Modeling Bioheat Transport at Macroscale

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*Macroscale thermal models have been developed for biological tissues either by the mixture theory of continuum mechanics or by the porous-media theory. The former uses scaling-down from the global scale; the latter applies scaling-up from the microscale by the volume averaging. The used constitutive relations for heat flux density vector include the Fourier law, the Cattaneo–Vernotte (Cattaneo, C., 1958, "A Form of Heat Conduction Equation Which Eliminates the Paradox of Instantaneous Propagation," Compt. Rend., **247**, pp. 431–433; Vernotte, P., 1958, "Les Paradoxes de la Théorie Continue de I'equation de la Chaleur," Compt. Rend., **246**, pp. 3154–3155) theory, and the dual-phase-lagging theory. The developed models contain, for example, the Pennes (1948, "Analysis of Tissue and Arterial Blood Temperature in the Resting Human Forearm," J. Appl. Physiol., **1**, pp. 93–122), Wulff (1974, "The Energy Conservation Equation for Living Tissues," IEEE Trans. Biomed. Eng., **BME-21**, pp. 494–495), Klinger (1974, "Heat Transfer in Perfused Tissue I: General Theory," Bull. Math. Biol., **36**, pp. 403–415), and Chen and Holmes (1980, "Microvascular Contributions in Tissue Heat Transfer," Ann. N.Y. Acad. Sci., **335**, pp. 137–150), thermal wave bioheat, dual-phase-lagging (DPL) bioheat, two-energy-equations, blood DPL bioheat, and tissue DPL bioheat models. We analyze the methodologies involved in these two approaches, the used constitutive theories for heat flux density vector and the developed models. The analysis shows the simplicity of the mixture theory approach and the powerful capacity of the porous-media approach for effectively developing accurate macroscale thermal models for biological tissues. Future research is in great demand to materialize the promising potential of the porous-media approach by developing a rigorous closure theory. The heterogeneous and nonisotropic nature of biological tissue yields normally a strong noninstantaneous response between heat flux and temperature gradient in nonequilibrium heat transport. Both blood and tissue macroscale temperatures satisfy the DPL-type energy equations with the same values of the phase lags of heat flux and temperature gradient that can be computed in terms of blood and tissue properties, blood-tissue interfacial convective heat transfer coefficient, and blood perfusion rate. The blood-tissue interaction leads to very sophisticated effect of the interfacial convective heat transfer, the blood velocity, the perfusion, and the metabolic reaction on blood and tissue macroscale temperature fields such as the spreading of tissue metabolic heating effect into the blood DPL bioheat equation and the appearance of the convection term in the tissue DPL bioheat equation due to the blood velocity.* [DOI: 10.1115/1.4002361]

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1 Introduction

The accurate description of heat transport in biological tissues is essential not only for fundamental understanding of biological processes/functions but also for many medical operations of thermal therapy, cryopreservation, and biopreservation [1–5]. Biological tissues are composed of dispersed cells separated by voids. Blood flows into these tissues through arteries and perfuses to the cells via blood capillaries. Returned blood from the capillaries is collected in veins and then pumped back to the heart. Heat transport in biological tissues is thus enriched by heat conduction in tissue and vascular system, blood-tissue convection, and perfusion through the capillaries within the tissue and also metabolic heat generation.

Heat transport in biological tissues may be studied from a molecular point of view, from a microscopic point of view, or from a macroscopic point of view [6]. The macroscale is a phenomenological scale that is much larger than the microscale of cells and voids and much smaller than the system length scale. The interest in the macroscale rather than the molecular scale and the microscale comes from the fact that a prediction at the molecular scale or the microscale is complicated because of either the huge numbers of particles at molecular scale or the complex microscale anatomical structure of biological media, and that we are usually more interested in large scales of heat transport for practical applications. Existence of such a macroscale description equivalent to the microscale behavior requires a good separation of length scale and has been well discussed in Ref. [7].

The macroscopic thermal models for blood-perfused tissues have been developed by two approaches: (1) scaling-down from the global scale based on the mixture theory of continuum mechanics and (2) scaling-up from the microscale based on porous-media theory. We present a concise synthesis of these two approaches and the models developed. Instead of a comprehensive review, our emphasis is limited to identify the essence of the two approaches and to discuss the fundamental heat-conduction theories they involved.

2 Scaling-Down by Mixture Theory

To develop a macroscale model of heat transport in living biological tissues, the mixture theory of continuum mechanics views

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blood and tissues as a mixture of continuum deformable media. In this approach, no microscale presentation of the system is provided and microscale quantities are not introduced. Phase properties are defined at the macroscale. The global balance equations are formed in terms of macroscale properties and with additional terms accounting for the interaction between blood and tissue. These global equations can then be localized to obtain the macroscale point equations. Required constitutive equations are supplied by direct postulation of desirable relations at macroscale.

There are two drawbacks associated with this approach. The first is the lack of connection between microscale and macroscale properties. The second is the difficulty in extension to multiphase systems with distinct properties of interfaces and common curves.

In this approach, a global balance is written with the integrand properties at the macroscale. For a property ψ of the α-phase, the conservation equation reads [8]

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_V (\rho\varepsilon\psi)^{\alpha}_{\mathrm{mac}}\mathrm{d}V + \int_S \mathbf{n}\cdot[(\rho\varepsilon)^{\alpha}_{\mathrm{mac}}(\mathbf{v}^{\alpha}_{\mathrm{mac}}-\mathbf{w})\psi^{\alpha}_{\mathrm{mac}} - (\varepsilon\mathbf{i})^{\alpha}_{\mathrm{mac}}]\mathrm{d}S - \int_V (\rho\varepsilon G)^{\alpha}_{\mathrm{mac}}\mathrm{d}V - \int_V (\rho\varepsilon f)^{\alpha}_{\mathrm{mac}}\mathrm{d}V = 0 \tag{1}$$

where t is time, the superscript α is used to indicate the α-phase properties, and the subscript "mac" is used to indicate the macroscale properties. ρ, ε, and $\mathbf{v}$ are the density, the volume fraction, and the velocity, respectively. V is the global volume at a given time instant t. The boundary of V, denoted by S, may have a velocity $\mathbf{w}$ in general. $\mathbf{i}$ is the diffusive flux of ψ across the boundary, $\mathbf{n}$ is the unit vector normal to S and pointing outward from V, G is the term accounting for production of ψ within the volume, and f is the external supply of ψ. This equation is a mathematical statement of the physical principle that the rate of change of some property in a volume is equal to the net flux of that property across the boundary of the volume plus production of the property and the external supply.

To transform Eq. (1) to a differential form at macroscale, we must use the two multiscale theorems (Eqs. (311) and (320) in Ref. [6]) to bring the time derivative inside the integral and to convert the boundary integral to a volume integral so that

$$\int_V \left[\frac{\partial(\rho\varepsilon\psi)^{\alpha}_{\mathrm{mac}}}{\partial t} + \nabla\cdot(\rho\varepsilon\mathbf{v}\psi)^{\alpha}_{\mathrm{mac}} - \nabla\cdot(\varepsilon\mathbf{i})^{\alpha}_{\mathrm{mac}} - (\rho\varepsilon G)^{\alpha}_{\mathrm{mac}} - (\rho\varepsilon f)^{\alpha}_{\mathrm{mac}}\right]\mathrm{d}V = 0 \tag{2}$$

Because the size of the volume is arbitrary, by the localization theorem [6], the integrand in Eq. (2) must be zero as long as Axiom 1 in Ref. [6] is satisfied so that the macroscale point equation can be obtained as

$$\frac{\partial(\rho\varepsilon\psi)^{\alpha}_{\mathrm{mac}}}{\partial t} + \nabla\cdot(\rho\varepsilon\mathbf{v}\psi)^{\alpha}_{\mathrm{mac}} - \nabla\cdot(\varepsilon\mathbf{i})^{\alpha}_{\mathrm{mac}} - (\rho\varepsilon G)^{\alpha}_{\mathrm{mac}} - (\rho\varepsilon f)^{\alpha}_{\mathrm{mac}} = 0 \tag{3}$$

Consider ψ being the internal energy of biological tissue. Equation (3) reduces to

$$\frac{\partial(\rho c\varepsilon T)^{t}_{\mathrm{mac}}}{\partial t} = -\nabla\cdot(\varepsilon\mathbf{q})^{t}_{\mathrm{mac}} + (\rho\varepsilon q_m)^{t}_{\mathrm{mac}} + (\rho\varepsilon q_c)^{t}_{\mathrm{mac}} + (\rho\varepsilon q_p)^{t}_{\mathrm{mac}} + (\rho\varepsilon q_e)^{t}_{\mathrm{mac}} \tag{4}$$

where the superscript t is used to indicate the tissue properties, c is the specific heat, And $\mathbf{q}$ is the heat flux density vector. q_m, q_c, and q_p are the volumetric rate of heat generation by the metabolic heating, the blood interfacial convective heat transfer, and the blood perfusion, respectively. q_e is the volumetric rate of external heat supply like the one used in hyperthermia therapy. There exists some confusion in the literature between q_c and q_p. The former comes actually from the interfacial convective heat transfer between the blood and the blood vessel, driving by the temperature difference between them. The latter, on the other hand, stems from the energy exchange due to the blood perfusion, the mass-transfer process of nutritive delivery of arterial blood to capillaries in the biological tissue.

The existing thermal models for biological tissues developed by this approach differ from each other mainly on how to model the heat flux density vector $\mathbf{q}$. Three constitutive relations for $\mathbf{q}$ have been used: the Fourier law, the Cattaneo–Vernotte (CV) relation, and the dual-phase-lagging (DPL) relation.

2.1 The Fourier Law. The Fourier law was the first constitutive relation of heat flux density and was proposed by the French mathematical physicist Joseph Fourier in 1807 based on experimentation and investigation [9]. For heat conduction in a homogeneous and isotropic medium, the Fourier law of heat conduction reads

$$\mathbf{q}(\boldsymbol{r},t) = -k\,\nabla\,T(\boldsymbol{r},t) \tag{5}$$

where $\boldsymbol{r}$ stands for the material point, t stands for the time, T stands for the temperature, and ∇ stands for the gradient operator. k is the thermal conductivity of the material, which is a thermodynamic property. By the state theorem of thermodynamics, k should be a function of two independent, intensive properties (normally pressure and temperature) [10]. The second law of thermodynamics requires that k is positive definite [9,11,12]. In engineering applications, we often take k as a material constant because variations in pressure and temperature are normally sufficiently small. The value of k is material dependent. If the material is not homogeneous or isotropic, k becomes a second-order tensor [9,11–13]. Along with the first law of thermodynamics, this equation leads to the classical *parabolic* heat-conduction equation

$$\frac{\partial T}{\partial t} = \alpha\Delta T + \frac{\alpha}{k}F \tag{6}$$

Here α is the thermal diffusivity of the material, F is the rate of internal energy generation per unit volume, and Δ is the Laplacian.

By using the Fourier law, Eq. (4) yields a group of thermal models for biological tissues

$$\frac{\partial(\rho\varepsilon cT)^{t}_{\mathrm{mac}}}{\partial t} = \nabla\cdot(\varepsilon k\,\nabla\,T)^{t}_{\mathrm{mac}} + (\rho\varepsilon q_m)^{t}_{\mathrm{mac}} + (\rho\varepsilon q_c)^{t}_{\mathrm{mac}} + (\rho\varepsilon q_p)^{t}_{\mathrm{mac}} + (\rho\varepsilon q_e)^{t}_{\mathrm{mac}} \tag{7}$$

The thermal models in this group includes the classical Pennes model [14], the Wulff model [15], the Klinger model [16], and the Chen and Holmes model [17]. Table 1 lists $(\rho c)^{t}_{\mathrm{mac}}$, $\varepsilon^{t}_{\mathrm{mac}}$, k^{t}_{mac}, $(\rho\varepsilon q_m)^{t}_{\mathrm{mac}}$, $(\rho\varepsilon q)^{t}_{\mathrm{mac}}$, $(\rho\varepsilon q_p)^{t}_{\mathrm{mac}}$, and $(\rho\varepsilon q_e)^{t}_{\mathrm{mac}}$ in these models.

The Fourier law of heat conduction is an early empirical law. It assumes that $\boldsymbol{q}$ and ∇T appear at the same time instant t and consequently implies that thermal signals propagate with an infinite speed. If the material is subjected to a thermal disturbance, the effects of the disturbance will be felt instantaneously at distances infinitely far from its source. Although this result is physically unrealistic, it has been confirmed by many experiments that the Fourier law of heat conduction holds for many media in the usual range of heat flux $\mathbf{q}$ and temperature gradient ∇T [9].

2.2 The CV Constitutive Relation. With the development of science and technology such as the application of ultrafast pulse-laser heating on metal films, heat conduction appears in a range of high heat flux and high unsteadiness. The drawback of infinite heat propagation speed in the Fourier law becomes unacceptable. This has inspired the work of searching for new constitutive rela-

Table 1 Pennes, Wulff, Klinger, and Chen and Holmes models with the confusion between q_c and q_p corrected (superscript b indicating blood properties, v_h indicating local mean blood velocity, $\mathbf{v}_p$ indicating mean perfusion velocity, Δh indicating enthalpy of formation in metabolic reaction, ϕ indicating extent of reaction, ω^b indicating blood perfusion rate, and ω^* indicating total perfusion bleed-off to the tissue only from the microvessels)

Model	$(\rho c)^t_{\text{mac}}$	$\varepsilon^t_{\text{mac}}$	k^t_{mac}	$(\rho\varepsilon q_m)^t_{\text{mac}}$	$(\rho\varepsilon q_c)^t_{\text{mac}}$	$(\rho\varepsilon q_p)^t_{\text{mac}}$	$(\rho\varepsilon q_e)^t_{\text{mac}}$
Pennes	Constant $(\rho c)^t_{\text{mac}}$	1	Constant k^t_{mac}	$(\rho\varepsilon q_m)^t_{\text{mac}}$	0	$(\rho c)^b_{\text{mac}}\omega^b(T^b_{\text{mac}}-T^t_{\text{mac}})$	0
Wulff	Constant $(\rho c)^t_{\text{mac}}$	1	Constant k^t_{mac}	$\rho^b_{\text{mac}}v_h\Delta h\nabla\phi$	$-(\rho c)^b_{\text{mac}}v_h\nabla T^t_{\text{mac}}$	0	0
Klinger	Constant $(\rho c)^t_{\text{mac}}$	1	Constant k^t_{mac}	$(\rho\varepsilon q_m)^t_{\text{mac}}$	$-(\rho c)^b_{\text{mac}}\mathbf{v}^b_{\text{mac}}\nabla T^t_{\text{mac}}$	0	0
Chen and Holmes	Constant $(\rho c)^t_{\text{mac}}$	1	$k_{\text{eff}}=(1-\varepsilon^t_{\text{mac}})k^b_{\text{mac}}+(\varepsilon k)^t_{\text{mac}}\approx k^t_{\text{mac}}$	$(\rho\varepsilon q_m)^t_{\text{mac}}$	$-(\rho c)^b_{\text{mac}}\mathbf{v}_p\cdot\nabla T^t_{\text{mac}}$	$(\rho c)^b_{\text{mac}}\omega^*(T^b_{\text{mac}}-T^t_{\text{mac}})$	0

tions. Among many proposed relations [9], the constitutive relation proposed by Cattaneo [18] and Vernotte [19,20],

$$\mathbf{q}(\boldsymbol{r},t)+\tau_q\frac{\partial\mathbf{q}(\boldsymbol{r},t)}{\partial t}=-k\nabla T(\boldsymbol{r},t) \tag{8}$$

is the most widely accepted. This relation is named the CV constitutive relation after the names of the proposers. Here $\tau_q>0$ is a material property and is called the *relaxation time*. The corresponding heat-conduction equation is thus

$$\frac{\partial T}{\partial t}+\tau_q\frac{\partial^2 T}{\partial t^2}=\alpha\Delta T+\frac{\alpha}{k}\left(F+\tau_q\frac{\partial F}{\partial t}\right) \tag{9}$$

Unlike its classical counterpart equation (6), this equation is of *hyperbolic* type, characterizes the combined diffusion and wavelike behavior of heat conduction, and predicts a *finite speed*,

$$V_{\text{CV}}=\sqrt{\frac{k}{\rho c\tau_q}} \tag{10}$$

for heat propagation [21].

Note that the CV constitutive relation is actually a first-order approximation of a more general constitutive relation (single-phase-lagging model [22]),

$$\mathbf{q}(\boldsymbol{r},t+\tau_q)=-k\nabla T(\boldsymbol{r},t) \tag{11}$$

according to which the temperature gradient established at a point $\boldsymbol{r}$ at time t gives rise to a heat flux vector at $\boldsymbol{r}$ at a *later* time $t+\tau_q$. There is a finite built-up time τ_q for the onset of heat flux at $\boldsymbol{r}$ after a temperature gradient is imposed there. Thus τ_q represents the time lag needed to establish the heat flux (the result) when a temperature gradient (the cause) is suddenly imposed. The higher $\partial\mathbf{q}/\partial t$ corresponds to a larger derivation of the CV constitutive relation from the classical Fourier law.

The value of τ_q is material dependent [23–25]. For most solid materials, τ_q varies from 10^{-10} s to 10^{-14} s. For gases, τ_q is normally in the range of 10^{-8}–10^{-10} s. The value of τ_q for some biological materials and materials with nonhomogeneous inner structures can be up to 10^2 s [26–31]. The long time delay in heterogeneous materials comes from the fact that the structural heat interaction occurs at multiscales [32]. Therefore, the thermal relaxation effects can be of relevance even in common engineering applications where the time scales of interest are of the order of a fraction of 1 minute.

Three factors contribute to the significance of the second term in the hyperbolic heat-conduction Eq. (9): the τ_q value, the rate of change of temperature, and the time scale involved. The wave nature of thermal signals will be over the diffusive behavior through this term when [22]

$$\frac{\partial T}{\partial t}\gg\frac{T_r}{2\tau_q}\exp(t/\tau_q) \tag{12}$$

where T_r is a reference temperature. Therefore, the wavelike features will become significant when (1) τ_q is large, (2) $\partial T/\partial t$ is high, or (3) t is small. Some typical situations where hyperbolic heat conduction differs from classical parabolic heat conduction include those concerned with a localized moving heat source with a high intensity, a rapidly propagating crack tip, shock wave propagation, thermal resonance, interfacial effects between dissimilar materials, laser material processing, transport in biological systems, and laser surgery [22–25,33–36].

When $\tau_q\to\infty$ but $k_e=k/\tau_q$ is finite, the CV constitutive relation (8) and the hyperbolic heat-conduction equation (9) become [34]

$$\frac{\partial\mathbf{q}(\boldsymbol{r},t)}{\partial t}=-k_e\nabla T(\boldsymbol{r},t) \tag{13}$$

and

$$\frac{\partial^2 T}{\partial t^2}=\alpha_e\Delta T+\frac{\alpha_e}{k_e}\frac{\partial F}{\partial t} \tag{14}$$

where $\alpha_e=k_e/(\rho c)$, ρ and c are the density and the specific heat of the material, respectively. Therefore, when τ_q is very large, a temperature gradient established at a point of the material results in an *instantaneous heat flux rate* at that point, and vice versa. Equation (14) is a classical wave equation that predicts thermal wave propagation with speed V_{CV}, like Eq. (9). A major difference exists, however, between Eqs. (9) and (14): The former allows damping of thermal waves, the latter does not [21].

Using the CV relation (Eq. (8)) as the constitutive relation for $\mathbf{q}^t_{\text{mac}}$, Eq. (4) yields

$$\frac{\partial(\rho\varepsilon cT)^t_{\text{mac}}}{\partial t}+\tau_q\frac{\partial^2(\rho\varepsilon cT)^t_{\text{mac}}}{\partial t^2}=\nabla\cdot(\varepsilon k\nabla T)^t_{\text{mac}}+\left(1+\tau_q\frac{\partial}{\partial t}\right)(\rho\varepsilon q_m+\rho\varepsilon q_c+\rho\varepsilon q_p+\rho\varepsilon q_e)^t_{\text{mac}} \tag{15}$$

This is known as a hyperbolic bioheat equation. It can well predict the experimental results of some biological materials [28] and has been used for the blood perfusion rate measurement [37–39], for the explanation of temperature oscillations in biological systems [40], for the prediction of temperature and thermal stress during skin cryopreservation [41], and for the prediction of temperature and thermal dose distributions in living tissue during thermal therapies [42]. The hyperbolic model also predicts considerably different temperature and thermal damage in skin tissues under different heating from the Pennes model [43,44] and provides more realistic predictions both for the case of heating with a high flux under an extremely short duration [43–45] and for the thermal behavior in surgical techniques with laser and radiofrequency heating [46].

2.3 The Dual-Phase-Lagging Constitutive Relation. It has been confirmed by many experiments that the CV constitutive relation generates a more accurate prediction than the classical Fourier law. However, some of its predictions do not agree with experimental results either [9,25,33]. A thorough study shows that the CV constitutive relation has only taken account of the fast-transient effects but not the microstructural interactions. These two effects can be reasonably represented by the dual-phase-lag between $\mathbf{q}$ and ∇T, a further modification of Eq. (5) [25,33],

$$\mathbf{q}(\boldsymbol{r},t+\tau_q) = -k\nabla T(\boldsymbol{r},t+\tau_T) \tag{16}$$

According to this relation, the temperature gradient at a point $\boldsymbol{r}$ of the material at time $t+\tau_T$ corresponds to the heat flux density vector at $\boldsymbol{r}$ at time $t+\tau_q$. The delay time τ_T is interpreted as being caused by the microstructural interactions (small-scale heat transport mechanisms occurring at the microscale or small-scale effects of heat transport in space) such as phonon-electron interaction or phonon scattering and is called the *phase-lag of the temperature gradient* [25,33]. The other delay time τ_q is interpreted as the relaxation time due to the fast-transient effects of thermal inertia (or small-scale effects of heat transport in time) and is called the *phase-lag of the heat flux*. Both of the phase-lags are treated as intrinsic thermal or structural properties of the material. The corresponding heat-conduction equation reads [47]

$$\frac{1}{\alpha}\frac{\partial T(\boldsymbol{r},t')}{\partial t} = \Delta T(\boldsymbol{r},t'-\tau) + \frac{1}{k}F(\boldsymbol{r},t'), \quad t' = t+\tau_q, \quad \tau = \tau_q - \tau_T,$$
$$\text{for} \quad \tau_q - \tau_T > 0 \quad \text{and} \quad t' > \tau_q \tag{17}$$

or

$$\frac{1}{\alpha}\frac{\partial T(\boldsymbol{r},t'-\tau)}{\partial t} = \Delta T(\boldsymbol{r},t') + \frac{1}{k}F(\boldsymbol{r},t'-\tau), t' = t+\tau_T, \tau = \tau_T - \tau_q,$$
$$\text{for} \quad \tau_q - \tau_T < 0 \quad \text{and} \quad t' > \tau_T \tag{18}$$

Unlike the relation (11) according to which the heat flux is the result of a temperature gradient in a transient process, the relation (16) allows either the temperature gradient or the heat flux to become the effect and the remaining one to be the cause. For materials with $\tau_q > \tau_T$, the heat flux density vector is the result of a temperature gradient. It is the other way around for materials with $\tau_T > \tau_q$. The relation (11) corresponds to the particular case where $\tau_q > 0$ and $\tau_T = 0$. If $\tau_q = \tau_T$ (not necessarily equal to zero), the response between the temperature gradient and the heat flux is instantaneous; in this case, the relation (16) is identical to the classical Fourier law (5). It may also be noted that while the classical Fourier law (5) is macroscopic in both space and time and the relation (11) is macroscopic in space but microscopic in time, the relation (16) is microscopic in both space and time. Also note that Eqs. (17) and (18) are of the delay and advance types, respectively. While the former has a wavelike solution and possibly resonance, the latter does not [47]. Both single-phase-lagging and dual-phase-lagging heat conduction have been shown to be admissible by the second law of extended irreversible thermodynamics [25], by the Boltzmann transport equation [47,48], and by the Galilean principle of relativity [49].

Expanding both sides of Eq. (16) using the Taylor series and retaining only the first-order terms of τ_q and τ_T, we obtain the following constitutive relation that is valid at point $\boldsymbol{r}$ and time t,

$$\mathbf{q}(\boldsymbol{r},t) + \tau_q\frac{\partial \mathbf{q}(\boldsymbol{r},t)}{\partial t} = -k\left\{\nabla T(\boldsymbol{r},t) + \tau_T\frac{\partial}{\partial t}[\nabla T(\boldsymbol{r},t)]\right\} \tag{19}$$

which is known as the Jeffreys-type constitutive equation of heat flux [34]. In literature this relation is also called the *dual-phase-lagging constitutive relation*. When $\tau_q = \tau_T$, this relation reduces to the classical Fourier law (5), and it reduces to the CV constitutive relation (8) when $\tau_T = 0$.

Eliminating $\mathbf{q}$ from Eq. (19) and the classical energy equation leads to the dual-phase-lagging heat-conduction equation that reads, if all thermophysical material properties are assumed to be constant

$$\frac{\partial T}{\partial t} + \tau_q\frac{\partial^2 T}{\partial t^2} = \alpha\Delta T + \alpha\tau_T\frac{\partial}{\partial t}(\Delta T) + \frac{\alpha}{k}\left(F + \tau_q\frac{\partial F}{\partial t}\right) \tag{20}$$

This equation is *parabolic* when $\tau_q < \tau_T$ [21]. Although a wave term $\tau_q\partial^2 T/\partial t^2$ exists in the equation, the mixed derivative $\alpha\tau_T\partial(\Delta T)/\partial t$ completely destroys the wave structure. The equation, in this case, therefore predicts a nonwavelike heat conduction that differs from the usual diffusion predicted by the classical parabolic heat conduction (6). When $\tau_q > \tau_T$, however, Eq. (20) can be approximated by Eq. (9) and then predominantly predicts wavelike thermal signals.

The dual-phase-lagging heat-conduction equation (20) forms a generalized, unified equation that reduces to the classical parabolic heat-conduction equation when $\tau_T = \tau_q$, the hyperbolic heat-conduction equation when $\tau_T = 0$ and $\tau_q > 0$, the energy equation in the phonon scattering model when $\alpha = \tau_R c^2/3$, $\tau_T = (9/5)\tau_N$, and $\tau_q = \tau_R$ [34,50], and the energy equation in the phonon-electron interaction model when $\alpha = k/(c_e + c_l)$, $\tau_T = c_l/G$, and $\tau_q = 1/G((1/c_e)+(1/c_l))^{-1}$ [51–53]. In the phonon scattering model, c is the average speed of phonons (sound speed), τ_R is the relaxation time for the Umklapp process in which momentum is lost from the phonon system, and τ_N is the relaxation time for normal processes in which momentum is conserved in the phonon system. In the phonon-electron interaction model, k is the thermal conductivity of the electron gas, G is the phonon-electron coupling factor, and c_e and c_l are the heat capacity of the electron gas and the metal lattice, respectively. This, together with its success in describing and predicting phenomena such as ultrafast pulse-laser heating, propagation of temperature pulses in superfluid liquid helium, nonhomogeneous lagging response in porous media, thermal lagging in amorphous materials, and effects of material defects and thermomechanical coupling, heat conduction in nanofluids, bicomposite media, and two-phase systems [21,25,54–63], has given rise to the research effort on various aspects of dual-phase-lagging heat conduction [21,25].

The dual-phase-lagging heat-conduction equation (Eq. (20)) has been shown to be well-posed in a finite region of n-dimensions ($n \geq 1$) under any linear boundary conditions including Dirichlet, Neumann, and Robin types [63]. Solutions of one-dimensional (1D) heat conduction have been obtained for some specific initial and boundary conditions in [25,33,54,64–70]. Analytical solutions have also been obtained in Ref. [21] for regular 1D, 2D, and 3D heat-conduction domains under essentially arbitrary initial and boundary conditions. The solution structure theorems were also developed for both mixed and Cauchy problems of dual-phase-lagging heat-conduction equations in Refs. [21,71] by extending those theorems for hyperbolic heat conduction [36]. These theorems build relationships among the contributions (to the temperature field) by the initial temperature distribution, the source term, and the initial time-rate of the temperature change, uncovering the structure of the temperature field and considerably simplifying the development of solutions. Xu and Wang [72] addressed thermal features of dual-phase-lagging heat conduction (particularly conditions and features of thermal oscillation and resonance and their contrast with those of classical and hyperbolic heat conduction). The issues associated with the Galilean principle of relativity have also been discussed in Ref. [49] for both single- and dual-phase-lagging heat-conduction models in moving media.

An experimental procedure for determining the value of τ_q has been proposed in Ref. [73]. The general problem of measuring short-time thermal transport effects has been discussed in Ref. [74]. Three methods have been developed in Ref. [21] for measuring τ_q. The equivalence has also been built-up in Refs. [25,55–60] between the Fourier heat conduction in porous media and the dual-phase-lagging heat conduction.

Tzou [25,69] also generalized Eq. (19), for $\tau_q \gg \tau_T$, by retaining terms up to the second order in τ_q but only the term of the first order in τ_T in the Taylor expansions of Eq. (16) to obtain a τ_q-second-order dual-phase-lagging model

$$\mathbf{q} + \tau_q\frac{\partial \mathbf{q}}{\partial t} + \frac{1}{2}\tau_q^2\frac{\partial^2 \mathbf{q}}{\partial t^2} = -k\left[\nabla T + \tau_T\frac{\partial}{\partial t}(\nabla T)\right] \tag{21}$$

For this case, the dual-phase-lagging heat-conduction equation (20) is generalized into

$$\frac{\partial T}{\partial t}+\tau_q\frac{\partial^2 T}{\partial t^2}+\frac{\tau_q^2}{2}\frac{\partial^3 T}{\partial t^3}=\alpha\Delta T+\alpha\tau_T\frac{\partial}{\partial t}(\Delta T)+\frac{\alpha}{k}\left(F+\tau_q\frac{\partial F}{\partial t}+\frac{\tau_q^2}{2}\frac{\partial^2 F}{\partial t^2}\right) \tag{22}$$

which is of hyperbolic type and thus predicts thermal wave propagation with a finite speed [25,69]

$$V_T=\frac{1}{\tau_q}\sqrt{\frac{2k\tau_T}{\rho c}} \tag{23}$$

The thermal wave from Eq. (9) is obviously different from that in Eq. (22). While the former is caused only by the fast-transient effects of thermal inertia, the latter comes from these effects, as well as the delayed response due to the microstructural interaction. Tzou [25] refers to the former wave as the CV-wave and the latter wave as the T-wave. By Eqs. (10) and (23), we have

$$V_T=\sqrt{\frac{2\tau_T}{\tau_q}}V_{\mathrm{CV}} \tag{24}$$

Therefore, the T-wave is always slower than the CV-wave because Eqs. (21) and (22) are valid only for $\tau_q \gg \tau_T$. This has been shown by the heat propagation in superfluid helium at extremely low temperatures [25]. It is interesting to note that Eq. (21) is the simplest constitutive relation that accounts for the dual-phase-lagging effects and yields a heat-conduction equation of hyperbolic type. If the second-order term in τ_T is also retained, the resulting heat-conduction equation will no longer be hyperbolic [25]. It is also of interest to note that Eq. (22) closely resembles the energy equation describing the ballistic behavior of heat transport in an electron gas [25,53].

Using the DPL relation [Eq. (19)] as the constitutive relation for $\mathbf{q}^t_{\mathrm{mac}}$, Eq. (4) yields

$$\frac{\partial(\rho\varepsilon cT)^t_{\mathrm{mac}}}{\partial t}+\tau_q\frac{\partial^2(\rho\varepsilon cT)^t_{\mathrm{mac}}}{\partial t^2}=\nabla\cdot[(\varepsilon k)^t_{\mathrm{mac}}\nabla T^t_{\mathrm{mac}}]+\tau_T\frac{\partial}{\partial t}\{\nabla\cdot[(\varepsilon k)^t_{\mathrm{mac}}\nabla T^t_{\mathrm{mac}}]\}+\left(1+\tau_q\frac{\partial}{\partial t}\right)(\rho\varepsilon q_m+\rho\varepsilon q_c+\rho\varepsilon q_p+\rho\varepsilon q_e)^t_{\mathrm{mac}} \tag{25}$$

This is known as the DPL model of bioheat transfer. By fitting the experiments data of meat samples in Ref. [28], τ_T and τ_q were found to be around 0.05 s and 15 s respectively. The readers are also referred to Refs. [2,75] for the other types of DPL models of bioheat transfer that developed by using Eq. (4) and the other order Taylor expansions of Eq. (16).

The thermal relaxation time is normally large for biological tissue so that the DPL model of bioheat transfer has received increasingly attention. A recent study of bioheat transfer in skin tissue shows that both τ_T and τ_q play a significant role for temperature, thermal stress, and thermal damage of skin tissue [76]. The study on the temperature rise behaviors in biological tissues during hyperthermia treatment also reveals their importance at the early stage of heating [77]. The DPL model also predicts significantly different temperature and thermal damage in laser-irradiated biological tissues from both the hyperbolic thermal wave and the Fourier-type Pennes models [78,79].

3 Scaling-Up by Porous-Media Theory

To develop a macroscale model of heat transport in living biological tissues, the method of volume averaging starts with a microscale description. Both conservation and constitutive equations are introduced at the microscale. The resulting microscale field equations are then averaged over a representative elementary volume (REV), the smallest differential volume resulting in statistically meaningful local averaging properties, to obtain the macroscale field equations. In the process of averaging, the *multiscale theorems* are used to convert integrals of gradient, divergence, curl, and partial time derivatives of a function into some combination of gradient, divergence, curl, and partial time derivatives of integrals of the function and integrals over the boundary of the REV [6]. Often in order to make averaging procedure tractable and to obtain desirable results, some assumptions are made before, during, and after averaging. These assumptions typically relate to the spatial and/or temporal distribution of properties, expected order of magnitude of various terms, and existence of certain relations among various properties, all based on intuitive and somewhat heuristic arguments.

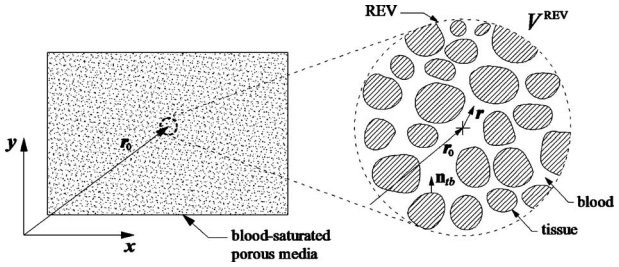

Fig. 1 Blood-saturated porous media and REV

The macroscale field equations obtained are not a closed system for determination of velocity, pressure, and temperature because of unclosed terms reflecting the microscale effect. To form a closed system, the approach used for Reynolds-stress closures in turbulence is usually employed to develop governing differential equations and boundary conditions for spatial deviations of pressure, velocity and temperature, the difference between microscale and macroscale values [80–85]. Resulting closure model is a set of differential equations defined on the microscale, which is difficult to solve due to complex microscale geometry. The closure problem is usually solved over a unit cell for a spatially periodic model of a porous medium. This leads to a local closure problem in terms of closure variables and a method of predicting the macroscale parameters in the macroscale models. The readers are referred to Refs. [6,86,87] for the details of the method of volume averaging and to Ref. [6] for a summary of the other methods of obtaining macroscale models.

3.1 Microscale Model. For developing a set of the volume-averaged (macroscale) governing equations for the blood flow and bioheat transfer, biological tissue is simplified to be a blood-saturated porous matrix including cells and interstices, the so-called tissue that is considered as a solid matrix [4]. Neglect the gravitational effect and assume that blood is incompressible and Newtonian. By the conservation of mass, momentum, and energy and the Fourier law of heat conduction, we have the microscale model for blood flow and heat conduction in biological tissues (Fig. 1) [4]

In the blood phase,

$$\nabla\cdot\mathbf{v}^b_{\mathrm{mic}}=0 \tag{26}$$

$$\rho^b_{\mathrm{mic}}\frac{\partial\mathbf{v}^b_{\mathrm{mic}}}{\partial t}+\rho^b_{\mathrm{mic}}\mathbf{v}^b_{\mathrm{mic}}\cdot\nabla\mathbf{v}^b_{\mathrm{mic}}=-\nabla p^b_{\mathrm{mic}}+\mu^b_{\mathrm{mic}}\nabla^2\mathbf{v}^b_{\mathrm{mic}} \tag{27}$$

$$(\rho c)^b_{\mathrm{mic}}\frac{\partial \mathrm{T}^b_{\mathrm{mic}}}{\partial t}+(\rho c)^b_{\mathrm{mic}}\mathbf{v}^b_{\mathrm{mic}}\cdot\nabla \mathrm{T}^b_{\mathrm{mic}}=\nabla\cdot(k^b_{\mathrm{mic}}\nabla \mathrm{T}^b_{\mathrm{mic}}) \tag{28}$$

In the tissue phase,

$$(\rho c)^t_{\mathrm{mic}}\frac{\partial \mathrm{T}^t_{\mathrm{mic}}}{\partial t}=\nabla\cdot(k^t_{\mathrm{mic}}\nabla \mathrm{T}^t_{\mathrm{mic}})+(q_m)^t_{\mathrm{mic}} \tag{29}$$

Boundary conditions,

$$\text{B.C.1}\quad \mathbf{v}^b_{\mathrm{mic}}=\mathbf{v}^b_{\mathrm{mic}}|_{A_{bt}}\quad\text{at}\quad A_{bt} \tag{30}$$

$$\text{B.C.2} \quad T^b_{\text{mic}} = T^t_{\text{mic}} \quad \text{at} \quad A_{bt} \tag{31}$$

$$\text{B.C.3} \quad \mathbf{n}_{bt} \cdot k^b_{\text{mic}} \nabla T^b_{\text{mic}} = \mathbf{n}_{bt} \cdot k^t_{\text{mic}} \nabla T^t_{\text{mic}} \quad \text{at} \quad A_{bt} \tag{32}$$

Here the subscript "mic" is used to indicate the microscale properties. Superscripts b and t refer to the blood and tissue phases, respectively. $\mathbf{v}$, p, and T are the velocity, the pressure, and the temperature, respectively. ρ, μ, c, and k are the density, the viscosity, the specific heat, and the thermal conductivity, respectively. q_m is the volumetric rate of heat generation by the metabolic reaction. A_{bt} represents the area of the blood-tissue interface contained in the REV; $\mathbf{n}_{bt}$ is the outward-directed surface normal from the b-phase toward the t-phase, and $\mathbf{n}_{bt}=-\mathbf{n}_{tb}$ (Fig. 1).

3.2 Scaling-Up by Volume Averaging. By applying the superficial averaging process to Eqs. (26), (28), and (29), we have

$$\frac{1}{V^{\text{REV}}} \int_{V^b} \nabla \cdot \mathbf{v}^b_{\text{mic}} dV = 0 \tag{33}$$

$$\frac{1}{V^{\text{REV}}} \int_{V^b} (\rho c)^b_{\text{mic}} \frac{\partial T^b_{\text{mic}}}{\partial t} dV + \frac{1}{V^{\text{REV}}} \int_{V^b} (\rho c)^b_{mic} \mathbf{v}^b_{\text{mic}} \cdot \nabla T^b_{\text{mic}} dV = \frac{1}{V^{\text{REV}}} \int_{V^b} \nabla \cdot (k^b_{\text{mic}} \nabla T^b_{\text{mic}}) dV \tag{34}$$

and

$$\frac{1}{V^{\text{REV}}} \int_{V^t} (\rho c)^t_{\text{mic}} \frac{\partial T^t_{\text{mic}}}{\partial t} dV = \frac{1}{V^{\text{REV}}} \int_{V^t} \nabla \cdot (k^t_{\text{mic}} \nabla T^t_{\text{mic}}) dV + \frac{1}{V^{\text{REV}}} \int_{V^t} (q_m)^t_{\text{mic}} dV \tag{35}$$

where V^{REV}, V^b, and V^t are the volumes of the REV, blood in REV, and tissue in REV, respectively. We should note that the superficial temperature is evaluated at the centroid of the REV, whereas the phase temperature is evaluated throughout the REV. Neglecting variations of ρc within the REV and considering the system to be rigid so that V^b and V^t are time independent, the volume-averaged form of Eqs. (26), (28), and (29) are

$$\langle \nabla \cdot \mathbf{v}^b_{\text{mic}} \rangle = 0 \tag{36}$$

$$(\rho c)^b_{\text{mac}} \frac{\partial \langle T^b_{\text{mic}} \rangle}{\partial t} + (\rho c)^b_{\text{mac}} \langle \mathbf{v}^b_{\text{mic}} \cdot \nabla T^b_{\text{mic}} \rangle = \langle \nabla \cdot (k^b_{\text{mic}} \nabla T^b_{\text{mic}}) \rangle \tag{37}$$

and

$$(\rho c)^t_{\text{mac}} \frac{\partial \langle T^t_{\text{mic}} \rangle}{\partial t} = \langle \nabla \cdot (k^t_{\text{mic}} \nabla T^t_{\text{mic}}) \rangle + \langle (q_m)^t_{\text{mic}} \rangle \tag{38}$$

where the angular brackets indicate superficial quantities such as

$$\langle T^b_{\text{mic}} \rangle = \frac{1}{V^{\text{REV}}} \int_{V^b} T^b_{\text{mic}} dV \tag{39}$$

and

$$\langle T^t_{\text{mic}} \rangle = \frac{1}{V^{\text{REV}}} \int_{V^t} T^t_{\text{mic}} dV \tag{40}$$

Applying the spatial averaging theorem (Theorem 40 in Ref. [6]) to Eq. (36) leads to

$$\langle \nabla \cdot \mathbf{v}^b_{\text{mic}} \rangle = \nabla \cdot \langle \mathbf{v}^b_{\text{mic}} \rangle + \frac{1}{V^{\text{REV}}} \int_{A_{bt}} \mathbf{n}_{bt} \cdot \mathbf{v}^b_{\text{mic}} dA = 0 \tag{41}$$

The surface integral represents the volumetric rate of blood bleeding off to the solid matrix through the interfacial vascular wall. Most microcirculatory systems are with a capillary blood filtration larger than reabsorption so that there is a net filtration of blood from the intravascular to the extravascular regions. However, this surface integral is negligibly small because the lymphatic system brings the excess blood from the interstitium to the intravascular compartment [4]. Therefore, Eq. (41) reduces into

$$\nabla \cdot \langle \mathbf{v}^b_{\text{mic}} \rangle = 0 \tag{42}$$

Note that the superficial average defined in Eqs. (39) and (40) is an unsuitable macroscale variable because it can yield erroneous results. For example, if the temperature of the blood were constant, the superficial average would differ from it [88]. On the other hand, intrinsic phase averages do not have this shortcoming. These averages are defined by

$$\langle T^b_{\text{mic}} \rangle^b = \frac{1}{V^b} \int_{V^b} T^b_{\text{mic}} dV \tag{43}$$

and

$$\langle T^t_{\text{mic}} \rangle^t = \frac{1}{V^t} \int_{V^t} T^t_{\text{mic}} dV \tag{44}$$

Also, intrinsic averages are related to superficial averages by

$$\langle T^b_{\text{mic}} \rangle = \varepsilon^b \langle T^b_{\text{mic}} \rangle^b \tag{45}$$

and

$$\langle T^t_{\text{mic}} \rangle = \varepsilon^t \langle T^t_{\text{mic}} \rangle^t \tag{46}$$

where ε^b and ε^t are the volume fractions of the blood and tissue with $\varepsilon^t = 1 - \varepsilon^b$.

By applying Eqs. (42), (45), and (46) and the spatial averaging theorem (Theorem 40 in Ref. [6]) and neglecting variations of physical properties within the REV, Eqs. (37) and (38) become

$$\underbrace{(\rho c \varepsilon)^b_{\text{mac}} \frac{\partial \langle T^b_{mic} \rangle^b}{\partial t}}_{\text{accumulation}} + \underbrace{(\rho c \varepsilon)^b_{\text{mac}} \langle \mathbf{v}^b_{\text{mic}} \rangle^b \cdot \nabla \langle T^b_{\text{mic}} \rangle^b}_{\text{convection}} = \underbrace{\nabla \cdot \left\{ k^b_{\text{mac}} \left[\varepsilon^b_{\text{mac}} \nabla \langle T^b_{\text{mic}} \rangle^b + \frac{1}{V^{\text{REV}}} \int_{A_{bt}} \mathbf{n}_{bt} \tilde{T}^b_{\text{mic}} dA \right] \right\}}_{\text{conduction}}$$

$$\underbrace{- (\rho c)^b_{\text{mac}} \nabla \cdot \langle \tilde{\mathbf{v}}^b_{\text{mic}} \tilde{T}^b_{\text{mic}} \rangle}_{\text{dispersion}} + \underbrace{\frac{1}{V^{\text{REV}}} \int_{A_{bt}} \mathbf{n}_{bt} \cdot k^b_{\text{mic}} \nabla T^b_{\text{mic}} dA}_{\text{interfacial flux}} \underbrace{- (\rho c)^b_{\text{mac}} \frac{1}{V^{\text{REV}}} \int_{A_{bt}} \mathbf{n}_{bt} \cdot \mathbf{v}^b_{\text{mic}} T^b_{\text{mic}} dA}_{\text{perfusion}} \tag{47}$$

and

$$\underbrace{(\rho c\varepsilon)^t_{\rm mac}\frac{\partial\langle T^t_{\rm mic}\rangle^t}{\partial t}}_{\text{accumulation}} = \underbrace{\nabla\cdot\left\{k^t_{\rm mac}\left[\varepsilon^t_{\rm mac}\nabla\langle T^t_{\rm mic}\rangle^t+\frac{1}{V^{\rm REV}}\int_{A_{bt}}\mathbf{n}_{tb}\widetilde{T}^t_{\rm mic}dA\right]\right\}}_{\text{conduction}} + \underbrace{\frac{1}{V^{\rm REV}}\int_{A_{bt}}\mathbf{n}_{tb}\cdot k^t_{\rm mic}\nabla T^t_{\rm mic}dA}_{\text{interfacial flux}} + \underbrace{\varepsilon^t_{\rm mac}\langle(q_m)^t_{\rm mic}\rangle^t}_{\substack{\text{metabolic}\\ \text{thermal source}}} \underbrace{-(\rho c)^b_{\rm mac}\frac{1}{V^{\rm REV}}\int_{A_{bt}}\mathbf{n}_{tb}\cdot\mathbf{v}^b_{\rm mic}\mathrm{T}^b_{\rm mic}dA}_{\text{perfusion}} \tag{48}$$

Here $\tilde{\mathbf{v}}^b_{\rm mic}=\mathbf{v}^b_{\rm mic}-\langle\mathbf{v}^b_{\rm mic}\rangle^b$, $\widetilde{T}^b_{\rm mic}=T^b_{\rm mic}-\langle T^b_{\rm mic}\rangle^b$, and $\widetilde{T}^t_{\rm mic}=T^t_{\rm mic}-\langle T^t_{\rm mic}\rangle^t$. A rigorous closure is not available at present for these spatial deviation velocity and temperature in the context of bioheat transfer. Nakayama and Kuwahara [4] recently modeled the blood interfacial convective heat transfer by using the Newton law of cooling and approximated the effect of the blood perfusion by using the perfusion rate and macroscale temperature difference between blood and tissues. This leads to a simplified two-equation macroscale model

$$(\rho c\varepsilon)^b_{\rm mac}\left(\frac{\partial T^b_{\rm mac}}{\partial t}+\mathbf{v}^b_{\rm mac}\cdot\nabla T^b_{\rm mac}\right)=\nabla\cdot(\mathbf{K}^b_{\rm mac}\cdot\nabla T^b_{\rm mac})+(\rho\varepsilon q_c)^b_{\rm mac}+(\rho\varepsilon q_p)^b_{\rm mac} \tag{49}$$

and

$$(\rho c\varepsilon)^t_{\rm mac}\frac{\partial T^t_{\rm mac}}{\partial t}=\nabla\cdot(\mathbf{K}^t_{\rm mac}\cdot\nabla T^t_{\rm mac})+(\rho\varepsilon q_c)^t_{\rm mac}+(\rho\varepsilon q_p)^t_{\rm mac}+(\varepsilon q_m)^t_{\rm mac} \tag{50}$$

where

$$T^b_{\rm mac}=\langle T^b_{\rm mic}\rangle^b \tag{51}$$

$$T^t_{\rm mac}=\langle T^t_{\rm mic}\rangle^t \tag{52}$$

$$\mathbf{K}^b_{\rm mac}=(\varepsilon\mathbf{k})^b_{\rm mac}+(\mathbf{k}_{\rm dis})^{bt}_{\rm mac} \tag{53}$$

$$\mathbf{K}^t_{\rm mac}=(\varepsilon\mathbf{k})^t_{\rm mac} \tag{54}$$

$$(\rho\varepsilon q_c)^b_{\rm mac}=-(\rho\varepsilon q_c)^b_{\rm mac}=-ha(T^b_{\rm mac}-T^t_{\rm mac}) \tag{55}$$

$$(\rho\varepsilon q_p)^b_{\rm mac}=-(\rho\varepsilon q_p)^b_{\rm mac}=-(\rho c\omega)^b_{\rm mac}(T^b_{\rm mac}-T^t_{\rm mac}) \tag{56}$$

Here $\mathbf{K}^b_{\rm mac}$ and $\mathbf{K}^t_{\rm mac}$ are the effective thermal conductivity tensor of blood and tissue, respectively, $\mathbf{k}$ is the thermal conductivity tensor, $\mathbf{k}_{\rm dis}$ is the thermal dispersion conductivity tensor, h is the convective heat transfer coefficient ($\mathrm{W/m^2\,K}$), a is the volumetric contact area between tissue and blood ($\mathrm{m^2/m^3}$), and ω is the perfusion rate ($\mathrm{kg/m^3\,s}$). Therefore, the microscale effects are represented by $\mathbf{k}_{\rm dis}$, ha, and ω in Eqs. (49) and (50). A rigorous theory regarding $\mathbf{k}_{\rm dis}$, ha, and ω is, however, not available at present.

A similar averaging has also been applied to blood momentum equation (Eq. (27)). The result is available, for example, in Refs. [84–86,88]. To examine the countercurrent heat exchange between the arterial and venous blood vessels in the circulatory systems, a three-energy equation model has also been developed in Ref. [4] by following a similar approach.

When the system is isotropic and the physical properties of blood and tissue are constant, Eqs. (49) and (50) reduce to

$$\gamma^b_{\rm mac}\left(\frac{\partial T^b_{\rm mac}}{\partial t}+\mathbf{v}^b_{\rm mac}\cdot\nabla T^b_{\rm mac}\right)=(k_{\rm eff})^b_{\rm mac}\Delta T^b_{\rm mac}-ha(T^b_{\rm mac}-T^t_{\rm mac})-(\rho c\omega)^b_{\rm mac}(T^b_{\rm mac}-T^t_{\rm mac}) \tag{57}$$

and

$$\gamma^t_{\rm mac}\frac{\partial T^t_{\rm mac}}{\partial t}=(k_{\rm eff})^t_{\rm mac}\Delta T^t_{\rm mac}+ha(T^b_{\rm mac}-T^t_{\rm mac})+(\rho c\omega)^b_{\rm mac}(T^b_{\rm mac}-T^t_{\rm mac})+(\varepsilon q_m)^t_{\rm mac} \tag{58}$$

where the effective thermal conductivities $(k_{\rm eff})^b_{\rm mac}$ and $(k_{\rm eff})^t_{\rm mac}$ are

$$(k_{\rm eff})^b_{\rm mac}=(\varepsilon k)^b_{\rm mac}+(k_{\rm dis})^{bt}_{\rm mac} \tag{59}$$

$$(k_{\rm eff})^t_{\rm mac}=(\varepsilon k)^t_{\rm mac} \tag{60}$$

The effective thermal capacities $\gamma^b_{\rm mac}$ and $\gamma^t_{\rm mac}$ are

$$\gamma^b_{\rm mac}=(\rho c\varepsilon)^b_{\rm mac} \tag{61}$$

$$\gamma^t_{\rm mac}=(\rho c\varepsilon)^t_{\rm mac} \tag{62}$$

3.3 Analysis. Rewrite Eqs. (57) and (58) in their operator form

$$\begin{bmatrix}\gamma^b_{\rm mac}\frac{\partial}{\partial t}+\gamma^b_{\rm mac}\mathbf{v}^b_{\rm mac}\cdot\nabla-(k_{\rm eff})^b_{\rm mac}\Delta+G & -G\\ -G & \gamma^t_{\rm mac}\frac{\partial}{\partial t}-(k_{\rm eff})^t_{\rm mac}\Delta+G\end{bmatrix}\times\begin{bmatrix}T^b_{\rm mac}\\ T^t_{\rm mac}\end{bmatrix}=\begin{bmatrix}0\\ (\varepsilon q_m)^t_{\rm mac}\end{bmatrix} \tag{63}$$

where the lumped convection-perfusion coefficient G is

$$G=ha+(\rho c\omega)^b_{\rm mac} \tag{64}$$

We then obtain an uncoupled form by evaluating the operator determinant and dividing by $G(\gamma^b_{\rm mac}+\gamma^t_{\rm mac})$

$$\frac{\partial T^b_{\rm mac}}{\partial t}+\tau_q\frac{\partial^2 T^b_{\rm mac}}{\partial t^2}+\frac{\gamma^b_{\rm mac}}{\gamma^b_{\rm mac}+\gamma^t_{\rm mac}}\mathbf{v}^b_{\rm mac}\cdot\nabla T^b_{\rm mac}=\alpha\Delta T^b_{\rm mac}+\alpha\tau_T\frac{\partial}{\partial t}(\Delta T^b_{\rm mac})+\frac{\alpha}{k}\left[F(\boldsymbol{r},t)+\tau_q\frac{\partial F(\boldsymbol{r},t)}{\partial t}\right]^b_{\rm mac} \tag{65}$$

$$\frac{\partial T^t_{\rm mac}}{\partial t}+\tau_q\frac{\partial^2 T^t_{\rm mac}}{\partial t^2}+\frac{\gamma^b_{\rm mac}}{\gamma^b_{\rm mac}+\gamma^t_{\rm mac}}\mathbf{v}^b_{\rm mac}\cdot\nabla T^t_{\rm mac}=\alpha\Delta T^t_{\rm mac}+\alpha\tau_T\frac{\partial}{\partial t}(\Delta T^t_{\rm mac})+\frac{\alpha}{k}\left[F(\boldsymbol{r},t)+\tau_q\frac{\partial F(\boldsymbol{r},t)}{\partial t}\right]^t_{\rm mac} \tag{66}$$

where

$$\tau_q = \frac{\gamma^b_{\text{mac}}\gamma^t_{\text{mac}}}{G(\gamma^b_{\text{mac}} + \gamma^t_{\text{mac}})} \tag{67}$$

$$\tau_T = \frac{\gamma^b_{\text{mac}}(k_{\text{eff}})^t_{\text{mac}} + \gamma^t_{\text{mac}}(k_{\text{eff}})^b_{\text{mac}}}{G[(k_{\text{eff}})^b_{\text{mac}} + (k_{\text{eff}})^t_{\text{mac}}]} \tag{68}$$

$$k = (k_{\text{eff}})^b_{\text{mac}} + (k_{\text{eff}})^t_{\text{mac}} \tag{69}$$

$$\rho c = \gamma^b_{\text{mac}} + \gamma^t_{\text{mac}} \tag{70}$$

$$\alpha = \frac{k}{\rho c} = \frac{(k_{\text{eff}})^b_{\text{mac}} + (k_{\text{eff}})^t_{\text{mac}}}{\gamma^b_{\text{mac}} + \gamma^t_{\text{mac}}} \tag{71}$$

$$\left[F(\boldsymbol{r},t) + \tau_q \frac{\partial F(\boldsymbol{r},t)}{\partial t}\right]^b_{\text{mac}} = (\varepsilon q_m)^t_{\text{mac}} - \frac{(k_{\text{eff}})^b_{\text{mac}}(k_{\text{eff}})^t_{\text{mac}}}{G}\Delta^2 T^b_{\text{mac}} - \frac{\gamma^b_{\text{mac}}}{G}\mathbf{v}^b_{\text{mac}} \cdot \left[\gamma^t_{\text{mac}}\frac{\partial}{\partial t}\nabla T^b_{\text{mac}} - (k_{\text{eff}})^t_{\text{mac}}\nabla \Delta T^b_{\text{mac}}\right] \tag{72}$$

$$\left[F(\boldsymbol{r},t) + \tau_q \frac{\partial F(\boldsymbol{r},t)}{\partial t}\right]^t_{\text{mac}} = -\frac{(k_{\text{eff}})^b_{\text{mac}}(k_{\text{eff}})^t_{\text{mac}}}{G}\Delta^2 T^t_{\text{mac}} - \frac{\gamma^b_{\text{mac}}}{G}\mathbf{v}^b_{\text{mac}} \cdot \left[\gamma^t_{\text{mac}}\frac{\partial}{\partial t}\nabla T^t_{\text{mac}} - (k_{\text{eff}})^t_{\text{mac}}\nabla \Delta T^t_{\text{mac}}\right] + \frac{1}{G}\left[\gamma^b_{\text{mac}}\frac{\partial}{\partial t} + \gamma^b_{\text{mac}}\mathbf{v}^b_{\text{mac}} \cdot \nabla - (k_{\text{eff}})^b_{\text{mac}}\Delta + G\right](\varepsilon q_m)^t_{\text{mac}} \tag{73}$$

Therefore, both T^b_{mac} and T^t_{mac} are governed by dual-phase-lagging heat-conduction equations (Eqs. (65) and (66)) with τ_q and τ_T as the phase lags of the heat flux and the temperature gradient, respectively [21,25,89]. Here, $F(\boldsymbol{r},t)$ is the volumetric heat source. k, ρc, and α are the effective thermal conductivity, capacity, and diffusivity, respectively. While the heat conduction in blood and tissue is assumed to be Fourier-type at microscale (Eqs. (28) and (29)), it is DPL-type at macroscale. It is thus more proper to use the DPL constitutive relation for the heat flux density vector in developing macroscale bioheat equations via scaling-down from the global scale based on the mixture theory of continuum mechanics.

Although both Eqs. (25) and (66) are of DPL-type for macroscale tissue temperature, the distinct difference exists between them. The explicit relation between T^t_{mic} and T^t_{mac} and the way for computing τ_q and τ_T are not available in the former; they are available in the latter (Eqs. (52), (67), and (68)). The former involves both T^b_{mac} and T^t_{mac}; the latter contains only the tissue temperature T^t_{mac}. The effect of blood conduction and convection is not considered in the former; it is incorporated in the latter.

There is a metabolic heat term $(\varepsilon q_m)^t_{\text{mac}}$ in the blood energy equation (Eqs. (65) and (72)) and a convective term $\mathbf{v}^b_{\text{mac}} \cdot \nabla T^t_{\text{mac}}$ in the tissue energy equation (Eq. (66)). Therefore, both microscale metabolic heat generation in tissue and microscale convection in blood are with their macroscale manifestation in both blood and tissue. The interaction between blood and tissue also yields a very rich way that the interfacial convective heat transfer, the blood velocity, the perfusion, and the metabolic reaction affect T^b_{mac} and T^t_{mac} (Eqs. (65), (66), (72), and (73)). It would be very difficult to model this rich interaction by the mixture theory of continuum mechanics.

Consider

$$\frac{\tau_T}{\tau_q} = 1 + \frac{(\gamma^2)^b_{\text{mac}}(k_{\text{eff}})^t_{\text{mac}} + (\gamma^2)^t_{\text{mac}}(k_{\text{eff}})^b_{\text{mac}}}{\gamma^b_{\text{mac}}\gamma^t_{\text{mac}}[(k_{\text{eff}})^b_{\text{mac}} + (k_{\text{eff}})^t_{\text{mac}}]} \geq 1 \tag{74}$$

By the condition for the existence of thermal waves that requires $\tau_T/\tau_q < 1$ [21,72], therefore, there is no thermal wave in bioheat transfer based on the model in Eqs. (65) and (66). It is also interesting to note that although each τ_q and τ_T is G dependent, the ratio τ_T/τ_q is not. Therefore the evaluation of τ_T/τ_q will be much simpler than τ_q or τ_T. Based on some simplified versions of Eq. (66), the lagging behavior has been recently examined in Refs. [75,90].

4 Concluding Remarks

Macroscale thermal models have been developed for biological tissues either by the mixture theory or by the porous-media theory. The former considers blood and tissues as a mixture of continuum deformable media and develops the macroscale point equations via scaling-down the global balance equations. In this approach, neither microscale presentation of the system nor microscale quantities are introduced. Phase properties are defined at the macroscale. The global balance equations are formed in terms of macroscale properties and with additional terms accounting for the interaction between blood and tissue. Required constitutive equations for the heat flux vector are supplied by the Fourier law, the CV relation, or the DPL relation. The thermal models developed in this approach include the classical Pennes model, the Wulff model, the Klinger model, and the Chen and Holmes model, the thermal wave bioheat model, and the DPL bioheat model. The heterogeneous and nonisotropic feature of biological tissue yields normally a strong noninstantaneous response between heat flux and temperature gradient in nonequilibrium heat transport. The DPL bioheat model is thus recommended in order to catch such a lagging behavior.

The porous-media theory considers biological tissue as a blood-saturated porous matrix, including cells and interstices, and develops the macroscale point equations via scaling-up the microscale model. In this approach, both conservation and constitutive equations are introduced at the microscale. The resulting microscale field equations are then averaged over a REV to obtain the macroscale field equations. In the process of averaging, the multiscale theorems are used to convert integrals of gradient, divergence, curl, and partial time derivatives of a function into some combination of gradient, divergence, curl, and partial time derivatives of integrals of the function and integrals over the boundary of the REV. The closure model must be provided for the unclosed terms in macroscale field equations that represent the microscale effect in order to form a closed system. The macroscale model developed by this approach shows the DPL-type bioheat transfer at macroscale for both blood and tissue phases and the sophisticated effect of the interfacial convective heat transfer, the blood velocity, the perfusion, and the metabolic reaction on macroscale temperature fields in blood and tissue.

Therefore, the mixture theory and porous-media approaches are top-down and bottom-up approaches, respectively, in nature. Simplicity is the main advantage of the former. However, it offers no connection between microscale and macroscale properties and is not capable to accurately describe the rich blood-tissue interaction. The porous-media approach successfully overcomes these drawbacks, thereby offering an effective way for developing accurate macroscale thermal models for biological tissues. The requirement of a rigorous closure model presents, however, unique challenges for materializing its promising potential. Future research is in great demand to define the potential of this promising approach by developing a rigorous closure theory.

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