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A Volume-Averaged Mathematical Model for Biotransport Part I Macro-micro Conservations in Tissue Transports

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***Abstract*--Modeling of biotransport phenomena inside human body has being paid attentions for last 50 years. Most of mathematical model only consider energy conservation which is bioheat. However in biosystems, the heat and chemical compositions with mas and momentum are coupled. In this research, due to the complexity of tissue structure, especially with Trans-vascular Blood Perfusion we rigorously derive and present a volume-averaged mathematical model which covers complete conservations of mass, momentum, energy and compositions. The model can be considered as a fundamental and general biotransport model used in any biosystems.**

***Keywords* – Biotransport, Conservation equation, Bioheat, Biosystem, Biophysics, Mathematical modeling, Volume averaging, Interfacial transfer**

I. INTRODUCTION

In biological and physiological systems, it is extremely important to measure, monitor, and predict temperature distribution, metabolic heat generation, diffusive behaviors (heat conduction and mass diffusion), velocity distribution and convective arterial-venous blood flows, perfusion in tortuous capillary flows, distributions of mass concentration of compositions etc. within human body. All of these desired quantities of the transport phenomenon (abbreviated as biotransport), defined as the total conservations of mass, momentum, energy, and mass compositions. It is desirable to have an accurate biotransport model which can help determine these biotransport quantities in human systems for translational research, clinical trials, medical therapies, and other patient-oriented healthcare services. For example, bioheat transfer model as a component of biotransport model is the basis of thermotherapy (hyperthermia), thermoregulations, cryosurgery, thermal ablation, thermography for diagnostics etc.

However, due to its biological complexity and nature dynamic behaviors, it is very difficult to predict, model and simulate the transport phenomena in biological and physiological systems on a microscopic scale due to its complexities of human tissue architecture (especially heterogeneity and anisotropy) and physiological physics (especially interactions between different media). In general, transport phenomena include the convection of micro-fluid flow, perfusion of arterial-venous blood in the tubes or through tortuous capillary structures, various diffusions due to molecular interaction, interfacial transfer (exchanges) between different bio-structures or bio-media, and interactions with external environment (such as gravitation, heat radiation, electromagnetic forces, or other possible external forces, convections to the existing environment etc.). A general model of biotransport should be developed in terms of the conservations of averaged mass, momentum, energy, and species mass. Therefore, a consistent model of biotransport should compose of bioheat, biomass, and bioconvection models [1]. The bioheat model is used to account for heat transfer in biological systems or tissues. It requires consider many important factors such as heat conduction in the tissue, heat convection and perfusion of the blood, heat storage capacity within the blood and tissue, metabolic heat generation, thermal and anatomical properties of selected organs and targeted tissues, geometries of tissue architecture, morphology and topology of blood vessels, their possible interactions with the environment etc. [2]. The heterogeneity of the tissue architecture and tortuosity of vessels

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are the important features to be considered for the modeling implementation. The biomass model is used for analyzing mass transfer of multi compositions, and bioconvection is introduced to take the consideration of any possible micro-fluid convection in biological systems such as tissues.

Such models and pertinent work can be found in many literatures and remarkable investigations. However, there still lacks of consistent and generic model which is rigorously derived.

A pioneer work in modeling bioheat transfer in tissues was landmarked by Harry Pennes [3] who proposed to contain two heat sources: produced by tissue metabolism and transferred by blood perfusion of vascular arterioles. It was the first time to incorporate perfusion heat source into the bioheat equation for analysis of temperature distribution in human resting farearm [4,5]. The model has been used in many biomedical applications and biomedical research. It is the basis for human thermotherapy (hyperthermia) (such as thermal therapy for prostate cancer [6] and the human thermoregulation [7].

II. Transport Theories and Microscopic

In many multiphase studies, the medium commonly refers to a phase, saying solid, liquid, or gas. However, in biological systems, a medium k can be referred to different biological media (subjects) such as veins, micro-blood-fluid (liquid) in veins or arteries, air and gases (gas), bones (solid), interstitial fluid flow in extravascular architecture (liquid), interventional dispersed particles such as nanoparticles (solid), fat, etc. People can also classify human biological media of tissues into cells, vasculatures (intra- or extravascular architecture) such as arterial vessels and veins, etc. In computational oncology models, people classify media representing cancer tumor as cancer cells, normal and malignant cells and interstitial vascular spaces.

III. Microscopic Biotransport Equations

A microscopic biotransport model with average mass, momentum, energy, and mass centration of composition conservations for a microscopic biological medium k can be expressed in a general form as

$$\frac{\partial(\rho_k \Psi_k)}{\partial t} + \nabla \cdot (\rho_k \vec{v}_k \Psi_k) = -\nabla \cdot \vec{F}_k^{\Psi} + S_k^{\Psi}$$

where Ψ_k is a generic transport quantity or variable of biological medium k at microscopic scale. ρ_k is selected microscopic medium's density, $\vec{v}_k$ is the velocity due to the medium movement or convection, $\vec{F}_k^{\Psi}$ is the total associated transfer flexes, and S_k^{Ψ} is the corresponding accumulated sources imposed on the biological system. Ψ_k can be refer to 1 for microscopic mass conservation, microscopic medium $\vec{v}_k$ for microscopic momentum conservation, microscopic medium enthalpy h_k for microscopic energy conservation, and mass concentration of compositions $C_{i,k}$ (i=1,2,3,…N) or microscopic mass concentration conservations, respectively. The derivation can be found in [8] when the authors developed a model for multi-phase model for the transport during solidification processing.

IV. Microscopic Medium Identification

Microscopically, the index k refers to a single physical medium (or subject), For example, viscous blood fluid in either arterials or veins, cells, air flow in airways, tissue architectures, gas in colons, fluid in interstitial space, bone, etc. Therefore, the above biotransport model with multiple conservations can be applied to these individual medium. As all known, the complexity of tissue architecture and heterogeneity and anisotropy of vascular architectures make it very difficult to describe the geometries and topologies of the boundaries between these identified medium on microscopic scale. The macroscopic description of the tissues and relevant biological factors such as perfusion and heat generations is necessary. In the macroscopic description, the concept of medium can be referred to not only pure substance like blood, but also mixed media. In analogous of the modeling in multiphase flows where the medium index refers to individual physical phase (either solid, or liquid, or gas), people can develop a multi-medium model (as a multi-medium treatment, coined by Roetzei and Xuan [2] for describing and modeling such complex and hybrid tissue systems. Since the Pennes's bioheat equation, many studies demonstrated the success of such

consideration to obtain a generic model of bioheat. In their remarkable works, the medium index and their physical meaning can be summarized as follows.

V. MACROSCOPIC MEDIUM IDENTIFICATION

On a macroscopic scale, human biological tissues can be classified into vascular region and extravascular regions [9]. The vascular region contains blood vessels (arteries or veins) and extravascular region contains tissue cells and interstitium that composes of extravascular matrix and interstitial fluid. In this classification, the subscript of biological medium index *k* can be *v* and *e*. In this way, the blood flow can be considered as an infiltrated flow in a saturated porous media (extravascular structure) as in [9].

One can classify three regions: bone (solid), vascular and extravascular regions. In this way the medium index k can be *b*, *v*, and *e*, respectively.

If there is no bone, one can has two media identifications. It should be noted that in the vascular region, both arteries and veins are be considered as hybrid medium. In order to account for the countercurrent heat exchange, the arterials and veins distinction should be identified. Under this consideration, one can classify the biological media into *b*, *ar*, *ve*, and *e*, media respectively. One can also identify media into bone, vascular region, cells, and extravascular matrix. If there is no bone, it can be three media: vascular region, cells, and intersititial space with intersititial fluid.

Similarly, in order to identify the interstitial fluid within the extravascular region, one can also classify biological media into *b*, *ar*, *ve*, *cell*, and *f*. It should be noted that more number of identified media, more equations of conservations being appeared in the model, which raise high computational complexity and requires intensive computations, although the physical descriptions becomes clearer. There is no unique medium identification. It depends on the objective of the model and simulation and availability of biological or biomedical data or parameters to be input and/or studied

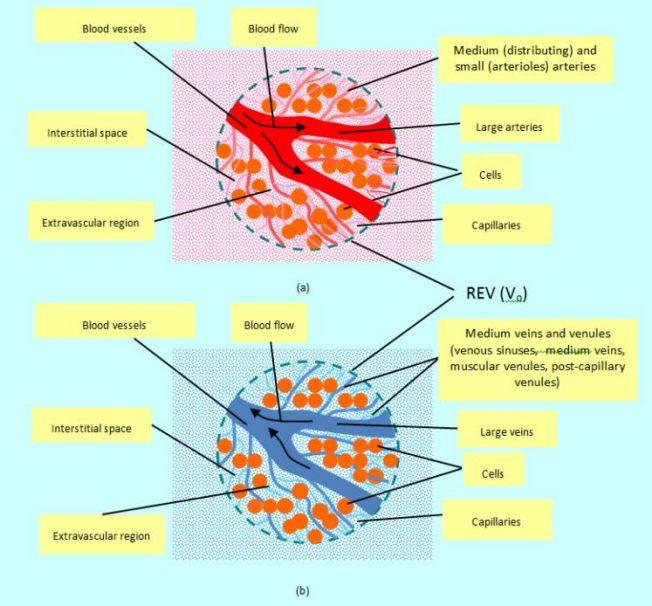

Figure 1 Representative elementary volume (REV) or control volume of human tissues with (a) vessels (arterials), extravascular regions (bone, cells, and intersititium); or (b) vessels (veins), extravascular regions (bone, cells, and intersititium) for countercurrent heat exchange

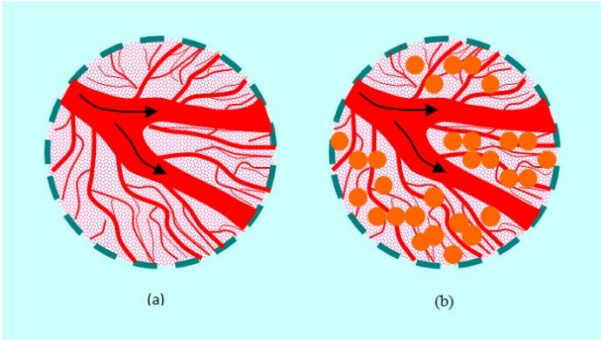

Figure 2 Different medium identification of human biological tissues within a REV: (a) two media: vessels (arteries) and extravascular region (k=v and e, i.e.,); (b) three media: vessels (arteries) , cells, and intersititium (i.e., k=v, c, and in).

The common medium identifications can be summarized in Table 1.

Table 1 Medium Identification in Bioheat Models

No. of Media to be Modeled	Physical Meaning of the Media	Medium Index k*	Components	Treatment	Reference
One-medium	Extravascular mixture (tissue)	e (or s)	Bone, cells, intersititial space (extravascular matrix)	As a soft-solid medium with heat exchange from arterial perfusion	[3]
One-medium	Extravascular mixture (tissue)	e (or s)	Bone, cells, intersititial space (extravascular matrix)	As a soft-solid medium with heat exchange from arterial perfusion	[10,11,12]
One-medium	Hybrid (mixed)	m=v+e	Blood, bones, cell, intersititial space (extravascular matrix)	As mixture of single medium	[13]
One-medium	Arterial vascular	a	Arteries	As a blood-fluid penetrated in porous media	[14]
	Veins (blood)	v	Veins	As a blood-fluid penetrated in porous media	
	Extravascular mixture (tissue)	e (or s)	Bone, cells, intersititial space (extravascular matrix)	As a soft-solid medium with heat exchange from arterial perfusion	
Two-media	Vascular mixture (blood)	v (or b)	Combined Arteries and/or Veins	As a fluid penetrated in porous media	[9]
	Extravascular mixture (tissue)	e (or s)	Bone, cells, intersititial space (extravascular matrix)	As solid porous matrix	
Two-media	Vascular mixture (blood)	v (or b)	Combined Arteries and/or Veins	As a fluid penetrated in porous media	[2]
	Extravascular mixture (tissue)	e (or s)	Bone, cells, intersititial space (extravascular matrix)	As solid porous matrix	
Three-media	Arterial vascular	a	Arteries	As a blood-fluid penetrated in porous media	[15]
	Veins (blood)	v	Veins	As a blood-fluid penetrated in porous media	
	Extravascular mixture (tissue)	e (or s)	Bone, cells, intersititial space (extravascular matrix)	As a soft-solid medium with heat exchange from arterial and venues perfusion	
Three-media	Arteries (blood)	a	Arteries	As a blood-fluid penetrated in porous media	[2]
	Veins (blood)	v	Veins	As a blood-fluid penetrated in porous media	
	Extravascular mixture (tissue)	e (or s)	Bone, cells, intersititial space (extravascular matrix)	As soft-solid tissue as porous matrix	
Three-media	Arteries (blood)	a	Arteries	As a blood-fluid penetrated in porous media	[9]
	Veins (blood)	v	Veins	As a blood-fluid penetrated in porous media	
	Extravascular mixture (tissue)	e (or s)	Bone, cells, intersititial space (extravascular matrix)	As soft-solid tissue as porous matrix	
* Note: Expressed in our notations					

VI. MICROSCOPIC CONSERVATIONS OF MASS, MOMENTUM, ENERGY, MASS CONCENTRATIONS

For $\Psi_k = 1$, $\vec{F}_k^{\Psi} = \vec{F}_k^{1} = 0$, and $S_k^{\Psi} = S_k^{m}$ (mass source per unit volume, or volumetric mass generation), the equation reduces to mass conservation equation as

$$\frac{\partial \rho_k}{\partial t} + \nabla \cdot (\rho_k \vec{v}_k) = S_k^m$$

In the tissue, either blood flow or interstitial fluid flow can be considered as incompressible, viscous medium and their densities don't vary. However, the biotransport equation is applied to gas, say, in airway ventilation or airflow in the study of pulmonary disease, the density of air cannot be assumed as constant. It changes with the volume and pressure in the airways. Therefore, the variation of density change should be considered and the above mass conservation equation in the fluid flow model in biotransport should be incorporated in the biotransport model.

For $\Psi_k = \vec{v}_k$, $\vec{F}_k^{\Psi} = \tau^v - p_k I$ (general stress), and $S_k^{\Psi} = S_k^v = b_k$ (acceleration per unit volume, or volumetric force), the microscopic general transport equation reduces to momentum conservation equation as

$$\frac{\partial (\rho_k \vec{v}_k)}{\partial t} + \nabla \cdot (\rho_k \vec{v}_k \vec{v}_k) = -\nabla p_k + \nabla \cdot \tau_k^v + \vec{b}_k$$

where $\vec{v}_k$ is the velocity of medium k, $\vec{F}_k^v = \tau^v - p_k I$ is the general stress in terms of pressure and share stress, and b_k is the external force per unit volume, including gravitation. This is the equation to account for any micro-fluid flows such as vascular blood flow in vessels, penetration in the interstitial structures, and air flow in respiratory systems. Mathematically it yields the Navies-Stocks' equation for fluid flows.

For $\Psi_k = h_k$, $\vec{F}_k^{\Psi} = \vec{q}_k^{h}$ and $S_k^{\Psi} = S_k^{q}$ (heat source per unit volume, also called volumetric heat source), the microscopic general transport equation reduces to energy conservation equation as

$$\frac{\partial (\rho_k h_k)}{\partial t} + \nabla \cdot (\rho_k \vec{v}_k h_k) = -\nabla \cdot \vec{q}_k^{h} + S_k^q$$

This equation is the bioheat equation in terms of enthalpy. One can easily reduce this equation to the one in terms of temperature by employing the relationships between enthalpy and temperature.

For $\Psi_k = C_{i,k}$, $\vec{F}_k^{\Psi} = \vec{j}_{i,k}^{\,j}$ and $S_k^{\Psi} = S_{i,k}^{j}$ (mass concentration source per unit volume, also called volumetric mass concentration source), the microscopic general transport equation reduces to mass conservation mass equation as

$$\frac{\partial (\rho_k C_{i,k})}{\partial t} + \nabla \cdot (\rho_k \vec{v}_k C_{i,k}) = -\nabla \cdot \vec{j}_{i,k}^{\,j} + S_{i,k}^{j} \quad (2)$$

This equation is biomass equation in terms of mass concentration of i component, Ci,k. The detailed derivation of microscopic transport equations can be found in Bird et al (2002). The summary of Microscopic conservation equations is given in Table 2.

As all know, due to the complexities of tissue anatomic structure, biological medium's heterogeneity and anisotropy, the coupling of many biophysical phenomena, physiological responses, it is extremely difficult to solve these equations on a microscopic scale. The accurate anatomic information on the geometries of boundaries between physical media (such as microscopic interfaces of blood vessels, surfaces of bone, cells distributions, interstitial extravascular structures, etc.) should be precisely given. The transport (exchange) between different media should be accurately depicted. Such modeling becomes very complicated and its computing is very intensive with high computational complexity.

Alternatively, people have been developing macroscopic model which considers an interesting medium modeling as an artificial hybrid of multiple physical media. Such paradigm can be implicitly seen in [3] that has been widely used in either biomedical/biomechanical research or clinical applications.

In the past, many bioheat models [4,5,14,15], were proposed without theoretical derivations.

VII. VOLUME AVERAGING TECHNIQUES AND THEORIES

The successes of using the volume averaging techniques (VAT) widely-used in many multi-phase or porous media systems inspirited its applications to model complex human biological systems. Many efforts have

been made to derive bioheat equation using VAT [1,2,917]. Among them, Nakayama and Kuwahara [9] and Khaled and Vafai, [1] used VAT to derive a general set of bioheat transfer equations for blood flows and its surrounding biological tissues, considered as porous media.

The detailed averaging theorems and associated averaging operations can be found in many literatures [8]. The main definitions and relations are highlighted as follows. The definition of volume average of transport quantities Ψ in human medium k is

$$< \Psi_k >= \frac{1}{V_o} \int_{V_o} X_k \Psi_k dV$$

where the variable V_o refers to the representative element volume (REV) of region of interest (ROI). The variable $X_k(x, y, z, t)$ is a medium existing function, being equal to unity in medium k and zero otherwise. For example, if one considers the tissue regions have 2 media, say vascular region or extravascular region (k=v and ve), one can imagines that there are two transport variables $\Psi_{k=v}$ and $\Psi_{k=ve}$. Within the control volume, the contribution of extravascular medium at the special position to the averaged value of the transport variable of the vascular medium $\Psi_{k=v}$ is none. Mathematically $X_{k=v}(x^*, y^*, z^*, t^*)$ is zero at the specified spatial position (x^*, y^*, z^*). Rigorously speaking, the medium existing function varies with time, since the lived human biological systems always changed with the environment. Even for a stationary patient who is lying or sitting still during a therapy, a patient's internal biological and physiological system may also be changed dynamically. The temperature variations of patient body or region of interest can cause the volumes of patient vessels expend or shrink, which indirectly influences the imposed existing function. However, in many common situations, such changes may be considered negligibly small for case study.

The intrinsic volume average is defined as the volume averaged transport quantity within a specified medium k. It is mathematically given as

$$< \Psi_k >^k = \frac{1}{V_k} \int_{V_o} X_k \Psi_k dV$$

$$= (\frac{V_o}{V_k}) \frac{1}{V_o} \int_{V_o} X_k \Psi_k dV = (\frac{V_o}{V_k}) < \Psi_k >$$

$$= \frac{1}{\varepsilon_k} < \Psi_k >$$

The variable V_k refers to the volume occupied by the specified medium k. Each human medium occupies a single spatial location with the respect of time varying. The intrinsic volume averaged transport variable represents the quantity averaged over the all selected medium; but ignoring the percentage of the medium space to the total volume within the observed control unit. In order to account for the appearance of the medium occupying the volume space, a superficial quantity is introduced in the volume averaging technique. Therefore, the superficial volume averaged transport quality $< \Psi_k >$ can be defined in the following. The definition gives the relationships to intrinsic counterpart $< \Psi_k >^k$ through a volume fraction (spatial occupation percentile) ε_k, V_k / V_o.

$$< \Psi_k >= \varepsilon_k < \Psi_k >^k \quad (6)$$

If one identifies a tissue rerest into N sub-regions composited of human entities (such as vascular region and extravascular region, or blood vessels, cells, interstitium), the medium index k can be (k=1,2,3, …N). The accumulated volume occupied by all the media should be identical to the representative elementary volume V_o. That is

$$V_o = \sum_{k=1,2,3,...}^{N} V_k \quad \text{or} \quad \sum_{k=1,2,3,...}^{N} \varepsilon_k = 1$$

Each medium's occupation over the representative elementary volume varies from position to position and from time to time. In general, the fraction is a dynamic variable which means it is a function of time. For example, tumor tissues evolutionarily grow or shrink at a relatively large time scale. In other words, theoretically, the occupations and medium distributions are dynamically changed over spatial and temporal spaces. Therefore, the occupation volume fraction is dependent of time and position (x, y, z). For a single patient, the value at specified time and position usually takes a different value. In most of case studies, the dependence of the fraction upon the time

change is neglected. The value at different biological position of a human can be dynamically monitored and obtained by using imaging modalities for example MRI. For internal tissue architecture comparisons, image registration is sometime necessary to align the image position for biological and anatomic studies.

For each visit case study of individual patent, the occupation volume fraction of human medium can be considered as constant value based on each individual's anatomic, biological and physiological systems. For modeling and simulating a therapeutic process, the occupation volume fraction becomes a dynamic parameter.

The difference between transport quantity and its volume averaged one is the spatial deviation [8,9], defined as

$$\widehat{\Psi}_k = (\Psi_k - < \Psi_k >^k) X_k$$

Based on the above definition, the volume averaged variable of the product of two transport quantities yields

$$< \Psi_k \Phi_k >^k =$$

$$< \Psi_k >^k < \Phi_k >^k + < \widehat{\Psi}_k \widehat{\Phi}_k >^k$$

The last term accounts for the dispersion effect due to volume averaging. Based on the volume averaging theorems, one has the following temporal derivative relationship

$$< \frac{\partial \Psi_k}{\partial t} >= \frac{\partial < \Psi_k >}{\partial t} - \frac{1}{V_o} \int_{A_k} \Psi_k \vec{w}_k \cdot \vec{n}_k dA$$

$$< \frac{\partial \Psi_k}{\partial t} >^k = \frac{1}{\varepsilon_k} < \frac{\partial \Psi_k}{\partial t} >$$

$$= \frac{1}{\varepsilon_k} (\frac{\partial < \Psi_k >}{\partial t} - \frac{1}{V_o} \int_{A_k} \Psi_k \vec{w}_k \cdot \vec{n}_k dA)$$

$$= \frac{1}{\varepsilon_k} [\frac{\partial (\varepsilon_k < \Psi_k >^k)}{\partial t} - \frac{1}{V_o} \int_{A_k} \Psi_k \vec{w}_k \cdot \vec{n}_k dA)]$$

$$= \frac{1}{\varepsilon_k} \frac{\partial (\varepsilon_k < \Psi_k >^k)}{\partial t} - \frac{1}{V_k} \int_{A_k} \Psi_k \vec{w}_k \cdot \vec{n}_k dA)$$

Therefore, one has

$$< \frac{\partial \Psi_k}{\partial t} >^k = \frac{1}{\varepsilon_k} \frac{\partial (\varepsilon_k < \Psi_k >^k)}{\partial t}$$

$$- \frac{1}{V_k} \int_{A_k} \Psi_k \vec{w}_k \cdot \vec{n}_k dA$$

Since

$$< \frac{\partial \Psi_k}{\partial t} >= \varepsilon_k < \frac{\partial \Psi_k}{\partial t} >^k$$

$$= \varepsilon_k (\frac{1}{V_k} \int_{V_o} \frac{\partial \Psi_k}{\partial t} dV) \varepsilon_k (\frac{1}{V_k} \int_{V_o} \frac{\partial \Psi_k}{\partial t} dV)$$

$$= \varepsilon_k \frac{\partial}{\partial t} (\frac{1}{V_k} \int_{V_o} \Psi_k dV) = \varepsilon_k \frac{\partial < \Psi_k >^k}{\partial t}$$

Comparing the above euqations, one has

$$\frac{\partial < \Psi_k >}{\partial t} - \frac{1}{V_o} \int_{A_k} \Psi_k \vec{w}_k \cdot \vec{n}_k dA = \varepsilon_k \frac{\partial < \Psi_k >^k}{\partial t}$$

or

$$\frac{\partial (\varepsilon_k < \Psi_k >^k)}{\partial t} - \frac{1}{V_o} \int_{A_k} \Psi_k \vec{w}_k \cdot \vec{n}_k dA \quad (11)$$

$$= \varepsilon_k \frac{\partial < \Psi_k >^k}{\partial t}$$

$$< \Psi_k >^k \frac{\partial \varepsilon_k}{\partial t} + \varepsilon_k \frac{\partial < \Psi_k >^k}{\partial t} \quad (12)$$

$$- \frac{1}{V_o} \int_{A_k} \Psi_k \vec{w}_k \cdot \vec{n}_k dA = \varepsilon_k \frac{\partial < \Psi_k >^k}{\partial t}$$

One has

$$< \Psi_k >^k \frac{\partial \varepsilon_k}{\partial t} - \frac{1}{V_o} \int_{A_k} \Psi_k \vec{w}_k \cdot \vec{n}_k dA = 0$$

Similarly, for spatial derivatives relationship, one can derive

$$< \nabla \Psi_k >= \nabla < \Psi_k > + \frac{1}{V_o} \int_{A_k} \Psi_k \vec{n}_k dA$$

$$< \nabla\Psi_k >^k = \frac{1}{\varepsilon_k} < \nabla\Psi_k >$$

$$= \frac{1}{\varepsilon_k}(\nabla < \Psi_k > + \frac{1}{V_o}\int_{A_k} \Psi_k \vec{n}_k dA)$$

Since

$$< \nabla\Psi_k >= \varepsilon_k < \nabla\Psi_k >^k$$

$$= \varepsilon_k \frac{1}{V_o}\int_{V_o} \nabla\Psi_k X_k dV$$

$$= \varepsilon_k \nabla(\frac{1}{V_o}\int_{V_o} \Psi_k X_k dV) = \varepsilon_k \nabla < \Psi_k >^k$$

Comparing the above equation with Equation, one has

$$\nabla < \Psi_k > + \frac{1}{V_o}\int_{A_k} \Psi_k \vec{n}_k dA$$

$$= \varepsilon_k \nabla < \Psi_k >^k + < \Psi_k >^k \nabla\varepsilon_k$$

$$+ \frac{1}{V_o}\int_{A_k} \Psi_k \vec{n}_k dA = \varepsilon_k \nabla < \Psi_k >^k$$

which yields

$$< \Psi_k >^k \nabla\varepsilon_k + \frac{1}{V_o}\int_{A_k} \Psi_k \vec{n}_k dA = 0$$

Adding the above two together, it yields

$$< \Psi_k >^k \frac{\partial\varepsilon_k}{\partial t} - \frac{1}{V_o}\int_{A_k} \Psi_k \vec{w}_k \cdot \vec{n}_k dA$$

$$+ < \Psi_k >^k \nabla\varepsilon_k + \frac{1}{V_o}\int_{A_k} \Psi_k \vec{n}_k dA = 0$$

$$< \Psi_k >^k (\frac{\partial\varepsilon_k}{\partial t} + \nabla\varepsilon_k)$$

$$- \frac{1}{V_o}\int_{A_k} \Psi_k \vec{w}_k \cdot \vec{n}_k dA + \frac{1}{V_o}\int_{A_k} \Psi_k \vec{n}_k dA = 0$$

$$< \Psi_k >^k \frac{d\varepsilon_k}{dt} - \frac{1}{V_o}\int_{A_k} \Psi_k \vec{w}_k \cdot \vec{n}_k dA$$

$$+ \frac{1}{V_o}\int_{A_k} \Psi_k \vec{n}_k dA = 0$$

This relationship holds any arbitrary variables and constant. Therefore, one sets $\Psi_k = 1$, it yields

$$\frac{d\varepsilon_k}{dt} = \frac{\partial\varepsilon_k}{\partial t} + \nabla\varepsilon_k = \frac{1}{V_o}\int_{A_k} \vec{w}_k \cdot \vec{n}_k dA - \frac{1}{V_o}\int_{A_k} \vec{n}_k dA$$

If there is no interface movement, $\vec{w}_k = 0$, $\frac{1}{V_o}\int_{A_k} \vec{w}_k \cdot \vec{n}_k dA = 0$, then $\frac{\partial\varepsilon_k}{\partial t}$ =0. That means the volume fraction is independent of time.

$$\frac{1}{V_o}\int_{A_k} \vec{n}_k dA = -\nabla\varepsilon_k$$

If $\frac{1}{V_o}\int_{A_k} \vec{n}_k d = 0$, then $\nabla\varepsilon_k = 0$.

The means the volume fraction is unchangeable with respect of spatial gradients. The value of ε_k remains constant. (17)

The topology of accumulated interfacial area (or boundaries between medium k and other media) gives the value of total derivative of occupation volume fraction by the medium k within the representative element volume (REV). It links the volume changes to its averaged interfacial boundary surrounding the medium. It should be noted that the medium can be either concentrated or distributed within the REV.

The topological variable becomes very an important physical and physiological parameter in evaluating cancer response and in deigning proper oncological treatments. It also links the microscopic geometric information from imaging modalities to macroscopic transports. Once we measured the interfacial area concentration, we can calculate the volume fraction.

VIII. MACROSCOPIC BIOTRANSPORT EQUATIONS

After taking the integration over the representative elementary volume and utilized volume averaging techniques and theorems, the macroscopic conservation equations to form a general macroscopic biotransport model can be expressed and listed in Table 2.

Mass conservation:

Γ_k is the total interfacial average mass transfer or exchange among media due to volume averaging. $\bar{M}_k$ is the total interfacial momentum transfer due to interaction of stresses at the interface and any possible interface (boundary between two media) movement. $\bar{Q}_k$ is the total interfacial energy exchange due to heat transfer at the interface, and due to free-energy difference between participating media (such phase change). In bioheat model, this term is dominated by blood heat exchange between vessels (arteries or veins) and extravascular medium within the targeted tissue. It takes the consideration of local thermal non-equilibrium efforts. $\bar{J}_{i,k}$ is the total interfacial mass concentration exchanges due to mass transfer at the interface, and due to interfacial movement and phase change. It accounts for the local mass non-equilibrium effects. The mass concentration, and hold multiple equations based on participating mass concentrations. The subscript i indexes one of participating mass concentration of compositions. $< \vec{b}_k >^k$, $< s_k^q >^k$, and $< S_{i,k}^j >^k$ are imposed volumetric forces, volumetric energy sources (heating generation or cooling sources), and volumetric mass sources for the i composition. These conservation equations form a general biotransport model. Theoretical speaking, a large number of problems requires solve these set of equations concurrently, since transfers of mass, momentum, and energy, and mass compositions are coupled together in most of biological systems. However, in many special cases, people can simply the problem by decouple these conservation equations and solve selected ones based on the physical dominations on the targeted biological systems. For example, people can provide reasonable assumptions such as there is no movement of components or media in the tissue, and time scale during medical treatment is very small, and biological objects (patient, human body, specified organs of tissue) under investigation are stationary. This way, one can only focus on temperature distribution and heat flux using bioheat model.

The modeling of macroscopic fluxes and interfacial balances and international transfer terms can be found in the second portion of this research presented in [18].

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Reference

[1] A.-R.A. Khaled, K. Vafai, "The role of porous media in modeling flow and heat transfer in biological tissues," *Int. J. Heat Mass Transfer*, 2003, 46, pp. 4989-5003

[2] W. Roetzel, Y. Xuan, "Transient response of the human limb to an external stimulus," *Int. J. Heat Mass Transfer*, 1998, 41, pp. 229–239

[3] H. H. Pennes, "Analysis of tissue and arterial blood temperature in the resting human forearm," *Journal of Applied Physiology*, 1948, 1, 93 122

[4] E. H. Wissler, "Comments on the new bioheat equation proposed by Weinbaum and Jiji," *Journal of Biomechanical Engineering*, 1987, 109, pp. 226-232

[5] E. H. Wissler," Pennes' 1948 paper revisited," *J. Applied Physiology*, 1998, pp. 35-41

[6] M.D. Sherar, A.S. Gladman, S.R.H. Davidson, J. Trachtenberg, M.R. Gertner, "Helical antenna arrays for interstitial microwave thermal therapy for prostate cancer: tissue phantom testing and simulations for treatment," Phys. Med. Biol., 2001, 46, pp. 1905-1918

[7] D. C. Sanyal,, and N.K. Maji, "Thermoregulation through skin under variable atmospheric and physiological conditions," *J. Theor. Biol.*, 2001, 208, 451–456

[8] J. Ni and C. Beckermann, "A Volume Averaged Two-Phase Model for Transport Phenomena during Solidification," *Metall. Trans. B*, Vol. 22B, pp. 349-361, June, 1991

[9] A. Nakayama,, and F. Kuwahara,, "A General Bioheat Transfer Model Based on the Theory of Porous Media," Int. J. Heat Mass Transfer, 2008, 51, pp. 3190–3199

[10] W. Wulff, "The Energy Conservation Equation for Living Tissue," *IEEE Trans. Biomed. Eng.*, BME, 1974, 21, pp. 494–495.

[11] H. G. Klinger, "Heat Transfer in Perfused Biological Tissue. I. General Theory," *Bull. Math. Biol.*, 1974, **36**, pp. 403–415

[12] H. G. Klinger, "Heat Transfer in Perfused Biological Tissue–II. The 'Macroscopic' Temperature Distribution in Tissue," *Bull. Math. Biol.*, 1978, **40**, pp. 183–199

[13] M.M. Chen, K.R. Holmes, "Microvascular contributions in tissue heat transfer," *Ann. N.Y. Acad. Sci.*, 1980, 335 137–150

[14] K. H. Keller,, and L. Jr. Seiler, "An Analysis of Peripheral Heat Transfer in Man," *J. Appl. Physiol.*, 1971, 30, pp. 779–786

[15] J. C. Chato, "Heat Transfer to Blood Vessels," *ASME J. Biomech. Eng.*, 1980, 102, pp. 110–118

[16] M. M. Osman, and E. M. Afify, "Thermal Modeling of the Normal Woman's Breast," *ASME J. Biomech. Eng.*, 1984, 106, pp. 123–130

[17] D. Shrivastava, and J. T. Vauhan, "A general bioheat transfer thermal model for a perfused tissue," *J. of Biomech Engineering*, 2009, July, 131, 074506-1

[18] Jun Ni, "A Volume-Averaged Mathematical Model for Biological Systems Part II Interfacial Transfers and Balances," in Proceeding of ICICSE 2015, IEEE Press.

Table 2. Summary of Microscopic and Macroscopic Conservation Equations

	Microscopic Conservation Equations	**Macroscopic Conservation Equations**	**Interfacial Balances**	**Dispersive Fluxes**
Mass	$\frac{\partial \rho_k}{\partial t}+\nabla\cdot(\rho_k\vec{v}_k)=S_k^m$	$\frac{\partial(\varepsilon_k\rho_k)}{\partial t}+\nabla\cdot(\varepsilon_k\rho_k<\vec{v}_k>^k)+\varepsilon_k<S_k^m>^k$ $=\Gamma_k$	$\sum_{k=1,2,3,\ldots}^{N}\Gamma_k=0$	-----
Momentum	$\frac{\partial(\rho_k\vec{v}_k)}{\partial t}+\nabla\cdot(\rho_k\vec{v}_k\vec{v}_k)$ $=-\nabla p_k+\nabla\cdot\tau_k^v+\vec{b}_k$	$\frac{\partial(\varepsilon_k<\vec{v}_k>^k)}{\partial t}+\nabla\cdot(\varepsilon_k\rho_k<\vec{v}_k>^k<\vec{v}_k>^k)$ $=-\nabla(\varepsilon_k<p_k>^k)+\nabla(<\tau_k>+<\tau_k>^T)$ $+\vec{M}_k+\varepsilon_k<\vec{b}_k>^k$	$\sum_{k=1,2,3,\ldots}^{N}\vec{M}_k+M^{\sigma_\zeta}=0$	$<\tau_k^d>=-<\rho_k\hat{\vec{v}}_k\hat{\vec{v}}_k>$
Energy	$\frac{\partial(\rho_k h_k)}{\partial t}+\nabla\cdot(\rho_k\vec{v}_k h_k)$ $=-\nabla\cdot\vec{q}_k^h+S_k^q$	$\frac{\partial(\varepsilon_k\rho_k<h_k>^k)}{\partial t}+\nabla\cdot(\varepsilon_k\rho_k<h_k>^k<\vec{v}_k>^k)$ $=\nabla(<q_k>+<q_k>^T)+\vec{Q}_k+\varepsilon_k<S_k^q>^k$	$\sum_{k=1,2,3,\ldots}^{N}\vec{Q}_k=0$	$<q_k^d>=<\rho_k\hat{h}_k\hat{\vec{v}}_k>$
Mass Concentration	$\frac{\partial(\rho_k C_{i,k})}{\partial t}+\nabla\cdot(\rho_k\vec{v}_k C_{i,k})$ $=-\nabla\cdot\vec{j}_{i,k}^{\,j}+S_{i,k}^j$	$\frac{\partial(\varepsilon_k\rho_k<C_{i,k}>^k)}{\partial t}+\nabla\cdot(\varepsilon_k\rho_k<C_{i,k}>^k<\vec{v}_k>^k)$ $=\nabla(<\vec{j}_k>+<\vec{j}_k>^T)+\vec{J}_{i,k}+\varepsilon_k<S_{i,k}^j>^k$	$\sum_{k=1,2,3,\ldots}^{N}\vec{J}_k=0$	$<j_k^d>=<\rho_k\hat{C}_{i,k}\hat{\vec{v}}_k>$

	Total Interfacial Transfers	**Interfacial Transfers due to Interface Movement**	**Interfacial Transfers due to Shear Stress/Fluxes**	**Interfacial Transfers due to Others**
Mass	Γ_k	$\Gamma_k=-\frac{1}{V_o}\int_{A_k}\rho_k(\vec{v}_k-\vec{w}_k)\cdot\vec{n}_k dA$	-----	
Momentum	$\vec{M}_k=\vec{M}_k^{\Gamma}+\vec{M}_k^{\tau}$	$\vec{M}_k^{\Gamma}=-\frac{1}{V_o}\int_{A_k}\rho_k\vec{v}_k(\vec{v}_k-\vec{w}_k)\cdot\vec{n}_k dA$	$\vec{M}_k^{\tau}=\frac{1}{V_o}\int_{A_k}(\tau_k-p_k I)\cdot\vec{n}_k dA$	$\vec{M}_{ki}^{\sigma}=\frac{1}{V_o}\int_{A_k}\sigma_\zeta\cdot\vec{n}_k dA$ $=-\sigma_\zeta\bar{\nabla}\varepsilon_k^{\sigma}$
Energy	$\vec{Q}_k=\vec{Q}_k^{\Gamma}+\vec{Q}_k^{q}$	$\vec{Q}_k^{\Gamma}=-\frac{1}{V_o}\int_{A_k}\rho_k h_k(\vec{v}_k-\vec{w}_k)\cdot\vec{n}_k dA$	$\vec{Q}_k^{q}=-\frac{1}{V_o}\int_{A_k}\vec{q}_k\cdot\vec{n}_k dA$	
Mass Concentration	$\vec{J}_{i,k}=\vec{J}_{i,k}^{\Gamma}+\vec{J}_{i,k}^{j}$	$\vec{J}_{i,k}^{\Gamma}=-\frac{1}{V_o}\int_{A_k}\rho_k C_{i,k}(\vec{v}_k-\vec{w}_k)\cdot\vec{n}_k dA$	$\vec{J}_{i,k}^{j}=-\frac{1}{V_o}\int_{A_k}\vec{j}_{i,k}\cdot\vec{n}_k dA$	