finite difference:

$$\begin{aligned}
\frac{\partial}{\partial x} \left(\kappa(x) \frac{\partial T(x,t)}{\partial x} \right) \Big|_{x=x_i} = & \frac{\kappa(x_i + \frac{\Delta x}{2})T(x_{i+1},t) - (\kappa(x_i + \frac{\Delta x}{2}) + \kappa(x_i - \frac{\Delta x}{2}))T(x_i,t) + \kappa(x_i - \frac{\Delta x}{2})T(x_{i-1},t)}{(\Delta x)^2} \\
& + \mathcal{O}((\Delta x)^2).
\end{aligned} \tag{55}$$

Equation 55. Spatial derivative approximation

Using the backwards finite difference formula [95]

$$\frac{\partial^\alpha T(x, t)}{\partial t^\alpha} = \frac{(\Delta t)^{-\alpha_j}}{\Gamma(1 - \alpha_j)} \sum_{m=0}^l a_{m,l}^{(\alpha)} (T(x_i, t_{l-m}) - T(x_i, 0)) + \mathcal{O}((\Delta t)^{2-\alpha}), \quad (56a)$$

$$\text{where} \quad a_{m,l}^{(\alpha)} \begin{cases} 1, & m=0 \\ (m+1)^{1-\alpha} - 2m^{1-\alpha} + (m-1)^{1-\alpha}, & 0 < m < l \\ (1-\alpha)l^{-\alpha} - l^{1-\alpha} + (l-1)^{1-\alpha}, & m=l \end{cases}. \quad (56b)$$

Equation 56. Time derivative approximation

Here, $a_{m,l}^{(\alpha)}$ are such that $a_{m,l}^{(\alpha)} < 0$ for $1 < m < l-1$ and $\sum_{m=0}^l a_{m,l}^{(\alpha)} > 0$ for $l > 0$. For notation purposes, denote $T(x_i, t_l)$ by T_i^l and $k(x_i \pm \frac{\Delta x}{2})$ by $k_{i \pm \frac{1}{2}}$. $\mathbf{T}^l$ will represent the column vector with entries T_i^l .

Considering suitable boundary conditions (Dirichlet or Neumann), equation (54) can be presented as a system of equations [6]. Assuming a time at level l , with knowledge of the historical temperature field, the system of equations can then be written in matrix form as done in [6]:

$$(\mathbf{I} - \Lambda \mathbf{M}) \mathbf{T}^l = - \sum_{m=1}^{l-1} [a_{m,l}^{(\alpha)} \mathbf{T}^{l-m}] + \mathbf{T}^0 + \mathbf{T}^0 \sum_{m=1}^{l-1} a_{m,l}^{(\alpha)} + \Lambda \mathbf{S}^l,$$

where

$$\mathbf{M} = \begin{bmatrix} \varphi_1(-1, 1/3)D-B & \varphi_1(1, -1/3)D & 0 & 0 & \dots & 0 & 0 & 0 \\ \varphi_2(0, 1)D & -\varphi_2(1, 1)D-B & \varphi_2(1, 0)D & 0 & \dots & 0 & 0 & 0 \\ \vdots & \ddots & \ddots & \dots & \dots & \dots & \ddots & \vdots \\ \vdots & \ddots & \ddots & \varphi_i(0, 1)D & \varphi_i(1, 1)D-B & \varphi_i(1, 0)D & \dots & \vdots \\ \vdots & \ddots & \ddots & \ddots & \ddots & \ddots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \dots & 0 & \varphi_{N-1}(-1/3, 1)D & \varphi_{N-1}(1/3, -1)D-B \end{bmatrix}$$

and $\varphi_i(w_1, w_2) = w_1 k_{i+\frac{1}{2}} + w_2 k_{i-\frac{1}{2}}$.

Upon review, a few errors in the matrix $\mathbf{M}$ were identified in the literature [6] and are corrected in the representation above. From the form of $\mathbf{M}$ it is clear $(\mathbf{I} - \Lambda \mathbf{M})$ is a diagonally dominant matrix, and hence invertible. In other words, by applying the inverse of $(\mathbf{I} - \Lambda \mathbf{M})$, one can obtain a unique solution $\mathbf{T}^l$. For more information, including convergence and stability results, see [6].

7.0 RESULTS AND DISCUSSION

This section discusses the numerical results of comparisons between the previously mentioned equations (TWMBT and a fractional version of Pennes' equation) and the classical Pennes' equation. Data from [24] were used for comparison and model validation. These are single case examples where variations in physical properties have not been quantified by any formal uncertainty quantification approach. For this reason, further investigations of uncertainty

quantification are needed. The boundary condition parameters used in the numerical simulations are listed below.

Table 2. Boundary Condition Parameters

Parameter	Symbol	Units	Assumed Value
Room Temperature	T_{∞}	$^{\circ}\text{C}$	20
Emissivity	ε	-	0.98
Evaporative heat transfer coefficient	h_{evap}	$\text{W/m}^2\text{Pa}$	0.0974
Convective heat transfer coefficient	h_{conv}	$\text{W/m}^2\text{K}$	10

A summary of both layer-specific and nonlayer specific physical properties used in the numerical simulations are listed below.

Table 3. Tissue Layer Properties

Property	Units	Layer	Assumed Value
Thickness	mm	Epidermis	0.082
		Dermis	2.7
		Fat	15
Density, ρ	kg/m^3	Epidermis	1210
		Dermis	1060
		Fat	850
Specific heat, c	J/kg K	Epidermis	2244
		Dermis	3663
		Fat	2070
Thermal conductivity, κ	W/m K	Epidermis	0.20
		Dermis	0.49
		Fat	0.16
Blood perfusion rate, ω	s^{-1}	Epidermis	0
		Dermis	1.25×10^{-3}
		Fat	1.25×10^{-3}
Blood density, ρ_b	kg/m^3	-	1060
Blood specific heat, c_b	J/kg K	-	3770
Metabolic heat, q_m	W/m^3	-	368.1

7.1 Model Comparison: TWMBT vs. Classical Pennes' Biohead Model

The Scalable Effects Simulation Environment (SESE) performs time-dependent simulations of Pennes' bioheat equation in a three-dimensional spatial domain and models the physical effects of electromagnetic radiation on an inhomogeneous structure. This was the approach used by Delisi et al. [24] and will be used as a reference for comparison. Results from the SESE model and experimental thermal data [24] are shown in Figure 1 at the center of a beam for a 10 s single-pulse exposure at 3.11 W with a 0.973 cm beam diameter ($1/e^2$). All of the following graphs assume the measurement is being taken at the center of the beam. The TWMBT shown in Figure 1 assumed

a peak radiant exposure of 189 J/cm^2 , the threshold modeled by SESE, and $\alpha = 0.125$. It is important to note a value of $2244.0 \text{ J/kg}^\circ\text{C}$ is used for the heat capacity of the epidermis layer in order to match that being used in SESE, however, the value established in the literature is $3600 \text{ J/kg}^\circ\text{C}$. This could account for the small difference in peak temperature reached in the thermal wave model.

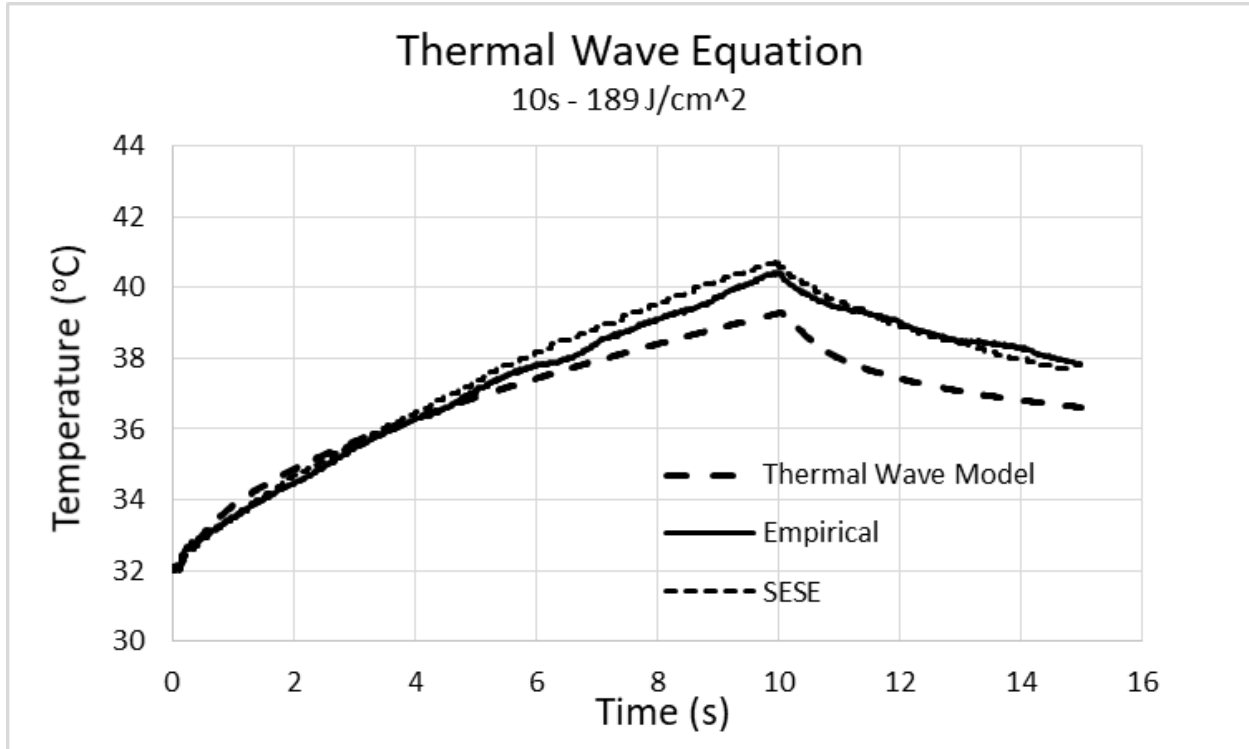


Figure 1. TWMBT vs. Pennes' 10s exposure model comparison

Results from the SESE model and experimental thermal data [24] are shown in Figure 2 for a 0.01s single-pulse exposure at 2780 W with a 1.04 cm beam diameter ($1/e^2$). The TWMBT shown in Figure 1 assumed peak radiant exposure 56.6 J/cm^2 and $\alpha = 0.000125$. However, it should be noted using the peak radiant exposure of a Gaussian beam to estimate the temperature rise predicts a rise of less than 10°C . To match empirical data, SESE's generated profile uses modified optical and thermal properties to approach the empirical trend which resulted in lower peak temperature. To obtain a curve comparison to the curves obtained by Delisi et al. [24], the parameter τ_q (or thermal relaxation time) was varied. As discussed above, the difference in peak temperature can be accounted for by the variations in tissue parameters. In this simulation, the SESE model predicts a higher peak temperature than the experimental data and fails to accurately capture the post exposure temperature profile.

The Thermal Wave Model (TWMBT) accounts for corrections to the energy storage density and the heat sources, while still maintaining the assumption that $T_b(\vec{r}, t)$ is a function of time. The traditional Pennes' bioheat equation assumes a constant arterial temperature to account for blood perfusion contribution as a heat source. The time-independent blood temperature assumption

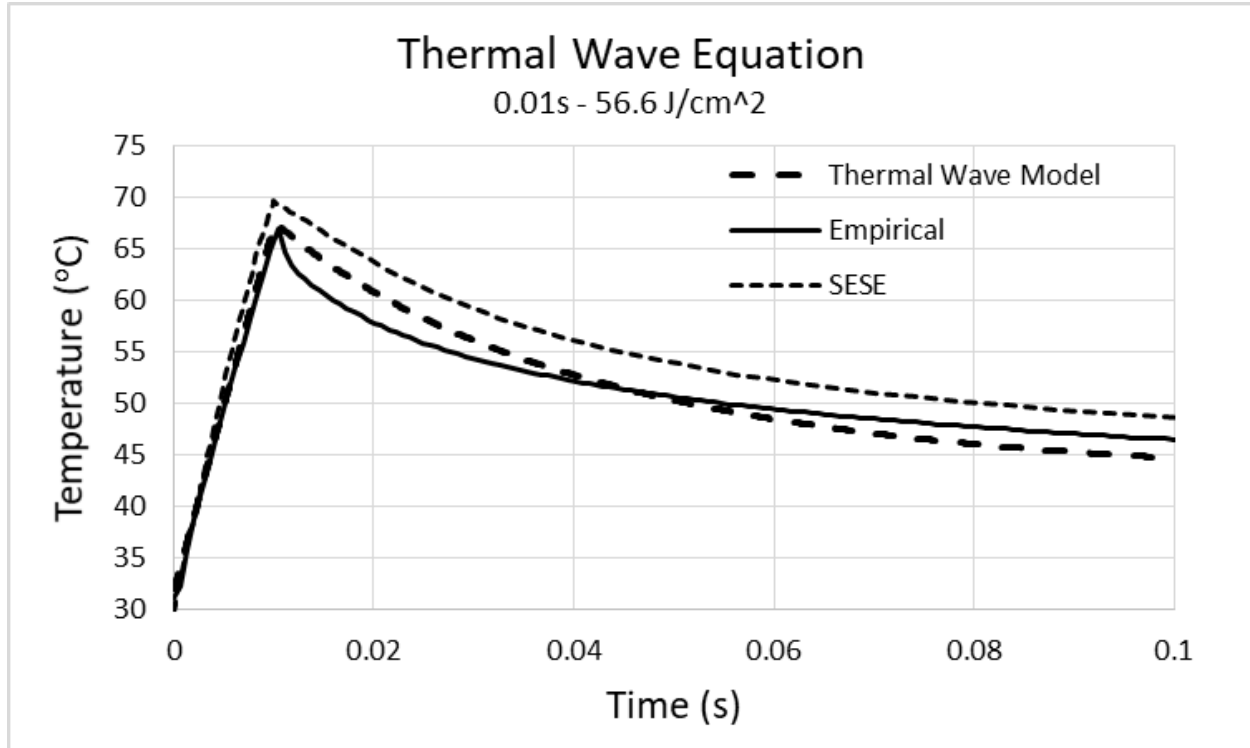


Figure 2. TWMBT vs. Pennes' .01s exposure model comparison

resulted in a zero rate of change in blood temperature, $\frac{\partial T_b}{\partial t}$, an assumption sustained in the Thermal Wave Model (TWMBT) approach. The effect of this assumption requires further investigation. Accounting for a dynamic external heat source (laser), $q_s(\vec{r}, t + \tau_q)$, mandates dynamic optical properties of the tissue. The use of static values for absorption and scattering result in underestimation or overestimation of the energy storage density. To compensate for the shortage in the energy density required to simulate the laser induced temperature rise, the specific heat of the tissue must be assigned a lower value and vice versa. Beside other uncertainties, the modeling approach grounded on static optical properties might have contributed to the large spread of values being used in both optical and thermal properties of the tissue. The temperature profile is influenced by the temporal rate of change in the storage energy coupled with the temporal rate of change in the heat sources and not just the values of the absorption coefficient, scattering coefficient, specific heat, and thermal conductivity of the target tissue.

Considering a non-Fourier heat flux term creates a hyperbolic PDE, which adds expected complexity. Also, the phase lag term τ_q pertains to a non-standard material parameter and is therefore not easily obtained. While efforts have been made to experimentally obtain τ_q , more work is needed. Estimation on in-vivo characteristic time τ_q could be realized through observing the temperature delay (or abrupt increase) inside the tissue heated by an external power [3]. An alternative approach is to use a parameter estimation algorithm like that proposed in [106] which simultaneously identifies the space or temperature dependent conductivity κ , blood perfusion rate ω_b , metabolic rate q_m , and thermal diffusivity. This particular algorithm derives a set of

balancing equations for the aforementioned parameters which are then simultaneously solved using Householder's transformation (see [106] for details).

For greater accuracy, the model could account for a dynamic external heat source (laser), $q_s(\vec{r}, t + \tau_q)$, but this would require knowledge of the dynamic optical properties of the tissue. Despite these difficulties, the TWMBT has great potential for improved accuracy on high-intensity, short-duration heating applications. The TWMBT captures finite thermal propagation speed, which in some cases could result in a more accurate temperature profile. In most cases, TWMBT can be solved using traditional finite-difference methods and would not require new toolboxes to implement. Further understanding of the TWMBT would provide insight into other more complicated models such as the Dual-Phase Lag model as well as nonlocal models.

7.2 Model Comparison: Fractional Pennes' vs. Classical Pennes'

Results from the SESE model and experimental thermal data [24] are given for a 10 s single-pulse exposure at 3.11 W with a 0.973 cm beam diameter ($1/e^2$). The fractional model shown in Figure 3 assumed peak radiant exposure of 189 J/cm^2 , the threshold modeled by SESE, to provide a suitable comparison. Heating used $\tau = 0.00008 \text{ s}$ and $\alpha = 0.5$. For the post exposure profile, values of $\tau = 3.0 \text{ s}$ and $\alpha = 0.5$ were used. The difference between the three curves is not significant ($< 2.0^\circ\text{C}$), but variability in input parameters could account for this difference.

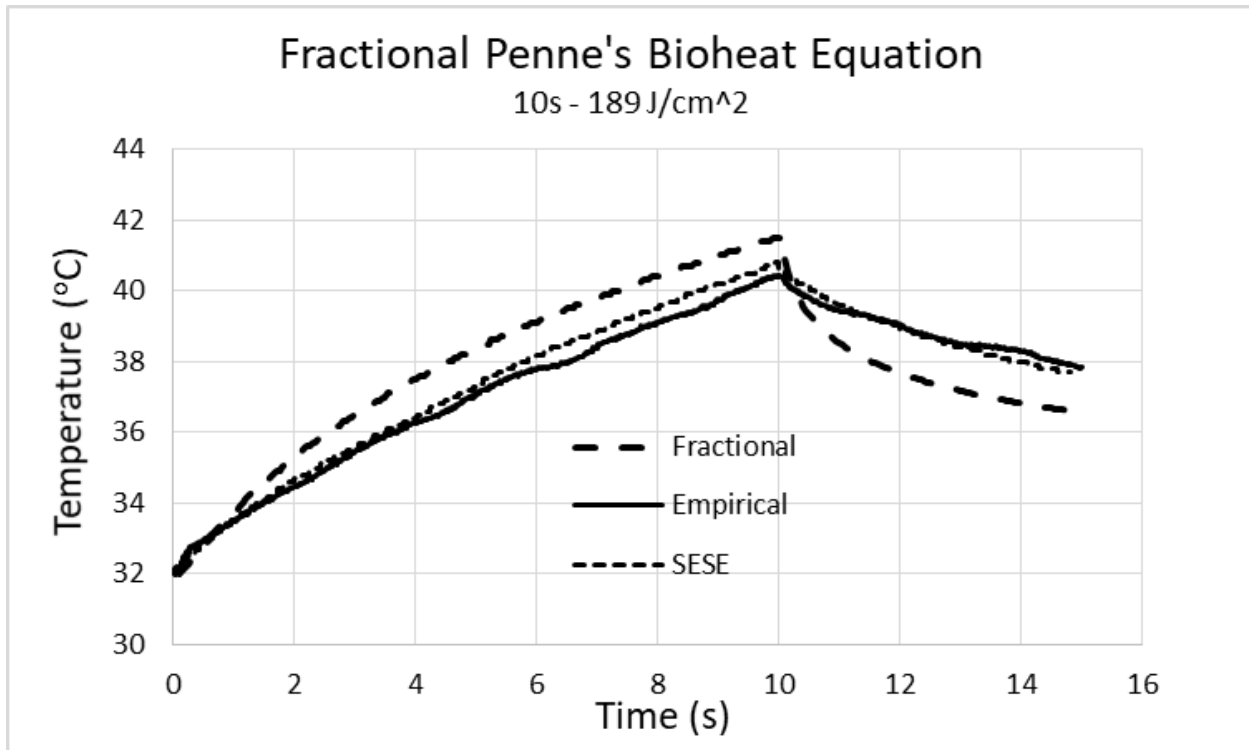


Figure 3. Fractional Pennes' vs. Traditional Pennes' 10s exposure model comparison

Results from the SESE model and experimental thermal data [24] are shown in Figure 4 for a 0.01-s single-pulse exposure at 2780 W with a 1.04 cm beam diameter ($1/e^2$). The fractional

model shown in Figure 4 assumed a peak radiant exposure of 56.6 J/cm^2 , the threshold modeled by SESE, to provide a suitable comparison. Heating used $\tau = 0.8 \text{ s}$ and $\alpha = 0.68$. The post exposure profile applied values of $\tau = 1.0 \text{ s}$ and $\alpha = 0.52$. While the post exposure portion of the fractional model does not accurately represent the temperature values, it does capture the rapid decrease in temperature that occurs immediately after the heat source is removed. The thermal profiles generated by SESE fail to capture the concavity seen in the cooling portion of the curve. Further investigation into the appropriate values of τ and α could provide better agreement with the experimental data.

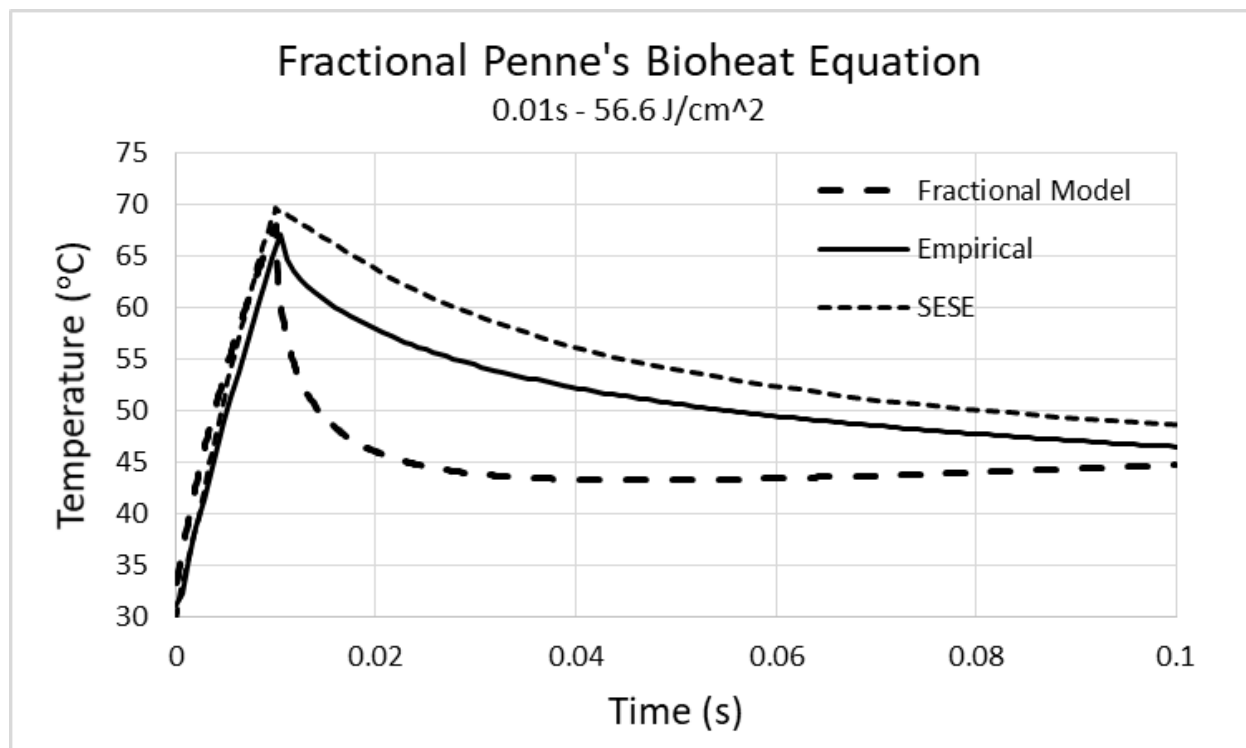


Figure 4. Fractional Pennes' vs. Traditional Pennes' .01s exposure model comparison

The flexibility to refine the post exposure trend without adjusting the tissue and/or air diffusion parameters to match the empirical trends could give fractional models an advantage over the classical Pennes' equation. The use of dynamic optical and thermal properties relies on available measurements, but these measurements might not account for the physical changes in the material (such as volume, mass, and density) that result from exposure to high temperatures. This approach can be used to account for this variability without relying on the accuracy of the optical and thermal parameters being used to simulate dynamic tissue properties. As previously discussed, SESE's generated profile uses modified optical and thermal properties to approach the empirical trend and this resulted in lower peak temperature. In the fractional version, τ and α values can be assumed to account for variability in optical and thermal properties. During post exposure, the effect of the variability in optical properties is eliminated, so these parameters will account for variability in thermal properties which probably do not follow the same temperature dependent trend (as during the exposure) because of the accumulated physical changes that took place in the material.

For $\alpha = 1$, the model should theoretically agree with the traditional Pennes' equation. However, due to algorithm convergence requirements, the current numerical implementation cannot accommodate this case. This can be overcome by using values approaching 1 to give a general idea of how the model performs. As α approaches unity, the profile results in a faster temperature rise at the beginning of the exposure and seems to move the temperature profile away from the SESE profile and the empirical data.

Introducing a scaling factor poses new difficulty since the physical meaning of τ is not clear. The physical meaning of τ is not well defined and requires further investigation. Similarly, further investigation into the influence of the order of the derivative α is needed.

As discussed in section 5, replacement of time-derivatives in existing integer-order models by fractional counterparts requires careful analysis of memory kernels used and requires further investigation for proper use. Generalization via fractional Taylor series expansion of both the heat flux and the temperature gradient is also another option. Due to the complexity introduced by the fractional derivatives, methods for solving fractional bio-models are varied. In simple cases, finite difference methods are used. Other methods include variations of the Crank-Nicholson method, variational iterative methods, and methods involving numerical inversion of Laplace transforms. Including dynamic optical and thermal properties (for a more accurate comparison) will likely require the use of a parallel computing algorithm.

8.0 CONCLUSIONS

Devising a model that accurately predicts the thermal profile of human skin is difficult because of the heterogeneous and dynamic nature of biological tissue. Pennes' equation (7) is perhaps the most widely used model because of its relative simplicity and accuracy. Theoretical analyses have been performed and numerical methods for various applications are available. The convenience and utility of both of these facts cannot be understated and, in addition, Pennes' equation largely agrees with experimental observations. However, the model has some simplifying assumptions which, on one hand, contribute to its ease of use, but also could have unintended results in the thermal profile (see section 4.1.1). Pennes made some simplifying assumptions in regard to the vascular system and blood flow, and significant research has gone into addressing concerns surrounding those assumptions. While refining Pennes' equation in this way may result in a slightly more accurate model, many of these approaches introduce significant model complexity to more accurately represent the influence of the vascular system. It is also known that Fourier's law assumes an unrealistic instant thermal propagation speed. The necessity for a phase-lag modification may be most apparent if the layer has a very small thickness [107] or the time scale of the problem is very short [108]. To account for a finite thermal propagation speed, a modified flux term is introduced and the treatment of this term creates new models, such as the TWMBT and the DPL type models. The dampening effect introduced in the single and dual phase lag approaches can be viewed in a convolution form of the thermal flux dampening with appropriate memory kernel [35]. This perspective also highlights the relationship between fractional order models, such as equations (42, 43), and the TWMBT and Dual Phase Lag models.

9.0 RECOMMENDATIONS

The models discussed in this report are considered to be extensions (or generalizations) of Pennes' bioheat equation that allow a finite thermal propagation speed to be considered. These extended models are expected to have an increased predictive ability since the original model can be retrieved with additional assumptions. Due to ease of use and potential for improved accuracy, further testing of the TWMBT is recommended. This includes further analysis of the theoretical implications of the current treatment of the non-Fourier flux term, further comparison with experimental data, and investigation (either experimentally and/or numerically) into the values and physical meaning of the phase lag parameter τ_q . As previously mentioned, this parameter gives the TWMBT a tool to account for variability, without relying as heavily on the accuracy of thermal and optical properties. Testing the TWMBT with data sets of varying exposure duration and laser intensity will help identify the cases where the wave nature of thermal signals dominates the diffusive behavior. At the time of writing, it is believed investigation into the Dual Phase Lag model is not as lucrative given that the single phase lag term can be viewed as a particular case of the dual phase lag approach and currently needs further investigation for practical application. However, continuing the theoretical development of fractional order models from the fading memory perspective would also provide a better general understanding of the TWMBT.

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APPENDIX A - BASIC FRACTIONAL CALCULUS DEFINITIONS

The Riemann-Liouville fractional integral of order $\alpha > 0$ (${}_a I^\alpha$) is given as

$${}_a I^\alpha [f(t)] = \frac{1}{\Gamma(\alpha)} \int_a^t (t-z)^{\alpha-1} f(z) dz, \quad (\text{A-1})$$

Equation A-1. Riemann-Liouville fractional integral

where $\Gamma(z)$ represents the Gamma function, defined as

$$\Gamma(z) = \int_0^\infty t^{z-1} e^{-t} dt, \quad \Re(z) > 0. \quad (\text{A-2})$$

Equation A-2. Gamma function

The integral (A-1) is well-defined provided f is a locally integrable function and $\Re(\alpha) > 0$. The base-point a represents a constant of integration, which for the remainder of this report is 0, and in some instances will be omitted from the notation. Clearly $I^1 f$ is a first antiderivative of f , and for positive integer values of α , $I^\alpha f$ can be viewed as an antiderivative of order α using the Cauchy formula for repeated integration. Given this perspective, the fundamental results about integrals still hold:

$$\frac{d}{dt} (I^{\alpha+1} [f(t)]) = I^\alpha [f(t)] \quad (\text{A-3a})$$

$$I^\alpha [I^\beta [f(t)]] = I^{\alpha+\beta} [f(t)]. \quad (\text{A-3b})$$

Equation A-3. Fractional integral properties

Another commonly used notation is $D^{-\alpha} [f(t)] = I^\alpha [f(t)]$. The Riemann-Liouville fractional derivative of order $\alpha > 0$ (${}_0 D_t^\alpha$) can then be written as

$${}_0 D_t^\alpha [f(t)] = D^m [{}_0 I^{m-\alpha} [f(t)]] = \frac{1}{\Gamma(m-\alpha)} \frac{d^m}{dt^m} \int_0^t \frac{f(z)}{(t-z)^{\alpha+1-m}} dz. \quad (\text{A-4})$$

Equation A-4. Riemann-Liouville fractional derivative

An alternative definition whose practical application was introduced by Caputo [109] effectively swaps the order of integration and differentiation. The Caputo derivative of fractional order $\alpha > 0$ (${}^C_0 D_t^\alpha$) of a function $f(t)$ is defined as

$${}^C_0 D_t^\alpha [f(t)] = {}_0 I^{m-\alpha} \left[\frac{d^m}{dt^m} [f(t)] \right] = {}_0 D_t^{-(m-\alpha)} [f^{(m)}] = \frac{1}{\Gamma(m-\alpha)} \int_0^t \frac{f^{(m)}(z)}{(t-z)^{\alpha+1-m}} dz, \quad (\text{A-5})$$

Equation A-5. Caputo fractional derivative

where $m-1 < \alpha < m$. For $m=1$ one has

$${}^C_0 D_t^\alpha [f(t)] = {}_0 I^{1-\alpha} \left[\frac{d}{dt} [f(t)] \right] = {}_0 D_t^{-(1-\alpha)} [f'] = \frac{1}{\Gamma(1-\alpha)} \int_0^t \frac{f'(z)}{(t-z)^\alpha} dz \quad (\text{A-6})$$

Equation A-6. Caputo fractional derivative $m=1$ case

Unlike the Riemann–Liouville fractional derivative, Caputo’s definition is useful in solving differential equations because it eliminates the need for fractional order initial conditions, which has clear advantages for modeling applications. In fact, the Laplace transform of a Caputo derivative is very similar to the the Laplace transform of a standard derivative.

LIST OF SYMBOLS, ABBREVIATIONS, AND ACRONYMS

κ	Thermal conductivity.
ω	The blood perfusion rate coefficient.
ρ	Density of the tissue.
σ	The Stefan-Boltzmann constant.
α	The order of a fractional derivative or fractional integral.
τ_T	The phase lag time for the temperature gradient.
ρ_b	The density of the perfused blood.
τ_q	The thermal relaxation time.
RH	The relative humidity of air.
$T(\vec{r}, t)$	The temperature at position $\vec{r}$ and time t .
T_∞	The air temperature surrounding the object.
T_b	The temperature of the perfused blood.
${}_0^C D_t^\alpha$	The Caputo derivative of fractional order α .
${}_0 D_t^\alpha$	The Riemann-Liouville fractional derivative of order α .
${}_a I^\alpha$	The Riemann-Liouville fractional integral of order $\alpha > 0$.
c	Specific heat of the tissue.
c_b	The specific heat of the perfused blood.
h_{conv}	The convective heat transfer coefficient.
h_{evap}	The evaporative heat transfer coefficient.
$p_{sat}(T)$	The temperature-dependent saturation pressure of water vapor.
SESE	Scalable Effects Simulation Environment
TWMBT	Thermal wave model for bioheat transfer