Mechanistic Modeling of Cancer Tumor Growth Using a Porous Media Approach

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Abstract

SARAH E. SHELTON: Mechanistic Modeling of Cancer Tumor Growth Using a Porous Media Approach.
(Under the direction of William G. Gray.)

Cancer is a disease affecting millions of people each year; and researchers and clinicians are still looking for more effective ways to prevent, detect, and treat it. Recently, mathematical modeling has emerged as a way to understand the process of tumor growth. This work involves the development of a set of equations to mechanistically represent a tumor at the macroscale, using a porous media approach. Model components include 3 solid tissue phases (host, viable tumor, and necrotic tumor) and 2 fluid phases (blood and extracellular fluid) that supply the cellular phases with nutrients required for growth. Growth and death processes are represented by mass transfer terms which are dependent on local nutrient concentrations. Selected constitutive relations are discussed and the form of the model adheres to the thermodynamically constrained averaging theory approach.

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List of Abbreviations and Symbols

Abbreviations:

CEI Constrained Entropy Inequality

CIT Classical Irreversible Thermodynamics

eq. equation

$\mathbf{G}_0$ Gap 0 phase of cell cycle

$\mathbf{G}_1$ Gap 1 phase of cell cycle

$\mathbf{G}_2$ Gap 2 phase of cell cycle

M Mitosis

REV Representative Elementary Volume

S DNA Synthesis phase of cell cycle

TCAT Thermodynamically Constrained Averaging Theory

VEGF Vascular Endothelial Growth Factor

English Letters:

b	phase qualifier for intravascular fluid (blood)
c	phase qualifier for cellular phase
C^{crit}	critical nutrient concentration

$C^{i\alpha}$	concentration of species i in phase α
$\mathbf{C}_s$	Green's deformation tensor
$\mathbf{d}$	rate of strain tensor, $\mathbf{d} = \frac{1}{2}\left[\nabla \mathbf{v} + (\nabla \mathbf{v})^T\right]$
f	phase qualifier for interstitial/extravascular fluid phase
h	phase qualifier for host tissue solid phase
i	species qualifier
$\mathbf{I}$	identity tensor
j_s	microscale solid phase Jacobian
k	Darcy's law permeability constant
K_d	necrotic death constant
K_s	Monod growth constant
l	phase qualifier for liquid phase
n	phase qualifier for necrotic tumor tissue solid phase
$\mathbf{n}$	outward normal vector
p	phase qualifier for viable/proliferative tumor tissue solid phase
p	pressure
$\mathbf{q}$	heat conduction vector
r_d	necrotic death rate
s	general solid phase qualifier
$\mathbf{t}$	stress tensor
$\mathbf{v}$	velocity of the quantitie of interest, may be specified as velocity of a phase, species, interface, etc. at any length scale

$\mathbf{w}$	velocity of the domain (of any entitity)
w	general fluid phase qualifier
$\mathbf{x}$	position of the solid phase
$\mathbf{X}$	initial position of the solid phase
Y	yield coefficient for Monod growth equation

TCAT Symbols:

a	italic font for scalar quantities
$\mathbf{a}$	bold font for vectors
$\boldsymbol{\mathsf{a}}$	bold, sans serif for tensors
f_a	subscipt qualifiers at the microscale
f^a	superscript qualifiers for intrinsic averages (macroscale)
$f^{\overline{a}}$	single overline superscript for mass averages (macroscale)
$f^{\overline{\overline{a}}}$	double overline superscript for uniquely defined averages (macroscale)
$\mathcal{M}_\alpha$	microscale mass conservation equation
$\mathcal{M}^{\overline{\overline{\alpha}}}$	macroscale mass conservation equation
$\boldsymbol{\mathcal{P}}_\alpha$	microscale momentum conservation equation
$\boldsymbol{\mathcal{P}}^{\overline{\overline{\alpha}}}$	macroscale momentum conservation equation
$\mathcal{E}_\alpha$	microscale energy conservation equation
$\mathcal{E}^{\overline{\overline{\alpha}}}$	macroscale energy conservation equation
$\mathcal{S}_\alpha$	microscale balance of entropy equation
$\mathcal{S}^{\overline{\overline{\alpha}}}$	macroscale balance of entropy equation

$\mathcal{T}_\alpha$	microscale thermodynamic equation
$\mathcal{T}^{\overline{\overline{\alpha}}}$	macroscale thermodynamic equation
$\overset{\kappa\to\alpha}{M}$	inter-phase mass transfer
$\overset{\kappa\to\alpha}{\mathbf{T}}$	inter-phase momentum transfer
$\overset{\kappa\to\alpha}{Q}$	inter-phase heat transfer
$\overset{\kappa\to\alpha}{\Phi}$	inter-phase entropy transfer
$\mathfrak{I}c\alpha$	Entities connected to the α phase
$\sum_{\kappa\in\mathfrak{I}_{c\alpha}}$	sum over the set of connected entities connected to phase α

Greek Letters:

α	general phase qualifier
Γ	boundary
γ	Darcy's law correction factor used by Byrne and Preziosi, 2003
ϵ	volume fraction, porosity
η	entropy per volume
θ	temperature
κ	general qualifier for a set of interfaces connected to a phase
μ	chemical potential
$\hat{\mu}$	dynamic viscosity
μ^*_{obs}	general observed Monod growth rate
μ^*_{max}	maximum growth rate
μ^*_p	observed growth rate of phase p

ρ	density
$\boldsymbol{\sigma}_s$	Lagrangian stress tensor
$\boldsymbol{\varphi}$	non-advective flux of entropy
Φ	entropy transfer
ψ	gravitational potential
ω	species mass fraction
Ω	domain

Mathematical Symbols:

∇	gradient
$\nabla \cdot$	divergence
$\nabla_X \mathbf{x}$	gradient of the solid spatial location vector relative to its initial location
$\cdot$	dot product
$:$	double dot product
$\int$	integral
$\sum$	sum
$\in$	set membership
$\langle\rangle_{\Omega,\Omega}$	averaging operator
$\frac{\mathrm{d}}{\mathrm{d}t}$	total derivative
$\frac{\partial}{\partial t}$	partial derivative
$\frac{\mathrm{D}}{\mathrm{D}t}$	material derivative

Chapter 1

Background

1.1 Cancer

Cancer is an incredibly complex disease, both in terms of its causes and effects on the body. A number of genetic, biochemical and physiologic processes are involved in the development of cancer, a process called carcinogenesis or oncogenesis. Clinically, cancer is so deadly because the cells have acquired the ability to proliferate (divide) at an abnormally high rate, invade into surrounding tissue, and travel to distant sites in the body and form new colonies of malignant cells (metastasis). Hanahan and Weinberg have astutely summarized the characteristics common to malignant tumors as the 6 "Hallmarks of Cancer" in their landmark paper published in 2000 [38], and their recent revision [39]. The six hallmarks of cancer include a variety of mechanisms that were first observed in studies of genetic alterations. However, these hallmarks implicate a number of biological pathways in which gene expression and the cell cycle can be influenced by the tumor microenvironment. Therefore, the hallmarks of cancer are not only of interest to geneticists, but also to modelers able to simulate the microenvironmental conditions and thereby predict some aspects of tumor growth and development. Furthermore, mechanical-chemical conditions may play important roles in determining tumor morphology, invasion, and metastasis; and mathematical modeling can bring a great deal of insight into these aspects. Over the years, the search for chemotherapeutics that target some of the pathways commonly altered in cancer has produced a number of novel drugs, but the efficacy of these drugs often is limited by their inefficient transfer to the tumor cells. Currently, more research is being devoted to understand the influence of the microenvironment on the tumor, and its ramifications on tumor progression and chemotherapeutic delivery.

The six hallmarks are common among all malignant tumors, see figure 1.1 . These characteristics were categorized as the most important cellular and genetic alterations in malignancy. They do not have to arise in a certain order, but some orders are more likely than others. For example, angiogenesis is normally induced before invasion and metastasis are able to begin. These six traits give cancer cells a selective advantage over normal cells which are restricted to normal tissue function and by fully-functional cell cycle controls.

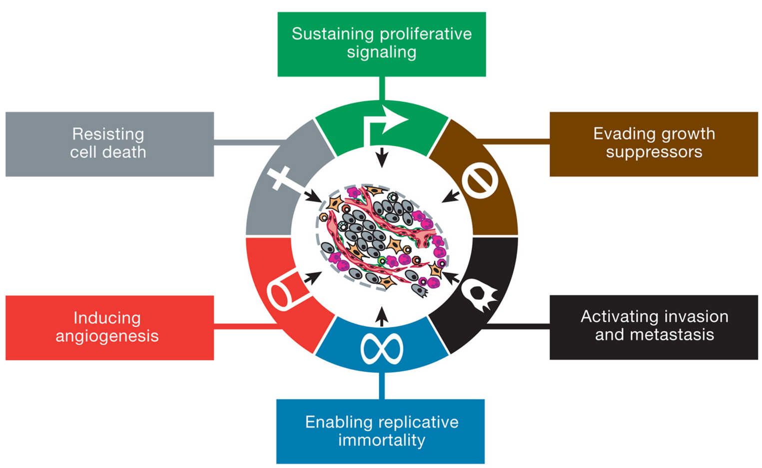

Figure 1.1: Hanahan and Weinberg's hallmarks of cancer. [39]

Hanahan and Weinberg's six hallmarks of cancer are [38, 39]:

Resisting cell death: Apoptosis (programmed cell death) is a normal cell activity that can be triggered when a cell is damaged. Malignant cells have acquired the ability to avoid signaling for apoptosis or are able to ignore the apoptotic triggers.

Sustaining proliferative signaling: Proliferation in normal cells is controlled by the careful production and release of growth factors and other signals. Malignant cells may make excessive pro-proliferative signals and avoid normal negative-feedback loops.

Evading growth suppressors: The genetics of normal cells include genes called tumor suppressors that function to prevent the excessive growth that causes tumor formation. One or more of these growth controls are inactivated cancer cells.

Inducing angiogenesis: Malignant cells have triggered the growth of new blood vessels to supply their growth with nutrients and oxygen.

Enabling replicative immortality: Normal cells have finite lifespans that are limited to a certain number of cycles of growth and division. Cancer cells must overcome this finite lifespan and become "immortal" to replicate sufficient times to form a malignant neoplasm.

Activating invasion and metastasis: In order for cancer cells to invade and colonize distant organs (metastasize), the cells must escape the limitations that normally keep cells restricted to their tissue of origin.

Acquiring the traits that define the hallmarks of cancer depends upon genetic alteration, usually by mutation. However the natural rate of mutation is slow because the cell has so many checks and double-checks to prevent and correct alterations in the genetic code. Furthermore, additional cellular systems normally recognize mistakes that are unable to be repaired and prevent the cell from replicating the damaged DNA and dividing into new cells. Therefore, genetic (including chromosomal) instability is another key concept in cancer because a single mutation is generally not considered to be sufficient in the development of cancer. However, genetic instability can increase the rate of mutation and thus can increase the chance that a cell that has acquired a few of the hallmarks will acquire the remaining traits. However, since so many aspects of normal cell function must be perturbed for a cell to become malignant, cancer develops over many years. The natural rate of mutation is so slow that it is not statistically likely that enough cancer-causing mutations will occur in a lifetime without an increase in genetic instability that increases the rate of mutation. The time scale of carcinogenesis in humans is on the order of decades, which is one reason why cancer is a disease of the aged population.

Cancer progression can be broken into sequential steps based on the physical and genetic alterations that accumulate over time. If we think of the genetic (also epigenetic and proteomic) changes that are important in cancer, the development of cancer can be broken into three stages: initiation, promotion, and progression. Initiation occurs when a cell is exposed to some genotoxic agent. If the cell suffers heritable damage, that it is not able to repair, it has the potential to become cancerous. Promotion refers to the proliferative stimulation of the damaged cell or cells. Without promotion, the damaged cells would remain quiescent and eventually apoptose, without passing on their genetic damage to any daughter cells. Initiation and promotion can occur simultaneously, such as from a single agent that induces both genetic damage and cellular proliferation. They can also occur sequentially with promotion following initiation, but not in reverse, because it is necessary to replicate *damaged* DNA in order to develop cancer. If promotion occurs without any initiation event, then a benign tumor may form from the excessive growth, but it will not have the genetic alterations necessary to become malignant without further initiation and promotion events. Progression occurs as the abnormal cells grow, divide, and develop further genetic alterations eventually becoming a neoplasm, known more commonly as a tumor. Over time, tumor cells with more mutations may gain a selective advantage, and so the phenotype of the cancer seems to get more aggressive over time [46].

Malignant neoplasms do not spontaneously arise from normal cells, but come from benign predecessors that have acquired new abilities to divide, invade, and metastasize. A number of terms exist to categorize the severity of abnormal growth. These terms refer to the physical, cellular abnormalities that are visible under a microscope. First, hyperplasia comes from the Greek meaning excessive growth and refers to an increase in cell number. Some cycles of hyperplasia are normal in certain tissues, but the term can also apply to abnormal increases in cell proliferation. Alternatively, dysplasia is abnormal growth, meaning that the cells are physically distinct from normal cells. These cellular abnormalities include alterations in cell shape and size, ratios of nucleus to cytoplasm, etc. A later stage of growth is called neoplasia, which is synonymous with tumor and means "new growth". A neoplasm may be benign, pre-cancerous, or malignant. In fact, many cancers progress through these steps sequentially. However exceptions exist, such as some benign tumors that never progress to malignant variants. An intracompartmental neoplasia is confined to its normal tissue compartment and may become malignant if it invades surrounding tissue compartments and then will be able to metastasize to other locations in the body as well [45]. Indeed, the "capacity to invade locally and to metastasize remains of greatest clinical significance, and is still the fundamental definition of malignancy" [57].

Other than invasion and metastasis, cancer is characterized by uncontrolled growth. Mutations can change the cellular growth rate in a number of ways that are seen in the hallmarks of cancer, and each mutation can have a specific influence on cellular activities and the cell cycle. Normally, the cell cycle (see Figure 1.2) is tightly controlled by intra- and extracellular signals. In general, the cell cycle consists of division of one cell into two (mitosis), the first stage of growth (gap 1), replication of DNA (synthesis), the second growth stage during which the cell has duplicate copies of DNA (gap 2). Then the cell divides again, and the cycle restarts. There is also a phase outside the proliferative cycle (G_0).

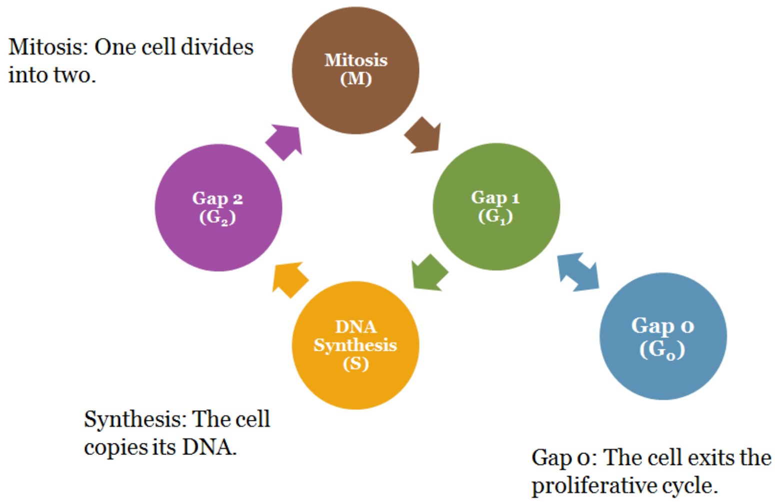

Figure 1.2: Phases of the cell cycle.

During gap 1 the cell grows in size and prepares to move to the next phase. From gap 1, the cell can continue on the proliferative track and enter the S phase or can exit the proliferative cycle and transition to the G_0 phase. Cells in gap 0 are quiescent or senescent and do not continue on the cell cycle unless they receive a signal to proliferate. The cells in G_0 may be terminally differentiated or may have become senescent in response to unrepairable DNA damage or other cellular damage. If a cell from G_0 receives a proliferative stimulus, it may return to the cycle and reenter the G_1 phase again. Cells that pass the gap 1 checkpoint move on to the S phase and make copies of their DNA, which is called DNA synthesis or replication. After DNA synthesis, cells move on to the gap 2 phase. At this point they contain duplicate copies of DNA and are preparing to begin mitosis. There is another cell cycle checkpoint in gap 2, before cells proceed to the M phase and start the cycle again. A number of cell cycle control molecules such as cyclins, cyclin dependent kinases, DNA damage sensors, and tumor suppressor genes determine if cells move from one phase to the next.

In cancer cells, some of this cellular machinery is damaged, deactivated, or overactive, causing the cell to continuously cycle from one phase to the next, without regard to normal cell cycle controls. This permanent cell cycling results in increased proliferation and enhances genetic instability and abnormality as cells with significant DNA damage are allowed to continue growing and dividing instead of being forced to apoptose or into a state of senescence as occurs in normal cells.

From a modeling perspective, cancer can be broken into two distinct types: avascular and vascular. Avascular tumors are small neoplasms, limited to 1-2 mm in size [40] [42], that do not contain their own blood supply. In general, avascular tumors are spheroidal in shape and contain large necrotic cores surrounded by a quiescent region and a thin rim of proliferating cells on the surface. They derive their nutrition from the diffusion of nutrients from the nearby vasculature of healthy tissue. Avascular tumors are limited in size because of insufficient delivery of nutrients and may develop necrotic regions where the tumor tissue is beyond the reach of diffusing nutrients and oxygen. Tumor cells must be within 200 μm of a vessel to be viable [40] and hypoxia is usually designated at a shorter distance, such as 120 μm from vasculature [8]. Avascular tumors are largely undetectable and asymptomatic. However, avascular tumors readily become more dangerous vascular tumors through the process of angiogenesis.

Angiogenesis is the creation of new capillaries from existing vasculature. One may imagine the process as a tree (the existing vasculature) growing new branches (the new vessels). Angiogenesis is such an important feature of malignancy that it is one of the hallmarks of cancer [38], [39], see Figure 1.1. Angiogenesis is influenced by a number of biochemical signaling molecules, the archetypal one being vascular endothelial growth factor (VEGF). VEGF and other other pro-angiogenic molecules are produced when tissues are exposed to hypoxia or become necrotic, making angiogenesis a reaction to the hypoxia and necrosis experienced by avascular tumors as they reach their size limit.

Neovasculature, the new network of blood vessels, is very different in tumors than the mature vasculature of healthy tissues. The new vasculature is immature and morphologically distinct from normal vasculature in multiple ways. Tumor neovasculature is “leakier”, meaning that it is more permeable and allows more and larger molecules to extravasate. There is evidence that tumor vasculature has altered cell-surface protein expression that may be therapeutically targetable [46]. It also grows chaotically, leading to the formation of highly tortuous vessels and many dead-end vessels.

A vascular tumor is one that has “switched on” angiogenesis, thus increasing its supply of oxygen and nutrients. Therefore, vascular tumors can grow to much larger sizes than avascular tumors because they are able to increase their nutrient supply to meet the metabolic needs of increasing numbers of tumor cells. The incorporation of vasculature into tumor tissue also presents the opportunity for metastasis through the circulatory system if tumor cells cross the vessel wall and enter into the blood stream. It is of great importance to be able to model vasculature tumors because it is this type of tumor that is of clinical significance and greater danger to the patient.

1.2 Tumor Modeling Approaches

Over the last decade, an increasing amount of interest and research devoted to mathematical modeling of tumor growth has developed. A number of review papers have cataloged the evolution of these models. See the following selection of reviews for an excellent overview.

Araujo and McElwain (2004) A history of the study of solid tumour growth: The contribution of mathematical modelling. [3]

Quaranta et al. (2005) Mathematical modeling of cancer: The future of prognosis and treatment. [62]

Roose et al. (2007) Mathematical models of avascular tumor growth. [64]

Lowengrub et al. (2010) Nonlinear modelling of cancer: bridging the gap between cells and tumours. [50]

Deisboeck et al. (2010) Multiscale cancer modeling. [19]

In general, tumor models can be divided into three categories: discrete, continuum and hybrid. Since tumor growth inherently involves the actions (growth, death, movement) of individual cells, the most intuitive type of model is a discrete model that treats each cell individually. In a discrete model the interactions between cells are modeled explicitly. However, this approach becomes unworkable when overwhelmed by the sheer number of cells needed to form a tumor and the surrounding tissue. Small tumors, visible with X-rays, have on the order of 10^8 cells, and palpable tumors have at least 10^9 cells [45]. While a discrete model may have utility in studying the growth of small, nascent tumors and some other cell-specific cancer processes, such as cell-cell adhesion and motility, metastasis, and angiogenesis, it is impractical for modeling tumors of this size and complexity that are of clinical interest.

Continuum models, on the other hand, do not treat cells individually, but as averaged populations. Continuum tumor models are based on the fields of continuum mechanics and on porous media or mixture theory, which will be discussed more fully in the following section. Hybrid models are a varied group that incorporate different aspects of discrete and continuum models, depending on the problem of interest. Hybrid models are sometimes misleadingly referred to as multiscale models because they incorporate the small scale interactions of individuals cells and larger tissue-scale effects as well. In this case, the description as "multiscale" does not imply mathematical connection of scales through the use of rigorous averaging theorems as it does for the thermodynamically constrained averaging theory approach. See Figure 1.3 for a comparison of discrete and continuum tumor models.

Characteristics of Mechanistic Tumor Models	**DISCRETE**	**CONTINUUM**
Types of Models	Cellular Automaton. Agent Based. Cellular Potts.	Porous Media. Mixture Theory.
Theoretical Basis	Particle Dynamics. Newtonian Mechanics.	Conservation Laws. Thermodynamics.
Scales of Interest	Sub-cellular scale. Cellular scale. Tissue/Multicellular scale.	Microscale. Macroscale. Megascale.
Advantages	Includes cell-specific information and effects.	Includes effects of tissue mechanics. Can model entire spatial and temporal scales of tumor evolution.
Disadvantages	Limited model domain size. Computational load. Inability to represent tissue mechanical effects.	Doesn't account for cellular heterogeneity. Can't model single-cell processes.
Common Characteristics	Multi-cellular tumor spheroid models. Track reorganization of cells in tumor or migration into host tissue. Hybrid models represent cells individually, treat extracellular water as continuum.	Interactions between cell number density and 1 or more chemical species. Consist of reaction-diffusion equations. Mechanical interactions between cells and surrounding environment. Tumors modeled as viscous fluid using Darcy's law.
Examples of Usage	Carcinogenesis. Angiogenesis. Cell-cell/ cell-matrix adhesion and motility. Invasion and metastasis. Cell transitions (epithelial to mesenchymal transition).	Tumor growth and morphology. Influences of the microenvironment on growth (nutrients, oxygen, pH, solid stress, signaling molecules). Drug-delivery.

Figure 1.3: Comparison of discrete and continuum approaches to tumor modeling.

1.3 Continuum, Multiphase Models

Multiphase, porous medium models are conceptually based in continuum mechanics, meaning that interactions among different portions of the mass are accounted for in an average sense. The field of continuum mechanics has been applied, in an environmental context, to single phase systems, such as rivers and lakes, but also to multiphase systems, for example oil and gas flow through a rock matrix. Multiphase models are based on the fundamental conservation laws of mass, momentum, and energy, and employ a number of different methods to supplement the conservation equations with constitutive relations to close the system of equations.

The smallest scale at which the continuum hypothesis holds is called the microscale or pore scale. At the microscale, a single (continuum) point contains a large number of molecules such that properties like density, temperature, and pressure of a phase are all defined. A single point contains only one phase, so at every location in the domain, the type and state of the phase occupying that location is known. It is at the microscale that well-known, classical conservation equations and thermodynamic expressions are written. However, many problems of interest are too large to solve at the microscale, or the microscale equations require variables (such as velocities) at a resolution that is too small to be observed or measured. Thus, many multiphase, porous media models are formulated at a larger scale, called the macroscale [56].

The macroscale depends on the concept of the representative elementary volume, or REV, a volume large enough to include all phases present and such that values of averages are independent of the size of the REV. The volume must also be much smaller than the length scale of the entire system (known as the megascale), so that quantities such as gradients are meaningful. Thermodynamically constrained averaging theory (TCAT) uses averaging theorems to formally and consistently convert microscale equations to the larger macroscale. These averaging theorems convert averages of microscale derivatives into derivatives of macroscale averages and are similar to the well known transport and divergence theorems [32].

Model formulation begins with identifying the system entities that must be explicitly modeled and then deriving the conservation equations for those entities. Multiphase systems must account for entities including interfaces (intersection of two phases), common curves (intersection of three phases), and common points (intersection of four phases) in addition to the standard phase equations. There are also averaging theorems for translating these different entities and different equations from one length scale to another [31].

Additional information is needed to reach a system of equations that is solvable, and this process is known as closure. Closure can be obtained by a variety of methods including simplification of the conservation equations and the addition of approximation equations. The TCAT approach produces conservation equations at the macroscale by formally averaging microscale equations up to the larger scale. This provides the appropriate conservation equations for mass, momentum, and energy that must be supplemented by expressions that describe reaction rates, growth and death rates, mass transfer across permeable interfaces, and mechanical parameters characteristic of the solids and fluids. The balance of entropy and thermodynamic equations are also employed to constrain the system of equations. These supplemental expressions are called constitutive relations and lead to a well-defined and complete set of equations that can be solved to describe tumor evolution. The complete set of equations must be solved numerically to model various scenarios of tumor growth impacted by nutrient supply, proposed therapies, and variability of parameters.

The multiphase approach can be applied to tumors to account for the behavior of fluids and tissue in an average sense. At the macroscale, the averaging length scale would be large enough to encompass millions of cells but small enough that variability of properties across the tumor would be simulated. This averaged approach eliminates the need to know the exact locations of each phase, interface, and flow path, thus increasing the size of the region that can be modeled.

1.4 A Brief History of Cancer Tumor Models

Early models of solid tumor growth focused on understanding the growth rate of cancer. Tumors tend to follow a Gompertzian growth pattern in which growth begins slowly, speeds up rapidly, and then decays as the population reaches a plateau. The Gompertz equation was developed to describe human mortality, but was applied to tumor growth curves by A.E. Casey in 1934 [12]. It is distinct from a logistic growth equation because it is not symmetric [69]. In Gompertzian growth, the initial increase in growth rate is nearly exponential and occurs more rapidly than the subsequent decline. Gompertzian tumor growth remains a popular equation for expressing the growth rate over the lifetime of *in vivo* and *in vitro* tumors [37], [5].

Many of the early tumor models considered spherical morphologies for the simplicity inherent in one-dimensional calculations. These models did not distinguish themselves as representing avascular or vascular tumors, but simply as a conglomeration of cancer cells. Beginning in the 1960's, these early models are best described as population models that track cell number. Researchers were looking for answers to how and why different tumors grow at different rates and why a single tumor grows at different rates over its lifetime. In 1966 Burton modeled proliferation based on oxygen distribution in a spherical tumor and found that the ratio of the radii of the low-oxygen inner core to the well-oxygenated rim supported the exponential retardation phase of the Gompertzian growth curve [10]. This result led Burton to conclude that tumor growth is a diffusion problem. Since Burton, and others after him, used diffusion from the exterior as the only source of nutrients, their models are conceptually equivalent, albeit less computationally sophisticated, to later avascular tumor models. Burton's work echoes an earlier mathematical model by Thomlinson and Gray [68] relating diffusion to tumor heterogeneity measured histologically.

Subsequent models inspired by the simplicity of Burton's model sought to explore other hypotheses related to growth controls. Some examined cellular death due to apoptosis, necrosis, or both. Other early researchers sought to understand the late-stage growth retardation as the result of a temporally variable mitotic rate. The year 1972 saw Greenspan separate the cellular phase into proliferative, quiescent, and necrotic compartments [36]. Also during the 1970's Liotta and Saidel expanded upon Burton's diffusion model and other population models to examine invasion and metastasis [47]. They based tumor expansion on diffusion equations and coupled the proliferation of malignant tumor cells and vascular endothelial cells using Michaelis-Menten reaction kinetics [25]. Their model assumed the tumor was growing in an infinite region of host tissue, such that tissue compression was assumed negligible. Additionally, Liotta et al. developed a stochastic model predicting the probability of the formation of metastases [49].

Early multiphase tumor models emerged in the late 1990's. These early multiphase models tended to include two phases, a cellular phase and a water phase surrounding and "bathing" the cells in nutrients. Please et al.'s "A new approach to modelling the formation of necrotic regions in tumours" [61] is a good example of an early multiphase model, inspired by earlier population models . They incorporated cells and extracellular water as incompressible phases. Oxygen concentration regulated cellular proliferation, and necrosis was triggered by intracellular pressure above that of the water phase. Their model exhibited exponential growth that transitioned to linear growth, mimicking the form of the Gompertzian growth curve. Later versions of models based on a similar system description also included other mechanisms such as necrosis, hydrodynamic drag, viscid cellular phase, attraction and repulsion between individual cells.

During the 1990's, more modelers and experimentalists started investigating mechanical effects on the growth of tumors. In 1997 Helmlinger et al. demonstrated *in vitro* that solid stress has an inhibitory effect on tumor growth [41]. They cultured avascular tumors on agarose gels of varying stiffness and noticed that stiffer substrates resulted in smaller tumors. After a few years, avascular tumor models began incorporating mechanical stress. Jones et al. [44] developed a model that tracked the mechanical stress that developed due to tumor growth. They did not, however, make the cellular proliferation rate dependent upon local stress. They observed that the cells near the boundary, which are highly proliferative, are under compression and the cells near the center of the tumor, which tend to be necrotic or quiescent, are under tension.

Ward and King published a series of well-known studies of avascular tumor growth in the late 1990's and early 2000's [70–74]. In their model, cellular proliferation increases volume and cell death decreases volume. They based their proliferation equation on earlier examples that had used the Michaelis-Menten form, and they used the concentration of a "generic nutrient" to sustain proliferation. Ward and King were interested specifically in the velocity field that develops due to cellular rearrangement induced by proliferation and necrosis. The long-time numerical solutions showed either steady state or linear growth, depending on model parameters.

In 2002 Breward et al. developed a two-phase continuum model of avascular tumor growth based on conservation of mass and momentum with oxygen dependent growth and death terms. In the model, tumor volume increased in order to reduce pressure within the tumor. The cellular phases were represented as viscous fluids with viscosity depending on the degree of differentiation of the cells. More differentiated cells were described as more viscous and poorly differentiated cells as less viscous. Interestingly, they observed that their simulations of well-differentiated (viscous) tumors grew more slowly than their poorly-differentiated (less viscous) counterparts. A year later, the same three researchers improved upon their model by adding blood vessels as a third phase.

The 2003 model by Breward et al. does not take vessel morphology (tortuosity, diameter, or blood flow rate) into account, but calculates mass transfer from the vessel from the age of the vessel. Younger vessels are assumed to be more fenestrated, or more "leaky", with a higher rate of mass transfer than more mature vessels. The model also allows for vessel collapse due to excess pressure. Angiogenesis is followed explicitly and is dependent upon the volume fractions of the tumor cells and the blood vessels. The angiogenic growth rate is highest where the tumor volume fraction is small, meaning that the rate of angiogenesis is highest at the boundary of the tumor and decreases toward the center. The local oxygen concentrations are not calculated using a diffusion equation, but instead are based on the number of blood vessels in the region and their maturity. Cellular growth and death are based on functions of the blood vessel volume fraction, stratified by age. The phases were treated as viscous fluids, and conservation of momentum utilized Darcy-style drag terms. This model exhibited high and rising interstitial and oncotic pressure, both of which had been observed experimentally by other researchers [9], [67], [48].

Also during 2003 Byrne and Preziosi published a multiphase model using mixture theory [11]. This model contains a solid cellular phase and an extracellular fluid phase. A novel feature is the dependence of the proliferation rate upon cellular stress, rather than on nutrient concentration alone. Thus, the steady-state tumor size may be reached because of nutrient deficiency or because of excess mechanical stress. Some of their assumptions, which are used widely in tumor modeling, include incompressibility of the phases, slow flow such that inertial forces are neglected, and a fully saturated, homogeneous porous medium. The constitutive form of the conservation of momentum equation took the form of an extension of Darcy's law for a deformable porous medium.

Darcy's law, and generalizations of it, are the most common form of closure for the momentum equation.

Darcy's law for a deformable porous material according to Byrne and Preziosi [11]:

$$\epsilon^{l}\left(\mathbf{v}^{\bar{l}}-\mathbf{v}^{\bar{c}}\right)=-\frac{k}{\hat{\mu}\left(1-\gamma\right)}\nabla P \tag{1.1}$$

In this equation, l stands for the liquid phase and c stands for the cellular phase. The constant k is the permeability coefficient and $\hat{\mu}$ is the viscosity. The constant γ is a correction term to generalize Darcy's law to deformable porous media. It is a dimensionless parameter based on the inter-phase mass transfer and an arbitrary constant that they note will be extremely small because the momentum transfer associated with phase change (which will be denoted as $\mathbf{v}^{\overline{\alpha}}\overset{\kappa\rightarrow\alpha}{M}$ here) will be negligible compared to the effects of drag.

Since 2000, there have been a many publications of hybrid models focusing on different aspects of tumor growth, development and invasion. A number of of these models have come out of the collaborations between Anderson [1, 4, 26–28, 53, 54, 62, 63], Chaplain [2, 13–15, 53, 54, 59, 63], Cristini [7, 16–19, 21–23, 50, 53, 60, 65, 66, 75–77], Frieboes [7, 16, 21–24, 50, 60, 65, 66, 75], Lowengrub [17, 18, 23, 24, 50–53, 75, 76], Macklin [24, 50–53], and Wise [7, 18, 23, 24, 50, 75–77].

Many of these models are based on mixture theory and contain diffuse interfaces to replace the narrow transition layers that arise at the tumor/host interface due to differential adhesive forces among the cell species. If the diffuse interlayer thickness can be considered negligible, the system reduces to the classical sharp interface model. "Computer simulation of glioma growth and morphology" by Frieboes et al. (2007) [24] is one such representative model. Conservation equations for mass, momentum, and energy were employed to describe the movement of macroscale units they named *"functional collective cell-migration units" (FCCMU's).* Being grounded in mixture theory instead of porous media, they do not have the construct of a macroscale REV, so they had the need to create a macroscale unit of volume. Some of their model parameters were informed by histology measurements, but they did not undertake experiments to determine all constitutive parameters. A few parameters determined experimentally were the glioma mitotic rate (1 day^{-}1), apoptotic rate (0.32 day^{-}1), and the diffusion penetration distance (100μm, previously measured in [17]). They based the rate of nutrient release from to the vasculature on the age of the vasculature and the solid pressure in the tissue. The simulations show cyclic patterns of growth associated with the build up of pressure, followed by necrosis and pressure relief. They also found that the tumor boundary moves at 50-100μm/week, leading to the growth of tumor mass equivalent to a sphere with a 5cm diameter in one year.

The model of Wise et al., (2008) [75] is based on Frieboes et al. (2007) [24] and is formed of fourth order reaction-diffusion equations and constitutive laws for fluxes and velocities (generalized Fick's law and generalized Darcy's law). The energy equations takes adhesion and thermodynamics into account. The model assumes phases of constant density, fully saturated porous media, and treats the tumors as viscous, intertia-less fluids. The model incorporates two species of tumor tissue (a viable tumor cell phase and a dead tumor cell phase) and the other phases in contact with the tumor (a water phase and a host tissue phase). This mixture theory model is a diffuse interface model that accounts only for an interface at the boundary of the tumor where it is in contact with the healthy tissue. The numerical solution uses an adaptive, non-linear multigrid, finite difference method in two or three spatial dimensions.

The model of Oden et al., (2010) [58] considers solid phases undergoing large elastic deformations and compressible, non-Newtonian, viscous fluids. Thermal effects and heat transfer are also accounted for in the model. Again, a diffuse interface, Cahn-Hilliard-type equation is employed in accounting for interactions between phases.

Oden's model includes a number of inconsistencies that he seems to have inherited from similar models. For example, there is confusion between phases and constituents of phases (which are called species here). There are also inconsistencies in his equations, such as a illogical flux, the validity of which Oden himself questions in the text, but he keeps it because it was inherited from previously published models. These types of artificial terms have been added over the years of tumor model development because the mathematics have been developed on an ad hoc basis. In the next chapters, this confusion will be avoided as equations are carefully derived to represent the different phases in the system.

1.5 Thermodynamically Constrained Averaging Theory (TCAT)

Thermodynamically constrained averaging theory provides a rigorous yet flexible method for developing multiphase, continuum models at any scale of interest. Many natural and engineered systems are characteristically multiphase, meaning that two or more fluid and solid phases occupy a shared domain. Some examples of systems where multiphase modeling is useful are groundwater flow, fuel cells, and petroleum reservoirs. More recently, biological tissues have been added to this list. These systems share the need for model development at the macroscale in order to represent a system of relevant size.

Other multiphase models posit conservation equations directly at the macroscale, which does not ensure any meaningful connection to the microscale. However, when using the TCAT approach macroscale variables are precisely defined by the averaging theorems. With consistent, rigorous, and precisely defined variables, there is no chance of inconsistent variable definitions among equations. Another benefit is that the macroscale variables maintain a clear connection to their microscale counterparts. Models that postulate conservation or constitutive equations directly at the macroscale run the risk of inaccurately accounting for the microscale physics or naming variables with no clear definition or physical meaning. Clear variable definitions, which are inherent to TCAT, are vital to the ability to observe and experimentally measure macroscale parameters.

After derivation of the appropriate conservation equations, the model still contains more variables than equations and thus must be closed through the formulation of constitutive relations. Many existing models reach closure through ad hoc selection or formulation of equations, but TCAT employs thermodynamics to close the system of equations instead. An entropy inequality and thermodynamic expression are developed and averaged to the macroscale to supplement the conservation equations. It is important to note that the field of thermodynamics involves systems that are at equilibrium, but we are dealing with dynamic systems undergoing changes in space and time. Therefore, the classical irreversible thermodynamics (CIT) approach has been used in TCAT because it includes the concept of local equilibrium which assumes that the system can be broken down into subsystems that can be considered to be at equilibrium [32].

Another benefit of TCAT is that model development proceeds systematically, and closure approximations are inserted near the end of the formulation. Therefore, there is an obvious path back to the exact (unclosed) system if closure approximations are deemed to be insufficient and need to be re-hypothesized. Other models that are formulated without this systematic procedure may not be modified as easily or logically.

The TCAT approach consists of the following steps (Gray and Miller, 2005)[32]:

- an entropy inequality (EI) expression for the entire system of concern is generated;

- an appropriate set of mass, momentum, and energy conservation equations is formulated at the desired scale for all relevant entities (volumes, areas, common curves, and common points) based upon clearly defined averages of microscale quantities;

- an appropriate microscale thermodynamic theory is averaged up to the desired scale, and differential forms of internal energy dependence for spatial and temporal derivatives are generated;
- the EI is augmented using the products of Lagrange multipliers with conservation equations and with differential, consistent-scale thermodynamic equations;
- the set of Lagrange multipliers is determined to select the combination of conservation equations that describes the physics of interest and to eliminate time derivatives from the augmented EI producing the constrained EI;
- geometric identities and approximations are applied to the constrained EI to eliminate additional remaining time derivatives as needed;
- the resultant simplified EI is used to guide the formulation of general forms of closure approximations consistent with the second law of thermodynamics;
- microscale and macroscale modeling and experimentation are used to advance appropriate forms of closure relations.

Readers with more interest in TCAT are directed to a series of papers by Gray and Miller [29, 30, 32–35, 43, 55, 56].

Chapter 2

Model Description

2.1 The Model Domain

The domain of this model consists of five phases: two fluid and three solid. One fluid phase is intravascular fluid, or blood, and the second is the interstitial fluid. Throughout this document the blood phase will be denoted by the letter b and interstitial fluid will be denoted by the letter f. Blood flows through the vasculature (arteries, arterioles, capillaries, venules, and veins) that supply the tissues in the domain region. The cells that make up the vascular walls are not included in the model, only the volume of blood occupying the luminal space of the blood vessels. The vasculature can be thought of as network of pliable, permeable pipes that stay fixed in space. Through the process of angiogenesis, new vasculature grows by branching off existing vasculature, initiated by biochemical signaling molecules such as vascular endothelial growth factor (VEGF). Blood itself is a mixture of plasma, red blood cells, white blood cells, platelets, etc., but here it will be treated as a single fluid that contains a dissolved chemical species i. Plasma makes up about 55% of blood volume and the cellular components make up the remaining 45% [53]. Blood is a non-Newtonian, shear thinning fluid meaning that its dynamic viscosity is high at small shear stress and decreases as velocity increases

[20].

The blood vessels exist to supply all the metabolic needs of the cells of the body and assist the lymphatic system in removing waste products. The somatic cells grow in densely packed arrangements, surrounded by fluid and extra-cellular matrix. The extravascular (outside the blood vessels) fluid is often called interstitial fluid or extra-cellular fluid and it occupies space (the pore space) called the interstitium or interstitial space. The interstitial fluid allows dissolved species to travel between the vasculature and the cells, and provides a medium for intercellular signaling molecules to travel between nearby cells. The interstitial fluid is very different from the blood in composition. The interstitial fluid is composed primarily of water and is often assumed to be incompressible and/or inviscid.

The cells maintain tissue integrity by cell to cell contact, and the extracellular matrix acts as a scaffolding system to give the tissue more structure and rigidity. In this model, the cellular and extracellular matrix components of the tissue will be treated as a single solid phase. Three solid tissues of this model are named depending on the type of cell each phase is made of: normal host tissue (h); viable tumor tissue able to proliferate (p); or necrotic tumor tissue (n).

Figure 2.1 shows the phases included in this model, but is not meant to represent the shape or organization of the domain. It is meant as an aid in visualizing the fluid phases and solid phases occupying shared regions in space. As seen in this figure, the intravascular phase appears as a network surrounded by interstitial fluid. Each of the solid phases can be described as porous media and are interspersed with the fluid phases. Normal host tissue is distinct from the tumor tissue, genetically and morphologically. Normal cells cannot become cancer cells and vice versa. The tumor grows by clonal expansion and regions of necrosis occur where tumor cells are at a sufficient distance from vasculature that they do not receive sufficient nutrition. The

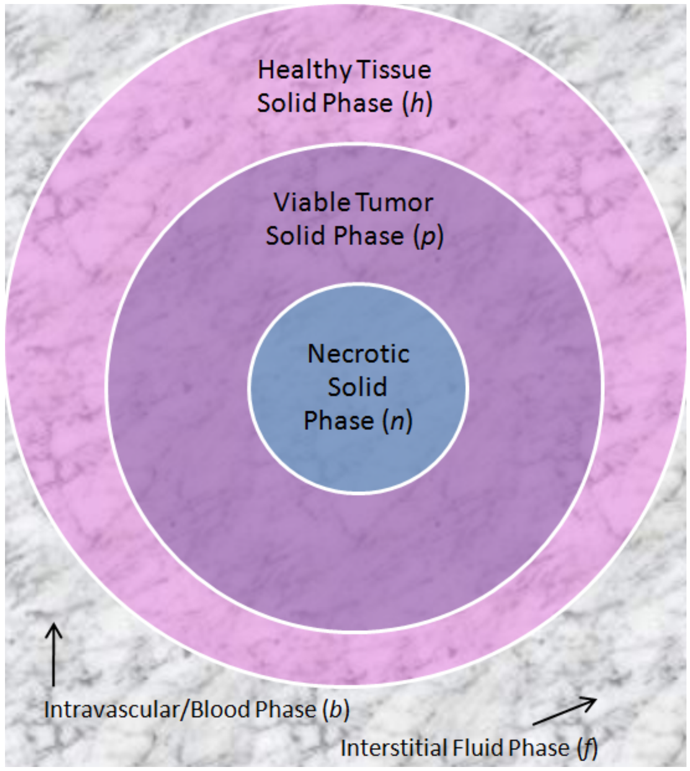

Figure 2.1: Phases represented in this model.

necrotic phase grows by the conversion of viable tumor solid to necrotic solid due to nutrient or oxygen deprivation. The functional form of this nutrient dependency will be discussed in Chapter 4. Figure 2.1 is a crude rendering of the model phases and is not drawn to scale. It represents just one of many possible tumor morphologies. Avascular tumors tend to grow spherically, but the vascular blood phase does not occupy the domain shared by the tumor tissue in this type of tumor. The necrotic core develops because the tumor receives its nutrition via diffusion from the outside in, and once the tumor radius is larger than the diffusion distance (200 μm on average [40]) necrosis occurs beyond this distance from the outer rim.

Vascular tumors are those that have initiated angiogenesis to grow new capillary vessels, originating from the pre-existing vasculature in the normal tissue and branching toward the tumor. Eventually the new capillaries perfuse the tumor tissue, supplying it with nutrients so that it can grow larger than the maximum size of an avascular tumor. Vascular tumors have initiated the growth of their own blood vessels, but the rate of proliferation often outstrips the rate of new blood vessel growth (angiogenesis), such that necroses develop in regions beyond the diffusion limited distance from any vasculature.

2.2 Initial Hypotheses and Assumptions

The process of specifying constitutive equations to close a mathematical model involves the careful formulation of a number of assumptions to mold the problem into a tractable set of equations. It is these assumptions that are made at the late stage of model formulation that often involve the greatest conceptual leaps and gross simplifications. It is important to take note of all assumptions made during the process of formulating the model so that the validity of the assumptions can be weighed if the model results do not behave as expected. It is in this stage that TCAT excels because the exact equations are kept as long as possible and assumptions implied by closure relations are explicitly discussed. However there is another set of assumptions or hypotheses that are equally important but often overlooked. These assumptions are those that are necessary to develop the model from the beginning- the conceptual framework that guides the manner in which the mathematical equations are formulated.

First, this model is multiphase in nature. Multiphase models are based upon the theory of continua with multiple interacting components called phases. Phases can be solid or fluid (including liquid and gas) and can be composed of a single constituent or multiple constituents called species. Conservation laws can be written for phases and for the individual species contained therein. The sum over all species must equal the phase equation. Not only can we write equations for three-dimensional phases, but also for lower dimensional regions, such as interfaces (two-dimensional) and common curves (one-dimensional). All of these regions are collectively called entities. A macroscale point may contain any number of entities, depending on the system of interest.

Since this is a macroscale model, we are making the assumption that a representative elementary volume (REV) exists and that the separation of length scales allows deterministic (exact) macroscale modeling using the averaging operators detailed at length in the following chapter. The clinical counterpart of the REV is the voxel, or volumetric pixel. A voxel is the smallest unit of resolution in a medical image, such as one created using magnetic resonance imaging (MRI). A voxel is a three-dimensional point in space that is associated with one or more measurements, such as signal intensity. Because of the resolution of the imaging modalities like MRI, the physical space represented by a single voxel incorporates a great number of cells, making the value associated with the voxel a volume average over all the cells and other components in the location of the voxel. The size of a voxel and an REV may not correspond, but the usefulness of information offered by a voxel in a tumor image implies that volume averaged quantites are useful in describing tumor morphology. Hence, it is also reasonable to assume that a macroscale model that make use of an REV will also be able to provide useful infomation.

Furthermore this model utilizes classical irreversible thermodynamics (CIT) to represent the thermodynamics of the system. Thermodynamic relations are needed to constrain the model using the TCAT approach and the current formulation of TCAT employs CIT, but is flexible and could be revised to reflect an alternative theory of thermodynamics. The remaining assumptions will be discussed, as needed, during the derivations that follow.

Chapter 3

Derivation of General Equations

3.1 Introduction to Conservation Equations

Mechanistic models are based upon the universal physical laws of conservation of mass, momentum, and energy. These are extensive quantities, meaning that they are additive, in contrast to intesive properties such as temperature and pressure, which do not combine additively. What will be done here is to introduce the most general form of the equations and then gradually work towards more specific formulations. First, the conceptual form of the conservation equation:

$$0 = (\text{Accumulation Rate}) + (\text{Net Outward Advection}) - (\text{Body Sources}) - (\text{Non-Advective Surface Sources}) - (\text{Generation Rate})\,. \qquad (3.1)$$

Since continuum mechanics uses differential equations to write conservation equations equation (3.1) is a rate equation. In this conceptual equation, accumulation represents the amount of the quantity (mass, momentum, energy) that is gained or lost over a set period of time. Advection refers to the the rate at which material crosses the boundary of the domain of interest due to the mean rate of the entity velocity. Since the conservation equations arbitrarily define advection as being in the outward direction, a positive value denotes material that leaves the domain and and negative value refers to material that enters the domain. Body sources act on the entire material in the domain, not solely on the boundary. On the other hand, non-advective surface sources are sources that act on the boundary. The rate of generation term accounts for material created within the domain. (A negative generation term would therefore account for material destroyed within the domain). Therefore, we can write conservation equations for single species that interact with one another, or for an entire phase, which may be composed of any number of species.

With these concepts in place, one can express the general conservation equation in mathematical form. The most general mathematical form of the equation we will call the "integral" form for obvious reasons. It can be written in vector form and non-vector form.

Non-Vector General Integral Conservation Equation:

$$0 = \frac{\mathrm{d}}{\mathrm{d}t}\int\limits_{\Omega} f \,\mathrm{d}\mathfrak{r} + \int\limits_{\Gamma} f\,(\mathbf{v}-\mathbf{w})\cdot\mathbf{n}\,\mathrm{d}\mathfrak{r} - \int\limits_{\Omega} f_B \,\mathrm{d}\mathfrak{r} - \int\limits_{\Gamma} f_N \,\mathrm{d}\mathfrak{r} - \int\limits_{\Omega} f_G \,\mathrm{d}\mathfrak{r} \tag{3.2}$$

Vector General Integral Conservation Equation

$$0 = \frac{\mathrm{d}}{\mathrm{d}t}\int\limits_{\Omega} \mathbf{f} \,\mathrm{d}\mathfrak{r} + \int\limits_{\Gamma} \mathbf{f}\,(\mathbf{v}-\mathbf{w})\cdot\mathbf{n}\,\mathrm{d}\mathfrak{r} - \int\limits_{\Omega} \mathbf{f}_B \,\mathrm{d}\mathfrak{r} - \int\limits_{\Gamma} \mathbf{f}_N \,\mathrm{d}\mathfrak{r} - \int\limits_{\Omega} \mathbf{f}_G \,\mathrm{d}\mathfrak{r} \tag{3.3}$$

In these general equations, the capital omega (Ω) stands for the entire domain and the capital gamma (Γ) stands for the boundary of the domain. The script r, as in $\mathrm{d}\mathfrak{r}$, stands for the region and can be used to denote a volume, surface, or curve. Note that the accumulation, body source, and generation terms are integrated over the domain, while the advective and non-advective surface sources are integrated over the boundary of the domain. A boldface font indicates vector quantities. In the second term of the equation, $\mathbf{v}$ and $\mathbf{w}$ are both vector quantities of velocity. The velocity of the material in question is $\mathbf{v}$, while the velocity of the boundary of the domain is $\mathbf{w}$. Therefore the domain is allowed to translate and only a difference in velocity between the material and the domain in the direction perpendicular to the boundary (hence the $\cdot\mathbf{n}$) accounts for advective flux. The subscripts B, N, and G stand for Body sources, Non-advective surface sources, and Generation, respectively. These terms must be specified individually, based on the problem at hand.

One can also write the integral or megascale form of the general conservation equation for a species within a phase. The letter i is used to represent the species of interest, within the phase α.

General Integral Conservation Equation for a Species in a Phase:

$$0 = \frac{\mathrm{d}}{\mathrm{d}t}\int\limits_{\Omega} f_{i\alpha}\,\mathrm{d}\mathfrak{r} + \int\limits_{\Gamma} f_{i\alpha}\left(\mathbf{v}_{i\alpha} - \mathbf{w}_{\alpha}\right)\cdot\mathbf{n}_{\alpha}\,\mathrm{d}\mathfrak{r} - \int\limits_{\Omega} f_{Bi\alpha}\,\mathrm{d}\mathfrak{r} - \int\limits_{\Gamma} f_{Ni\alpha}\,\mathrm{d}\mathfrak{r} - \int\limits_{\Omega} f_{Gi\alpha}\,\mathrm{d}\mathfrak{r} \quad (3.4)$$

To go to the next level of specificity, one can use a variety of derivative forms using theorems like the well known divergence and transport theorems.

Divergence Theorem:

$$\int\limits_{\Omega} \nabla\cdot\mathbf{f}\,\mathrm{d}\mathfrak{r} = \int\limits_{\Gamma} \mathbf{n}\cdot\mathbf{f}\,\mathrm{d}\mathfrak{r} \quad (3.5)$$

Transport Theorem:

$$\frac{\mathrm{d}}{\mathrm{d}t}\int\limits_{\Omega} f\,\mathrm{d}\mathfrak{r} = \int\limits_{\Omega} \frac{\partial f}{\partial t}\,\mathrm{d}\mathfrak{r} + \int\limits_{\Gamma} \left(\mathbf{w}\cdot\mathbf{n}\right) f\,\mathrm{d}\mathfrak{r} \quad (3.6)$$

It is useful to note that these are not the only theorems that can be used to localize the integral form of the equation to the microscale. There exist other theorems for localization which can convert the integral equation to equations of reduced dimensionality, where the equation is averaged over one or two dimension and varies along the remaining dimensions. Thus, it may be useful to state that the transport and divergence theorems are used to localize the integral/megascale form of the equation to the microscale that varies in three dimensions. Now that the terms microscale and megascale have been introduced, a discussion of length scales is warranted.

3.2 Translating Length Scales

By utilizing the divergence theorem (3.5) and transport theorem (3.6) on equation (3.4), we get the microscale point form of the species conservation equation:

$$\frac{\partial f_{i\alpha}}{\partial t} + \nabla\cdot\left(f_{i\alpha}\mathbf{v}_{i\alpha}\right) - f_{Bi\alpha} - \nabla\cdot f_{Ni\alpha} - f_{Gi\alpha} = 0 \tag{3.7}$$

The microscale equations are the classical form of the conservation equations in continuum mechanics. However, since it is often desirable to produce models at the macroscale TCAT employs a number of averaging theorems. These averaging theorems are listed in Miller and Gray (2005), [56]. The averaging operator has the following definition.

$$\langle \mathcal{P}_i \rangle_{\Omega_j,\Omega_k,w} = \frac{\int\limits_{\Omega_j} w\mathcal{P}_1 \,\mathrm{d}\mathfrak{r}}{\int\limits_{\Omega_k} w \,\mathrm{d}\mathfrak{r}} \tag{3.8}$$

The angle brackets on the left side of equation (3.8) is called the averaging operator and will be used frequently in subsequent derivations. The averaging operator always has two or three subscripts following it. The first indicates the domain over which the property $\mathcal{P}$ is averaged; this is in the numerator of the right hand side of the equation. The second subscript is the averaging domain in the denominator of the right hand side. The third and final subscript is an optional weight applied to the numerator and denominator. If the third subscript of an averaging operator is absent then the weight is one. For clarity, microscale quantities will be represented with a subscript phase qualifier. Macroscale variable receive a superscript. The superscript can be unadorned to signify an intrinsic average, topped with a single over-line to denote a mass-averaged quantity, or can receive a double over-line to indicate that the macroscale quantity has a unique definition that must be provided.

$$\text{Intrinsic Average: } \langle f_\alpha \rangle_{\Omega_\alpha,\Omega_\alpha} = \frac{\int\limits_{\Omega_\alpha} f_\alpha \, \mathrm{d}\mathfrak{r}}{\int\limits_{\Omega_\alpha} \mathrm{d}\mathfrak{r}} = f^\alpha \tag{3.9}$$

$$\text{Mass Average: } \langle f_\alpha \rangle_{\Omega_\alpha,\Omega_\alpha,\rho_\alpha} = \frac{\int\limits_{\Omega_\alpha} \rho_\alpha f_\alpha \, \mathrm{d}\mathfrak{r}}{\int\limits_{\Omega_\alpha} \rho_\alpha \, \mathrm{d}\mathfrak{r}} = f^{\overline{\alpha}} \tag{3.10}$$

In the following derivation, phases will be indicated by a single Greek letter, such as α. The letter kappa (κ) will be reserved to denote a set of interfaces connected to a particular phase.

3.3 Mass

The microscale conservation of mass equation for the generic phase α consists of two terms: the accumulation term and the net outward flux of mass from phase α to other entities.

$$\mathcal{M}_\alpha = \frac{\partial \rho_\alpha}{\partial t} + \nabla \cdot (\mathbf{v}_\alpha \rho_\alpha) = 0 \tag{3.11}$$

The microscale form of the equation ($\mathcal{M}_\alpha$) can be manipulated to find the macroscale form of the equation ($\mathcal{M}^{\overline{\overline{\alpha}}}$) by employing the averaging operators discussed in section

3.2.

$$\mathcal{M}^{\overline{\overline{\alpha}}} = \langle \mathcal{M}_\alpha \rangle_{\Omega_\alpha,\Omega} = 0 \tag{3.12}$$

$$\mathcal{M}^{\overline{\overline{\alpha}}} = \left\langle \frac{\partial \rho_\alpha}{\partial t} + \nabla \boldsymbol{\cdot} (\mathbf{v}_\alpha \rho_\alpha) \right\rangle_{\Omega_\alpha,\Omega} \tag{3.13}$$

The averaging operator may be split across sums of terms.

$$\mathcal{M}^{\overline{\overline{\alpha}}} = \left\langle \frac{\partial \rho_\alpha}{\partial t} \right\rangle_{\Omega_\alpha,\Omega} + \langle \nabla \boldsymbol{\cdot} (\mathbf{v}_\alpha \rho_\alpha) \rangle_{\Omega_\alpha,\Omega} \tag{3.14}$$

To evaluate the first term, the intrinsic average of microscale mass density, we need the three dimensional transport averaging theorem, **T[3,(3,0),0]**:

$$\left\langle \frac{\partial f_\alpha}{\partial t} \right\rangle_{\Omega_\alpha,\Omega} = \frac{\partial}{\partial t} \langle f_\alpha \rangle_{\Omega_\alpha,\Omega} - \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \boldsymbol{\cdot} \mathbf{v}_\kappa f_\alpha \rangle_{\Omega_\kappa,\Omega} \tag{3.15}$$

Thus, the derivative of the microscale density is averaged according to theorem **T[3,(3,0),0)]**.

$$\left\langle \frac{\partial \rho_\alpha}{\partial t} \right\rangle_{\Omega_\alpha,\Omega} = \frac{\partial}{\partial t} \langle \rho_\alpha \rangle_{\Omega_\alpha,\Omega} - \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \boldsymbol{\cdot} \mathbf{v}_\kappa \rho_\alpha \rangle_{\Omega_\kappa,\Omega} \tag{3.16}$$

Leading to:

$$\left\langle \frac{\partial \rho_\alpha}{\partial t} \right\rangle_{\Omega_\alpha,\Omega} = \frac{\partial (\epsilon^\alpha \rho^\alpha)}{\partial t} - \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \boldsymbol{\cdot} \mathbf{v}_\kappa \rho_\alpha \rangle_{\Omega_\kappa,\Omega} \tag{3.17}$$

Since the second term of (3.11) contains a divergence within an averaging operator, one needs to use the three dimensional divergence averaging theorem, **(D[3,(3,0),0])**:

$$\langle \nabla\cdot \mathbf{f}_\alpha \rangle_{\Omega_\alpha,\Omega} = \nabla\cdot \langle \mathbf{f}_\alpha \rangle_{\Omega_\alpha,\Omega} + \sum_{\kappa\in\mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha\cdot \mathbf{f}_\alpha \rangle_{\Omega_\kappa,\Omega} \tag{3.18}$$

Applying this theorem to the divergence term of the mass equation, one gets the following.

$$\langle \nabla\cdot (\mathbf{v}_\alpha \rho_\alpha) \rangle_{\Omega_\alpha,\Omega} = \nabla\cdot \langle \mathbf{v}_\alpha \rho_\alpha \rangle_{\Omega_\alpha,\Omega} + \sum_{\kappa\in\mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha\cdot \mathbf{v}_\alpha \rho_\alpha \rangle_{\Omega_\kappa,\Omega} \tag{3.19}$$

Now evaluate the averaging operator of the first term on the right side of (3.19).

$$\nabla\cdot \langle \mathbf{v}_\alpha \rho_\alpha \rangle_{\Omega_\alpha,\Omega} = \nabla\cdot \left(\langle \mathbf{v}_\alpha \rangle_{\Omega_\alpha,\Omega_\alpha,\rho_\alpha} \langle \rho_\alpha \rangle_{\Omega_\alpha,\Omega_\alpha} \langle 1 \rangle_{\Omega_\alpha,\Omega} \right) = \nabla\cdot \left(\mathbf{v}^{\overline{\alpha}} \rho^\alpha \epsilon^\alpha \right) \tag{3.20}$$

Now combine the terms from (3.11) and (3.19) left in the averaging operator:

$$\sum_{\kappa\in\mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha\cdot \mathbf{v}_\alpha \rho_\alpha \rangle_{\Omega_\kappa,\Omega} - \sum_{\kappa\in\mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha\cdot \mathbf{v}_\kappa \rho_\alpha \rangle_{\Omega_\kappa,\Omega} = \sum_{\kappa\in\mathfrak{I}_{c\alpha}} \langle \rho_\alpha \mathbf{n}_\alpha\cdot (\mathbf{v}_\alpha - \mathbf{v}_\kappa) \rangle_{\Omega_\kappa,\Omega} \tag{3.21}$$

The mass transfer between the κ interface and the α phase is defined as follows:

$$\overset{\kappa\to\alpha}{M} = \langle \rho_\alpha \mathbf{n}_\alpha\cdot (\mathbf{v}_\kappa - \mathbf{v}_\alpha) \rangle_{\Omega_\kappa,\Omega} \tag{3.22}$$

This gets substituted for the interface terms.

$$\sum_{\kappa\in\mathfrak{I}_{c\alpha}} \langle \rho_\alpha \mathbf{n}_\alpha\cdot (\mathbf{v}_\alpha - \mathbf{v}_\kappa) \rangle_{\Omega_\kappa,\Omega} = -\overset{\kappa\to\alpha}{M} \tag{3.23}$$

Now recombine all macroscale quantities to form the equation for macroscale conservation of mass for a phase.

$$\mathcal{M}^{\overline{\overline{\alpha}}} = \frac{\partial(\epsilon^{\alpha}\rho^{\alpha})}{\partial t} + \nabla\cdot\left(\mathbf{v}^{\overline{\alpha}}\rho^{\alpha}\epsilon^{\alpha}\right) - \overset{\kappa\to\alpha}{M} = 0 \tag{3.24}$$

3.4 Momentum

The microscale conservation of momentum equation for a phase can be written as:

$$\boldsymbol{\mathcal{P}}_{\alpha} = \frac{\partial(\rho_{\alpha}\mathbf{v}_{\alpha})}{\partial t} + \nabla\cdot(\rho_{\alpha}\mathbf{v}_{\alpha}\mathbf{v}_{\alpha}) - \nabla\cdot\mathbf{t}_{\alpha} - \rho_{\alpha}\mathbf{g}_{\alpha} = 0 \tag{3.25}$$

From left to right, these terms represent the accumulation, net outward flux, non-advective surface sources, and body sources of momentum. The variables ρ_{α} and $\mathbf{v}_{\alpha}$ were introduced as density and velocity in the derivation of mass section, and this equation also includes $\mathbf{t}_{\alpha}$, which is the stress tensor, and $\mathbf{g}_{\alpha}$ which is the gravity vector. The macroscale conservation equation of momentum equation can be derived by applying the averging operator to the microscale equation, expressed as:

$$\boldsymbol{\mathcal{P}}^{\overline{\overline{\alpha}}} = \langle\boldsymbol{\mathcal{P}}_{\alpha}\rangle_{\Omega_{\alpha},\Omega} \tag{3.26}$$

The averaging operator can be applied to each term individually.

$$\begin{aligned}\langle\boldsymbol{\mathcal{P}}_{\alpha}\rangle_{\Omega_{\alpha},\Omega} = &\left\langle\frac{\partial(\rho_{\alpha}\mathbf{v}_{\alpha})}{\partial t}\right\rangle_{\Omega_{\alpha},\Omega} + \langle\nabla\cdot(\rho_{\alpha}\mathbf{v}_{\alpha}\mathbf{v}_{\alpha})\rangle_{\Omega_{\alpha},\Omega}\\ &- \langle\nabla\cdot\mathbf{t}_{\alpha}\rangle_{\Omega_{\alpha},\Omega} - \langle\rho_{\alpha}\mathbf{g}_{\alpha}\rangle_{\Omega_{\alpha},\Omega} = 0\end{aligned} \tag{3.27}$$

Beginning with the first term in equation (3.27) this derivation will evaluate the averaging operator. Since there is a partial derivative term within the averaging operator, one will need to apply the vector form of theorem **T[3,(3,0),0]**.

T[3,(3,0),0]:

$$\left\langle \frac{\partial \mathbf{f}_\alpha}{\partial t} \right\rangle_{\Omega_\alpha,\Omega} = \frac{\partial}{\partial t}\langle \mathbf{f}_\alpha \rangle_{\Omega_\alpha,\Omega} - \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot \mathbf{v}_\kappa \mathbf{f}_\alpha \rangle_{\Omega_\kappa,\Omega} \tag{3.28}$$

Applying **T[3,(3,0),0]** to the derivative term gives:

$$\left\langle \frac{\partial (\rho_\alpha \mathbf{v}_\alpha)}{\partial t} \right\rangle_{\Omega_\alpha,\Omega} = \frac{\partial}{\partial t}\langle \rho_\alpha \mathbf{v}_\alpha \rangle_{\Omega_\alpha,\Omega} - \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot \mathbf{v}_\kappa \rho_\alpha \mathbf{v}_\alpha \rangle_{\Omega_\kappa,\Omega} \tag{3.29}$$

The term $\langle \rho_\alpha \mathbf{v}_\alpha \rangle_{\Omega_\alpha,\Omega}$ can be evaluated as:

$$\langle \rho_\alpha \mathbf{v}_\alpha \rangle_{\Omega_\alpha,\Omega} = \langle 1 \rangle_{\Omega_\alpha,\Omega} \langle \rho_\alpha \rangle_{\Omega_\alpha,\Omega_\alpha} \langle \mathbf{v}_\alpha \rangle_{\Omega_\alpha,\Omega_\alpha,\rho_\alpha} = \epsilon^\alpha \rho^\alpha \mathbf{v}^{\overline{\alpha}} \tag{3.30}$$

Therefore the derivative term term may be written as:

$$\left\langle \frac{\partial (\rho_\alpha \mathbf{v}_\alpha)}{\partial t} \right\rangle_{\Omega_\alpha,\Omega} = \frac{\partial (\epsilon^\alpha \rho^\alpha \mathbf{v}^{\overline{\alpha}})}{\partial t} - \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot \mathbf{v}_\kappa \rho_\alpha \mathbf{v}_\alpha \rangle_{\Omega_\kappa,\Omega} \tag{3.31}$$

Next is the evaluation of the second term of equation (3.27). Since there is a divergence operator within the averaging operator, apply theorem **D[3,(3,0),0]**:

$$\langle \nabla \cdot \mathbf{f}_\alpha \rangle_{\Omega_\alpha,\Omega} = \nabla \cdot \langle \mathbf{f}_\alpha \rangle_{\Omega_\alpha,\Omega} + \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot \mathbf{f}_\alpha \rangle_{\Omega_\kappa,\Omega} \tag{3.32}$$

Applying this theorem to the divergence term leads to:

$$\langle \nabla \cdot (\rho_\alpha \mathbf{v}_\alpha \mathbf{v}_\alpha) \rangle_{\Omega_\alpha,\Omega} = \nabla \cdot \langle \rho_\alpha \mathbf{v}_\alpha \mathbf{v}_\alpha \rangle_{\Omega_\alpha,\Omega} + \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot \rho_\alpha \mathbf{v}_\alpha \mathbf{v}_\alpha \rangle_{\Omega_\kappa,\Omega} \tag{3.33}$$

The product of velocities cannot be assessed conveniently. Instead, add and subtract the macroscale velocity ($\mathbf{v}^{\overline{\alpha}}$).

$$\begin{aligned}\langle \rho_\alpha \mathbf{v}_\alpha \mathbf{v}_\alpha \rangle_{\Omega_\alpha,\Omega} &= \left\langle \rho_\alpha \left[\mathbf{v}^{\overline{\alpha}} + (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}))(\mathbf{v}^{\overline{\alpha}} + (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}) \right] \right\rangle_{\Omega_\alpha,\Omega} \\ &= \left\langle \rho_\alpha \mathbf{v}^{\overline{\alpha}} \mathbf{v}^{\overline{\alpha}} + \rho_\alpha (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}})(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}) \right\rangle_{\Omega_\alpha,\Omega} \end{aligned} \tag{3.34}$$

The averaging operator can be applied to the first part of Equation(3.34):

$$\langle 1 \rangle_{\Omega_\alpha,\Omega} \langle \rho_\alpha \rangle_{\Omega_\alpha,\Omega_\alpha} \mathbf{v}^{\overline{\alpha}} \mathbf{v}^{\overline{\alpha}} = \epsilon^\alpha \rho^\alpha \mathbf{v}^{\overline{\alpha}} \mathbf{v}^{\overline{\alpha}} \tag{3.35}$$

Thus the definition of $\langle \rho_\alpha \mathbf{v}_\alpha \mathbf{v}_\alpha \rangle_{\Omega_\alpha,\Omega}$ can be written as:

$$\langle \rho_\alpha \mathbf{v}_\alpha \mathbf{v}_\alpha \rangle_{\Omega_\alpha,\Omega} = \nabla\cdot \left(\epsilon^\alpha \rho^\alpha \mathbf{v}^{\overline{\alpha}} \mathbf{v}^{\overline{\alpha}} \right) + \nabla\cdot \left\langle \rho_\alpha (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}})(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}) \right\rangle_{\Omega_\alpha,\Omega} \tag{3.36}$$

Therefore the second term of (3.27) term may be written as:

$$\begin{aligned}\langle \nabla\cdot (\rho_\alpha \mathbf{v}_\alpha \mathbf{v}_\alpha) \rangle_{\Omega_\alpha,\Omega} = \nabla\cdot \left(\epsilon^\alpha \rho^\alpha \mathbf{v}^{\overline{\alpha}} \mathbf{v}^{\overline{\alpha}} \right) + \nabla\cdot \left\langle \rho_\alpha (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}})(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}) \right\rangle_{\Omega_\alpha,\Omega} \\ + \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot \rho_\alpha \mathbf{v}_\alpha \mathbf{v}_\alpha \rangle_{\Omega_\kappa,\Omega} \end{aligned} \tag{3.37}$$

The third term in Equation (3.27) also contains a divergence within the averaging operator, so one needs to apply theorem **D[3,(3,0),0]**

$$- \langle \nabla\cdot \mathbf{t}_\alpha \rangle_{\Omega_\alpha,\Omega} = -\nabla\cdot \langle \mathbf{t}_\alpha \rangle_{\Omega_\alpha,\Omega} - \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot \mathbf{t}_\alpha \rangle_{\Omega_\kappa,\Omega} \tag{3.38}$$

The second term in equation (3.37) can be added to this equation.

$$\begin{aligned} - \left\langle \nabla\cdot \mathbf{t}^{\overline{\overline{\alpha}}} \right\rangle_{\Omega_\alpha,\Omega} + \nabla\cdot \left\langle \rho_\alpha (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}})(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}) \right\rangle_{\Omega_\alpha,\Omega} = \\ - \nabla\cdot \langle \mathbf{t}_\alpha \rangle_{\Omega_\alpha,\Omega} + \nabla\cdot \left\langle \rho_\alpha (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}})(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}) \right\rangle_{\Omega_\alpha,\Omega} - \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot \mathbf{t}_\alpha \rangle_{\Omega_\kappa,\Omega} \end{aligned} \tag{3.39}$$

The macroscale stress tensor is defined as $\mathbf{t}^{\overline{\overline{\alpha}}} = \langle \mathbf{t}_\alpha - \rho_\alpha(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}})(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}) \rangle_{\Omega_\alpha,\Omega_\alpha}$. Therefore:

$$-\nabla\cdot\langle \mathbf{t}_\alpha \rangle_{\Omega_\alpha,\Omega} + \nabla\cdot\left\langle \rho_\alpha(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}})(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}) \right\rangle_{\Omega_\alpha,\Omega} = -\nabla\cdot\left(\epsilon^\alpha \mathbf{t}^{\overline{\overline{\alpha}}}\right) \tag{3.40}$$

Thus, the terms remaining from averaging the third (non-advective surface source) term of eq. (3.27) are as follows.

$$-\langle \nabla\cdot\mathbf{t}_\alpha \rangle_{\Omega_\alpha,\Omega} + \nabla\cdot\left\langle \rho_\alpha(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}})(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}) \right\rangle_{\Omega_\alpha,\Omega} = -\nabla\cdot\left(\epsilon^\alpha \mathbf{t}^{\overline{\overline{\alpha}}}\right) - \sum_{\kappa\in\mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha\cdot\mathbf{t}_\alpha \rangle_{\Omega_\kappa,\Omega} \tag{3.41}$$

The fourth term of equation (3.27) can be evaluated as:

$$\langle \rho_\alpha \mathbf{g}_\alpha \rangle_{\Omega_\alpha,\Omega} = \langle 1 \rangle_{\Omega_\alpha,\Omega} \langle \rho_\alpha \rangle_{\Omega_\alpha,\Omega_\alpha} \langle \mathbf{g}_\alpha \rangle_{\Omega_\alpha,\Omega_\alpha} = \epsilon^\alpha \rho^\alpha \mathbf{g}^{\overline{\alpha}} \tag{3.42}$$

Combining all the terms, the macroscale conservation of momentum equation for a phase can be expressed as:

$$\frac{\partial(\epsilon^\alpha \rho^\alpha \mathbf{v}^{\overline{\alpha}})}{\partial t} + \nabla\cdot\left(\epsilon^\alpha \rho^\alpha \mathbf{v}^{\overline{\alpha}} \mathbf{v}^{\overline{\alpha}}\right) - \nabla\cdot(\epsilon^\alpha \mathbf{t}^{\overline{\overline{\alpha}}}) - \epsilon^\alpha \rho^\alpha \mathbf{g}^{\overline{\alpha}} - \sum_{\kappa\in\mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha\cdot\mathbf{v}_\kappa \rho_\alpha \mathbf{v}_\alpha \rangle_{\Omega_\kappa,\Omega} + \sum_{\kappa\in\mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha\cdot\rho_\alpha \mathbf{v}_\alpha \mathbf{v}_\alpha \rangle_{\Omega_\kappa,\Omega} - \sum_{\kappa\in\mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha\cdot\mathbf{t}_\alpha \rangle_{\Omega_\kappa,\Omega} = 0 \tag{3.43}$$

or

$$\frac{\partial(\epsilon^\alpha \rho^\alpha \mathbf{v}^{\overline{\alpha}})}{\partial t} + \nabla\cdot\left(\epsilon^\alpha \rho^\alpha \mathbf{v}^{\overline{\alpha}} \mathbf{v}^{\overline{\alpha}}\right) - \nabla\cdot(\epsilon^\alpha \mathbf{t}^{\overline{\overline{\alpha}}}) - \epsilon^\alpha \rho^\alpha \mathbf{g}^{\overline{\alpha}} - \sum_{\kappa\in\mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha\cdot(\mathbf{v}_\kappa \rho_\alpha \mathbf{v}_\alpha - \rho_\alpha \mathbf{v}_\alpha \mathbf{v}_\alpha + \mathbf{t}_\alpha) \rangle_{\Omega_\kappa,\Omega} = 0 \tag{3.44}$$

Expanding the boundary term of the macroscale conservation of momentum equation for a phase by substituting in $\mathbf{v}^{\overline{\alpha}} + (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}})$ for two of the $\mathbf{v}_\alpha$ terms gives:

$$\sum_{\kappa\in\mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot (\mathbf{v}_\kappa \rho_\alpha \mathbf{v}_\alpha - \rho_\alpha \mathbf{v}_\alpha \mathbf{v}_\alpha + \mathbf{t}_\alpha)\rangle_{\Omega_\kappa,\Omega} = \sum_{\kappa\in\mathfrak{I}_{c\alpha}} \left\langle \mathbf{n}_\alpha \cdot (\mathbf{v}_\kappa \rho_\alpha (\mathbf{v}^{\overline{\alpha}} + (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}})) - \rho_\alpha (\mathbf{v}^{\overline{\alpha}} + (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}))\mathbf{v}_\alpha + \mathbf{t}_\alpha)\right\rangle_{\Omega_\kappa,\Omega} \tag{3.45}$$

Further expansion gives:

$$\sum_{\kappa\in\mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot (\mathbf{v}_\kappa \rho_\alpha \mathbf{v}_\alpha - \rho_\alpha \mathbf{v}_\alpha \mathbf{v}_\alpha + \mathbf{t}_\alpha)\rangle_{\Omega_\kappa,\Omega} = \sum_{\kappa\in\mathfrak{I}_{c\alpha}} \left\langle \mathbf{n}_\alpha \cdot (\mathbf{v}_\kappa \rho_\alpha \mathbf{v}^{\overline{\alpha}} + \mathbf{v}_\kappa \rho_\alpha (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}) - \rho_\alpha \mathbf{v}^{\overline{\alpha}} \mathbf{v}_\alpha + \rho_\alpha (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}})\mathbf{v}_\alpha + \mathbf{t}_\alpha)\right\rangle_{\Omega_\kappa,\Omega} \tag{3.46}$$

Combining like terms and simplifying yields:

$$\sum_{\kappa\in\mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot (\mathbf{v}_\kappa \rho_\alpha \mathbf{v}_\alpha - \rho_\alpha \mathbf{v}_\alpha \mathbf{v}_\alpha + \mathbf{t}_\alpha)\rangle_{\Omega_\kappa,\Omega} = \sum_{\kappa\in\mathfrak{I}_{c\alpha}} \left\langle \mathbf{n}_\alpha \cdot (\rho_\alpha (\mathbf{v}_\kappa - \mathbf{v}_\alpha)\mathbf{v}^{\overline{\alpha}} + \rho_\alpha (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}})(\mathbf{v}_\kappa - \mathbf{v}_\alpha) + \mathbf{t}_\alpha)\right\rangle_{\Omega_\kappa,\Omega} \tag{3.47}$$

By definition:

$$\overset{\kappa\to\alpha}{M} = \langle \mathbf{n}_\alpha \cdot \rho_\alpha (\mathbf{v}_\kappa - \mathbf{v}_\alpha)\rangle_{\Omega_\kappa,\Omega} \tag{3.48}$$

The interphase momentum transfer due to mechanical effects can also be defined, as follows.

$$\overset{\kappa\to\alpha}{\mathbf{T}} = \left\langle \mathbf{n}_\alpha \cdot (\rho_\alpha (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}})(\mathbf{v}_\kappa - \mathbf{v}_\alpha) + \mathbf{t}_\alpha)\right\rangle_{\Omega_\kappa,\Omega} \tag{3.49}$$

Substituting these definitions into the boundary term defined by (3.47) one obtains the following.

$$\sum_{\kappa \in \mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot (\mathbf{v}_\kappa \rho_\alpha \mathbf{v}_\alpha - \rho_\alpha \mathbf{v}_\alpha \mathbf{v}_\alpha + \mathbf{t}_\alpha) \rangle_{\Omega_\kappa,\Omega} = \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \left(\mathbf{v}^{\overline{\alpha}} \overset{\kappa\to\alpha}{M} + \overset{\kappa\to\alpha}{\mathbf{T}} \right) \tag{3.50}$$

Therefore the macroscale conservation of momentum equation for a phase may be expressed as:

$$\frac{\partial(\epsilon^\alpha \rho^\alpha \mathbf{v}^{\overline{\alpha}})}{\partial t} + \nabla \cdot \left(\epsilon^\alpha \rho^\alpha \mathbf{v}^{\overline{\alpha}} \mathbf{v}^{\overline{\alpha}} \right) - \nabla \cdot (\epsilon^\alpha \mathbf{t}^{\overline{\overline{\alpha}}}) - \epsilon^\alpha \rho^\alpha \mathbf{g}^{\overline{\alpha}} - \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \left(\mathbf{v}^{\overline{\alpha}} \overset{\kappa\to\alpha}{M} + \overset{\kappa\to\alpha}{\mathbf{T}} \right) = 0 \tag{3.51}$$

3.5 Total Energy

The microscale conservation of energy equation for a phase containing one species can be written as:

$$\mathcal{E}_\alpha = \frac{\partial E_{T\alpha}}{\partial t} + \nabla \cdot (E_{T\alpha} \mathbf{v}_\alpha - \mathbf{q}_\alpha - \mathbf{t}_\alpha \cdot \mathbf{v}_\alpha) - h_\alpha - \rho_\alpha \frac{\partial \psi_\alpha}{\partial t} = 0 \tag{3.52}$$

where $E_{T\alpha}$ is the total energy and is given by:

$$E_{T\alpha} = \frac{1}{2} \rho_\alpha \mathbf{v}_\alpha \cdot \mathbf{v}_\alpha + \rho_\alpha \psi_\alpha + E_\alpha \tag{3.53}$$

E_α is the internal energy and ψ_α is the gravitational potential. The macroscale energy can be obtained by averaging the microscale equation

$$\mathcal{E}^{\overline{\overline{\alpha}}} = \langle \mathcal{E}_\alpha \rangle_{\Omega_\alpha,\Omega} \tag{3.54}$$

Begin by applying the averaging operator to each term of the microscale equation.

$$\langle \mathcal{E}_\alpha \rangle_{\Omega_\alpha,\Omega} = \left\langle \frac{\partial E_{T\alpha}}{\partial t} \right\rangle_{\Omega_\alpha,\Omega}$$

$$+ \langle \nabla \boldsymbol{\cdot} (E_{T\alpha}\mathbf{v}_\alpha - \mathbf{q}_\alpha - \mathbf{t}_\alpha \boldsymbol{\cdot} \mathbf{v}_\alpha) \rangle_{\Omega_\alpha,\Omega} - \left\langle h_\alpha + \rho_\alpha \frac{\partial \psi_\alpha}{\partial t} \right\rangle_{\Omega_\alpha,\Omega} = 0 \tag{3.55}$$

Beginning with the first term in equation (3.55) the averaging operator will be evaluated. Since there is a partial derivative term within the averaging operator, apply theorem (T[3,(3,0),0]).

$$\begin{aligned} &\left\langle \frac{\partial}{\partial t}\left(\frac{1}{2}\rho_\alpha \mathbf{v}_\alpha \boldsymbol{\cdot} \mathbf{v}_\alpha + \rho_\alpha \psi_\alpha + E_\alpha\right)\right\rangle_{\Omega_\alpha,\Omega} = \\ &\frac{\partial}{\partial t}\left\langle \frac{1}{2}\rho_\alpha \mathbf{v}_\alpha \boldsymbol{\cdot} \mathbf{v}_\alpha + \rho_\alpha \psi_\alpha + E_\alpha \right\rangle_{\Omega_\alpha,\Omega} \\ &- \sum_{\kappa \in \mathfrak{J}_{c\alpha}} \langle \mathbf{n}_\alpha \boldsymbol{\cdot} \mathbf{v}_\kappa E_{T\alpha} \rangle_{\Omega_\kappa,\Omega} \end{aligned} \tag{3.56}$$

The averaging for the internal energy and the gravitational potential can be evaluated as:

$$\langle E_\alpha \rangle_{\Omega_\alpha,\Omega} = E^{\overline{\overline{\alpha}}} \tag{3.57}$$

$$\langle \rho_\alpha \psi_\alpha \rangle_{\Omega_\alpha,\Omega} = \epsilon^\alpha \rho^\alpha \psi^{\overline{\alpha}} \tag{3.58}$$

The kinetic energy term can be evaluated by adding and subtracting $\mathbf{v}^{\overline{\alpha}}$:

$$\left\langle \frac{1}{2}\rho_\alpha \mathbf{v}_\alpha \boldsymbol{\cdot} \mathbf{v}_\alpha \right\rangle_{\Omega_\alpha,\Omega} = \left\langle \frac{1}{2}\rho_\alpha \left[\mathbf{v}^{\overline{\alpha}} + \left(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}\right)\right] \boldsymbol{\cdot} \left[\mathbf{v}^{\overline{\alpha}} + \left(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}\right)\right] \right\rangle_{\Omega_\alpha,\Omega} \tag{3.59}$$

Expanding the term on the right gives:

$$\begin{aligned} &\left\langle \frac{1}{2}\rho_\alpha \left[\mathbf{v}^{\overline{\alpha}} + \left(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}\right)\right] \boldsymbol{\cdot} \left[\mathbf{v}^{\overline{\alpha}} + \left(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}\right)\right] \right\rangle_{\Omega_\alpha,\Omega} = \left\langle \frac{1}{2}\rho_\alpha \mathbf{v}^{\overline{\alpha}} \boldsymbol{\cdot} \mathbf{v}^{\overline{\alpha}} \right\rangle_{\Omega_\alpha,\Omega} \\ &+ \left\langle \rho_\alpha \left[\mathbf{v}^{\overline{\alpha}} \boldsymbol{\cdot} (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}})\right] \right\rangle_{\Omega_\alpha,\Omega} + \left\langle \frac{1}{2}\rho_\alpha (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}) \boldsymbol{\cdot} (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}) \right\rangle_{\Omega_\alpha,\Omega} \end{aligned} \tag{3.60}$$

The product of macroscale velocity term is easiest to evaluate.

$$\left\langle \frac{1}{2}\rho_\alpha \mathbf{v}^{\overline{\alpha}} \cdot \mathbf{v}^{\overline{\alpha}} \right\rangle_{\Omega_\alpha,\Omega} = \frac{1}{2}\rho^\alpha \epsilon^\alpha \mathbf{v}^{\overline{\alpha}} \cdot \mathbf{v}^{\overline{\alpha}} \tag{3.61}$$

The second term on the right side of (3.60) evaluates to zero.

$$\left\langle \rho_\alpha \left[\mathbf{v}^{\overline{\alpha}} \cdot (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}) \right] \right\rangle_{\Omega_\alpha,\Omega} = 0 \tag{3.62}$$

The third term on the right side of (3.60) can be defined as kinetic energy due to microscale variations in velocity.

$$\left\langle \frac{\rho_\alpha}{2} (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}) \cdot (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}) \right\rangle_{\Omega_\alpha,\Omega} = \rho^\alpha \epsilon^\alpha K_E^{\overline{\overline{\alpha}}} \tag{3.63}$$

Now substituting the evaluated terms back into (3.55)

$$\begin{aligned} \langle \mathcal{E}_\alpha \rangle_{\Omega_\alpha,\Omega} = &\frac{\partial}{\partial t} \left(\frac{1}{2}\rho^\alpha \epsilon^\alpha \mathbf{v}^{\overline{\alpha}} \cdot \mathbf{v}^{\overline{\alpha}} + \rho^\alpha \epsilon^\alpha \psi^{\overline{\alpha}} + E^{\overline{\overline{\alpha}}} + \rho^\alpha \epsilon^\alpha K_E^{\overline{\overline{\alpha}}} \right) \\ &- \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot \mathbf{v}_\kappa E_{T\alpha} \rangle_{\Omega_\kappa,\Omega} + \langle \nabla \cdot (E_{T\alpha} \mathbf{v}_\alpha - \mathbf{q}_\alpha - \mathbf{t}_\alpha \cdot \mathbf{v}_\alpha) \rangle_{\Omega_\alpha,\Omega} \\ &- \left\langle h_\alpha + \rho_\alpha \frac{\partial \psi_\alpha}{\partial t} \right\rangle_{\Omega_\alpha,\Omega} = 0 \end{aligned} \tag{3.64}$$

Note that,

$$E_T^{\overline{\overline{\alpha}}} = \frac{1}{2}\rho^\alpha \epsilon^\alpha \mathbf{v}^{\overline{\alpha}} \cdot \mathbf{v}^{\overline{\alpha}} + \rho^\alpha \epsilon^\alpha \psi^{\overline{\alpha}} + E^{\overline{\overline{\alpha}}} + \rho^\alpha \epsilon^\alpha K_E^{\overline{\overline{\alpha}}} \tag{3.65}$$

Evaluate the divergence terms of (3.64) by applying the averging theorem **D[3,(3,0),0]**

$$\begin{aligned} &\langle \nabla \cdot (E_{T\alpha} \mathbf{v}_\alpha - \mathbf{q}_\alpha - \mathbf{t}_\alpha \cdot \mathbf{v}_\alpha) \rangle_{\Omega_\alpha,\Omega} \\ &\quad = \nabla \cdot \langle E_{T\alpha} \mathbf{v}_\alpha - \mathbf{q}_\alpha - \mathbf{t}_\alpha \cdot \mathbf{v}_\alpha \rangle_{\Omega_\alpha,\Omega} \end{aligned}$$

$$+ \sum_{\kappa \in \mathfrak{J}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot (E_{T\alpha} \mathbf{v}_\alpha - \mathbf{q}_\alpha - \mathbf{t}_\alpha \cdot \mathbf{v}_\alpha) \rangle_{\Omega_\kappa, \Omega} \tag{3.66}$$

Looking at the terms inside the averaging operator, there are products of microscale variables that cannot be directly evaluated, therefore requiring use of expansions similar to that used for the kinetic energy term in the partial derivative.

$$\begin{aligned} &\nabla \cdot \langle E_{T\alpha} \mathbf{v}_\alpha - \mathbf{q}_\alpha - \mathbf{t}_\alpha \cdot \mathbf{v}_\alpha \rangle_{\Omega_\alpha, \Omega} \\ &\quad = \nabla \cdot \left\langle \left[\frac{E_T^{\overline{\overline{\alpha}}}}{\rho^\alpha \epsilon^\alpha} + \left(\frac{E_{T\alpha}}{\rho_\alpha} - \frac{E_T^{\overline{\overline{\alpha}}}}{\rho^\alpha \epsilon^\alpha} \right) \right] \rho_\alpha \left[\mathbf{v}^{\overline{\alpha}} + \left(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}} \right) \right] \right\rangle_{\Omega_\alpha, \Omega} \\ &\quad - \nabla \cdot \langle \mathbf{q}_\alpha + \mathbf{t}_\alpha \cdot [\mathbf{v}^{\overline{\alpha}} + (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}})] \rangle_{\Omega_\alpha, \Omega} \end{aligned} \tag{3.67}$$

The energy terms can be distributed through and each term separated.

$$\begin{aligned} &\nabla \cdot \langle E_{T\alpha} \mathbf{v}_\alpha - \mathbf{q}_\alpha - \mathbf{t}_\alpha \cdot \mathbf{v}_\alpha \rangle_{\Omega_\alpha, \Omega} = \\ &\nabla \cdot \left\langle \frac{E_T^{\overline{\overline{\alpha}}}}{\rho^\alpha \epsilon^\alpha} \rho_\alpha \mathbf{v}^{\overline{\alpha}} \right\rangle_{\Omega_\alpha, \Omega} + \nabla \cdot \left\langle \frac{E_T^{\overline{\overline{\alpha}}}}{\rho^\alpha \epsilon^\alpha} \rho_\alpha \left(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}} \right) \right\rangle_{\Omega_\alpha, \Omega} \\ &+ \nabla \cdot \left\langle \left(\frac{E_{T\alpha}}{\rho_\alpha} - \frac{E_T^{\overline{\overline{\alpha}}}}{\rho^\alpha \epsilon^\alpha} \right) \rho_\alpha \mathbf{v}^{\overline{\alpha}} \right\rangle_{\Omega_\alpha, \Omega} + \nabla \cdot \left\langle \left(\frac{E_{T\alpha}}{\rho_\alpha} - \frac{E_T^{\overline{\overline{\alpha}}}}{\rho^\alpha \epsilon^\alpha} \right) \rho_\alpha \left(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}} \right) \right\rangle_{\Omega_\alpha, \Omega} \\ &- \nabla \cdot \langle \mathbf{q}_\alpha + \mathbf{t}_\alpha \cdot [\mathbf{v}^{\overline{\alpha}} + (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}})] \rangle_{\Omega_\alpha, \Omega} \end{aligned} \tag{3.68}$$

Evaluate terms in (3.68) as follows, noting that macroscale variables can be taken out of averaging operators.

$$\nabla \cdot \left\langle \frac{E_T^{\overline{\overline{\alpha}}}}{\rho^\alpha \epsilon^\alpha} \rho_\alpha \mathbf{v}^{\overline{\alpha}} \right\rangle_{\Omega_\alpha, \Omega} = \nabla \cdot \left(\frac{E_T^{\overline{\overline{\alpha}}} \mathbf{v}^{\overline{\alpha}}}{\rho^\alpha \epsilon^\alpha} \langle \rho_\alpha \rangle_{\Omega_\alpha, \Omega} \right) = \nabla \cdot \left(E_T^{\overline{\overline{\alpha}}} \mathbf{v}^{\overline{\alpha}} \right) \tag{3.69}$$

$$\nabla \cdot \left\langle \frac{E_T^{\overline{\overline{\alpha}}}}{\rho^\alpha \epsilon^\alpha} \rho_\alpha \left(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}} \right) \right\rangle_{\Omega_\alpha, \Omega} = \nabla \cdot \left(\frac{E_T^{\overline{\overline{\alpha}}}}{\rho^\alpha \epsilon^\alpha} \langle \rho_\alpha \mathbf{v}_\alpha \rangle_{\Omega_\alpha, \Omega} \right) - \nabla \cdot \left(\frac{E_T^{\overline{\overline{\alpha}}} \mathbf{v}^{\overline{\alpha}}}{\rho^\alpha \epsilon^\alpha} \langle \rho_\alpha \rangle_{\Omega_\alpha, \Omega} \right) \tag{3.70}$$

This term evaluates to zero because the averaged microscale velocity and the macroscale velocity cancel.

$$\nabla\cdot\left\langle \frac{E_T^{\overline{\overline{\alpha}}}}{\rho^\alpha\epsilon^\alpha}\rho_\alpha\left(\mathbf{v}_\alpha-\mathbf{v}^{\overline{\alpha}}\right)\right\rangle_{\Omega_\alpha,\Omega} = \nabla\cdot\left(E_T^{\overline{\overline{\alpha}}}\mathbf{v}^{\overline{\alpha}}\right)-\nabla\cdot\left(E_T^{\overline{\overline{\alpha}}}\mathbf{v}^{\overline{\alpha}}\right)=0 \tag{3.71}$$

Following the same procedure as above, the third term on the right side of (3.68) also evaluates to zero.

$$\nabla\cdot\left\langle\left(\frac{E_{T\alpha}}{\rho_\alpha}-\frac{E_T^{\overline{\overline{\alpha}}}}{\rho^\alpha\epsilon^\alpha}\right)\rho_\alpha\mathbf{v}^{\overline{\alpha}}\right\rangle_{\Omega_\alpha,\Omega}=0 \tag{3.72}$$

Therefore, after evaluation, equation (3.68) becomes the following.

$$\begin{aligned}\nabla\cdot\langle E_{T\alpha}\mathbf{v}_\alpha-\mathbf{q}_\alpha-\mathbf{t}_\alpha\cdot\mathbf{v}_\alpha\rangle_{\Omega_\alpha,\Omega} &= \nabla\cdot\left(E_T^{\overline{\overline{\alpha}}}\mathbf{v}^{\overline{\alpha}}\right)\\ &+\nabla\cdot\left\langle\left(\frac{E_{T\alpha}}{\rho_\alpha}-\frac{E_T^{\overline{\overline{\alpha}}}}{\rho^\alpha\epsilon^\alpha}\right)\rho_\alpha\left(\mathbf{v}_\alpha-\mathbf{v}^{\overline{\alpha}}\right)\right\rangle_{\Omega_\alpha,\Omega}\\ &-\nabla\cdot\left\langle\mathbf{q}_\alpha+\mathbf{t}_\alpha\cdot[\mathbf{v}^{\overline{\alpha}}+(\mathbf{v}_\alpha-\mathbf{v}^{\overline{\alpha}})]\right\rangle_{\Omega_\alpha,\Omega}\end{aligned} \tag{3.73}$$

Substitute the definitions of $E_{T\alpha}$ and $E_T^{\overline{\overline{\alpha}}}$ into the second term on the right side of (3.73) to obtain:

$$\begin{aligned}&\nabla\cdot\left\langle\left(\frac{E_{T\alpha}}{\rho_\alpha}-\frac{E_T^{\overline{\overline{\alpha}}}}{\rho^\alpha\epsilon^\alpha}\right)\rho_\alpha\left(\mathbf{v}_\alpha-\mathbf{v}^{\overline{\alpha}}\right)\right\rangle_{\Omega_\alpha,\Omega}\\ &=\nabla\cdot\left\langle\left(\frac{E_\alpha}{\rho_\alpha}+\frac{\mathbf{v}_\alpha\cdot\mathbf{v}_\alpha}{2}+\psi_\alpha\right)\rho_\alpha\left(\mathbf{v}_\alpha-\mathbf{v}^{\overline{\alpha}}\right)\right\rangle_{\Omega_\alpha,\Omega}\\ &-\nabla\cdot\left\langle\left(\frac{E^{\overline{\overline{\alpha}}}}{\epsilon^\alpha\rho^\alpha}+\frac{\mathbf{v}^{\overline{\alpha}}\cdot\mathbf{v}^{\overline{\alpha}}}{2}+K_E^{\overline{\overline{\alpha}}}+\psi^{\overline{\alpha}}\right)\rho_\alpha\left(\mathbf{v}_\alpha-\mathbf{v}^{\overline{\alpha}}\right)\right\rangle_{\Omega_\alpha,\Omega}\end{aligned} \tag{3.74}$$

The same technique of adding and subtracting macroscale quantities will be used to expand the microscale velocities.

$$\nabla\cdot\left\langle\left(\frac{E_{T\alpha}}{\rho_\alpha}-\frac{E_T^{\overline{\overline{\alpha}}}}{\rho^\alpha\epsilon^\alpha}\right)\rho_\alpha\left(\mathbf{v}_\alpha-\mathbf{v}^{\overline{\alpha}}\right)\right\rangle_{\Omega_\alpha,\Omega}$$
$$=\nabla\cdot\left\langle\left(\frac{E_\alpha}{\rho_\alpha}+\frac{[\mathbf{v}^{\overline{\alpha}}+(\mathbf{v}_\alpha-\mathbf{v}^{\overline{\alpha}})]\cdot[\mathbf{v}^{\overline{\alpha}}+(\mathbf{v}_\alpha-\mathbf{v}^{\overline{\alpha}})]}{2}+\psi_\alpha\right)\rho_\alpha\left(\mathbf{v}_\alpha-\mathbf{v}^{\overline{\alpha}}\right)\right\rangle_{\Omega_\alpha,\Omega}$$
$$-\nabla\cdot\left\langle\left(\frac{E^{\overline{\overline{\alpha}}}}{\epsilon^\alpha\rho^\alpha}+\frac{\mathbf{v}^{\overline{\alpha}}\cdot\mathbf{v}^{\overline{\alpha}}}{2}+K_E^{\overline{\overline{\alpha}}}+\psi^{\overline{\alpha}}\right)\rho_\alpha\left(\mathbf{v}_\alpha-\mathbf{v}^{\overline{\alpha}}\right)\right\rangle_{\Omega_\alpha,\Omega} \tag{3.75}$$

Expand the product of velocity to separate the terms.

$$\nabla\cdot\left\langle\left(\frac{E_{T\alpha}}{\rho_\alpha}-\frac{E_T^{\overline{\overline{\alpha}}}}{\rho^\alpha\epsilon^\alpha}\right)\rho_\alpha\left(\mathbf{v}_\alpha-\mathbf{v}^{\overline{\alpha}}\right)\right\rangle_{\Omega_\alpha,\Omega}$$
$$=\nabla\cdot\left\langle\left(\frac{E_\alpha}{\rho_\alpha}+\frac{\mathbf{v}^{\overline{\alpha}}\cdot\mathbf{v}^{\overline{\alpha}}}{2}+\mathbf{v}^{\overline{\alpha}}\cdot(\mathbf{v}_\alpha-\mathbf{v}^{\overline{\alpha}})+\frac{(\mathbf{v}_\alpha-\mathbf{v}^{\overline{\alpha}})\cdot(\mathbf{v}_\alpha-\mathbf{v}^{\overline{\alpha}})}{2}+\psi_\alpha\right)\rho_\alpha\left(\mathbf{v}_\alpha-\mathbf{v}^{\overline{\alpha}}\right)\right\rangle_{\Omega_\alpha,\Omega}$$
$$-\nabla\cdot\left\langle\left(\frac{E^{\overline{\overline{\alpha}}}}{\epsilon^\alpha\rho^\alpha}+\frac{\mathbf{v}^{\overline{\alpha}}\cdot\mathbf{v}^{\overline{\alpha}}}{2}+K_E^{\overline{\overline{\alpha}}}+\psi^{\overline{\alpha}}\right)\rho_\alpha\left(\mathbf{v}_\alpha-\mathbf{v}^{\overline{\alpha}}\right)\right\rangle_{\Omega_\alpha,\Omega} \tag{3.76}$$

The $\frac{\mathbf{v}^{\overline{\alpha}}\cdot\mathbf{v}^{\overline{\alpha}}}{2}$ terms cancel.

$$\nabla\cdot\left\langle\left(\frac{E_{T\alpha}}{\rho_\alpha}-\frac{E_T^{\overline{\overline{\alpha}}}}{\rho^\alpha\epsilon^\alpha}\right)\rho_\alpha\left(\mathbf{v}_\alpha-\mathbf{v}^{\overline{\alpha}}\right)\right\rangle_{\Omega_\alpha,\Omega}$$
$$=\nabla\cdot\left\langle\left(\frac{E_\alpha}{\rho_\alpha}+\mathbf{v}^{\overline{\alpha}}\cdot(\mathbf{v}_\alpha-\mathbf{v}^{\overline{\alpha}})+\frac{(\mathbf{v}_\alpha-\mathbf{v}^{\overline{\alpha}})\cdot(\mathbf{v}_\alpha-\mathbf{v}^{\overline{\alpha}})}{2}+\psi_\alpha\right)\rho_\alpha\left(\mathbf{v}_\alpha-\mathbf{v}^{\overline{\alpha}}\right)\right\rangle_{\Omega_\alpha,\Omega}$$
$$-\nabla\cdot\left\langle\left(\frac{E^{\overline{\overline{\alpha}}}}{\epsilon^\alpha\rho^\alpha}+K_E^{\overline{\overline{\alpha}}}+\psi^{\overline{\alpha}}\right)\rho_\alpha\left(\mathbf{v}_\alpha-\mathbf{v}^{\overline{\alpha}}\right)\right\rangle_{\Omega_\alpha,\Omega} \tag{3.77}$$

Substitute (3.77) into (3.73).

$$\nabla\cdot\langle E_{T\alpha}\mathbf{v}_\alpha-\mathbf{q}_\alpha-\mathbf{t}_\alpha\cdot\mathbf{v}_\alpha\rangle_{\Omega_\alpha,\Omega}=\nabla\cdot\left(E_T^{\overline{\overline{\alpha}}}\mathbf{v}^{\overline{\alpha}}\right)$$
$$+\nabla\cdot\left\langle\left(\frac{E_\alpha}{\rho_\alpha}+\mathbf{v}^{\overline{\alpha}}\cdot(\mathbf{v}_\alpha-\mathbf{v}^{\overline{\alpha}})+\frac{(\mathbf{v}_\alpha-\mathbf{v}^{\overline{\alpha}})\cdot(\mathbf{v}_\alpha-\mathbf{v}^{\overline{\alpha}})}{2}+\psi_\alpha\right)\rho_\alpha\left(\mathbf{v}_\alpha-\mathbf{v}^{\overline{\alpha}}\right)\right\rangle_{\Omega_\alpha,\Omega}$$

$$- \nabla \cdot \left\langle \left(\frac{E^{\overline{\overline{\alpha}}}}{\epsilon^\alpha \rho^\alpha} + K_E^{\overline{\overline{\alpha}}} + \psi^{\overline{\alpha}} \right) \rho_\alpha \left(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}} \right) \right\rangle_{\Omega_\alpha, \Omega}$$

$$- \nabla \cdot \left\langle \mathbf{q}_\alpha + \mathbf{t}_\alpha \cdot [\mathbf{v}^{\overline{\alpha}} + (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}})] \right\rangle_{\Omega_\alpha, \Omega} \tag{3.78}$$

Rearrange (3.78) to isolate the macroscale form of the stress tensor, $\mathbf{t}^{\overline{\overline{\alpha}}} = \langle \mathbf{t}_\alpha - \rho_\alpha \left(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}} \right) \left(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}} \right) \rangle_{\Omega_\alpha, \Omega_\alpha}$.

$$\nabla \cdot \langle E_{T\alpha} \mathbf{v}_\alpha - \mathbf{q}_\alpha - \mathbf{t}_\alpha \cdot \mathbf{v}_\alpha \rangle_{\Omega_\alpha, \Omega} = \nabla \cdot \left(E_T^{\overline{\overline{\alpha}}} \mathbf{v}^{\overline{\alpha}} \right)$$

$$- \nabla \cdot \left\langle \left[\mathbf{t}_\alpha - \rho_\alpha (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}})(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}) \right] \cdot \mathbf{v}^{\overline{\alpha}} \right\rangle_{\Omega_\alpha, \Omega}$$

$$- \nabla \cdot \left\langle \mathbf{q}_\alpha + \mathbf{t}_\alpha \cdot (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}) \right\rangle_{\Omega_\alpha, \Omega} + \nabla \cdot \left\langle \left(\frac{E_\alpha}{\rho_\alpha} - \frac{E^{\overline{\overline{\alpha}}}}{\epsilon^\alpha \rho^\alpha} - K_E^{\overline{\overline{\alpha}}} \right) \rho_\alpha (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}) \right\rangle_{\Omega_\alpha, \Omega}$$

$$+ \nabla \cdot \left\langle \frac{(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}) \cdot (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}})}{2} \rho_\alpha \left(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}} \right) \right\rangle_{\Omega_\alpha, \Omega}$$

$$+ \nabla \cdot \left\langle \rho_\alpha \left(\psi_\alpha - \psi^{\overline{\alpha}} \right) \left(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}} \right) \right\rangle_{\Omega_\alpha, \Omega} \tag{3.79}$$

Define the macroscale heat flux vector.

$$\mathbf{q}^{\overline{\overline{\alpha}}} = \left\langle \mathbf{q}_\alpha + \mathbf{t}_\alpha \cdot (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}) \right\rangle_{\Omega_\alpha, \Omega_\alpha} + \left\langle \left(\frac{E_\alpha}{\rho_\alpha} - \frac{E^{\overline{\overline{\alpha}}}}{\epsilon^\alpha \rho^\alpha} - K_E^{\overline{\overline{\alpha}}} \right) \rho_\alpha (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}) \right\rangle_{\Omega_\alpha, \Omega_\alpha}$$

$$+ \left\langle \frac{(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}) \cdot (\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}})}{2} \rho_\alpha \left(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}} \right) \right\rangle_{\Omega_\alpha, \Omega_\alpha} \tag{3.80}$$

Applying these definitions to (3.79) yields

$$\nabla \cdot \langle E_{T\alpha} \mathbf{v}_\alpha - \mathbf{q}_\alpha - \mathbf{t}_\alpha \cdot \mathbf{v}_\alpha \rangle_{\Omega_\alpha, \Omega} = \nabla \cdot \left(E_T^{\overline{\overline{\alpha}}} \mathbf{v}^{\overline{\alpha}} - \epsilon^\alpha \mathbf{t}^{\overline{\overline{\alpha}}} \cdot \mathbf{v}^{\overline{\alpha}} - \epsilon^\alpha \mathbf{q}^{\overline{\overline{\alpha}}} \right)$$

$$+ \nabla \cdot \left\langle \rho_\alpha \left(\psi_\alpha - \psi^{\overline{\alpha}} \right) \left(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}} \right) \right\rangle_{\Omega_\alpha, \Omega} \tag{3.81}$$

Substituting (3.81) plus the boundary terms into (3.64) gives

$$\begin{aligned}\langle \boldsymbol{\mathcal{E}}_\alpha \rangle_{\Omega_\alpha,\Omega} &= \frac{\partial E_T^{\overline{\overline{\alpha}}}}{\partial t} + \nabla\cdot \left(E_T^{\overline{\overline{\alpha}}} \mathbf{v}^{\overline{\alpha}} - \epsilon^\alpha \mathbf{t}^{\overline{\overline{\alpha}}} \mathbf{v}^{\overline{\alpha}} - \epsilon^\alpha \mathbf{q}^{\overline{\overline{\alpha}}} \right) - \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot \mathbf{v}_\kappa E_{T\alpha} \rangle_{\Omega_\kappa,\Omega} \\ &+ \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot (E_{T\alpha} \mathbf{v}_\alpha - \mathbf{q}_\alpha - \mathbf{t}_\alpha \cdot \mathbf{v}_\alpha) \rangle_{\Omega_\kappa,\Omega} - \left\langle h_\alpha + \rho_\alpha \frac{\partial \psi_\alpha}{\partial t} \right\rangle_{\Omega_\alpha,\Omega} \\ &+ \nabla\cdot \left\langle \rho_\alpha \left(\psi_\alpha - \psi^{\overline{\alpha}} \right) \left(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}} \right) \right\rangle_{\Omega_\alpha,\Omega} \end{aligned} \tag{3.82}$$

Define:

$$\epsilon^\alpha h^\alpha = \langle h_\alpha \rangle_{\Omega_\alpha,\Omega} \tag{3.83}$$

To obtain:

$$\begin{aligned}\langle \boldsymbol{\mathcal{E}}_\alpha \rangle_{\Omega_\alpha,\Omega} &= \frac{\partial E_T^{\overline{\overline{\alpha}}}}{\partial t} + \nabla\cdot \left(E_T^{\overline{\overline{\alpha}}} \mathbf{v}^{\overline{\alpha}} - \epsilon^\alpha \mathbf{t}^{\overline{\overline{\alpha}}} \mathbf{v}^{\overline{\alpha}} - \epsilon^\alpha \mathbf{q}^{\overline{\overline{\alpha}}} \right) - \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot \mathbf{v}_\kappa E_{T\alpha} \rangle_{\Omega_\kappa,\Omega} \\ &+ \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot (E_{T\alpha} \mathbf{v}_\alpha - \mathbf{q}_\alpha - \mathbf{t}_\alpha \cdot \mathbf{v}_\alpha) \rangle_{\Omega_\kappa,\Omega} - \epsilon^\alpha h^\alpha - \left\langle \rho_\alpha \frac{\partial \psi_\alpha}{\partial t} \right\rangle_{\Omega_\alpha,\Omega} \\ &+ \nabla\cdot \left\langle \rho_\alpha \left(\psi_\alpha - \psi^{\overline{\alpha}} \right) \left(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}} \right) \right\rangle_{\Omega_\alpha,\Omega} \end{aligned} \tag{3.84}$$

The boundary terms can be combined.

$$\sum_{\kappa \in \mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot \left[E_{T\alpha} (\mathbf{v}_\alpha - \mathbf{v}_\kappa) - \mathbf{q}_\alpha - \mathbf{t}_\alpha \cdot \mathbf{v}_\alpha \right] \rangle_{\Omega_\kappa,\Omega} \tag{3.85}$$

Expand using the method used previously, with the macroscale quantities averaged over the interface: $\mathbf{v}_\alpha^{\overline{\kappa}}$ and $E_{T\alpha}^{\overline{\overline{\kappa}}}$.

$$\sum_{\kappa \in \mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot \left[E_{T\alpha} (\mathbf{v}_\alpha - \mathbf{v}_\kappa) - \mathbf{q}_\alpha - \mathbf{t}_\alpha \cdot \mathbf{v}_\alpha \right] \rangle_{\Omega_\kappa,\Omega} =$$

$$\sum_{\kappa\in\mathfrak{J}_{c\alpha}}\left\langle \mathbf{n}_\alpha\cdot\left[\frac{E_{T\alpha}^{\overline{\overline{\kappa}}}}{\epsilon^\alpha\rho_\alpha^\kappa}+\left(\frac{E_{T\alpha}}{\rho_\alpha}-\frac{E_{T\alpha}^{\overline{\overline{\kappa}}}}{\epsilon^\kappa\rho_\alpha^\kappa}\right)\right]\left[\rho_\alpha(\mathbf{v}_\alpha-\mathbf{v}_\kappa)-\mathbf{q}_\alpha-\mathbf{t}_\alpha\cdot\left(\mathbf{v}_\alpha^{\overline{\kappa}}+\mathbf{v}_\alpha-\mathbf{v}_\alpha^{\overline{\kappa}}\right)\right]\right\rangle_{\Omega_\kappa,\Omega} \tag{3.86}$$

Define a mass exchange term between the κ interface and the α phase.

$$\overset{\kappa\to\alpha}{M}=\langle\mathbf{n}_\alpha\cdot\rho_\alpha(\mathbf{v}_\kappa-\mathbf{v}_\alpha)\rangle_{\Omega_\kappa,\Omega} \tag{3.87}$$

and substitute into (3.86).

$$\begin{aligned}&\sum_{\kappa\in\mathfrak{J}_{c\alpha}}\langle\mathbf{n}_\alpha\cdot[E_{T\alpha}(\mathbf{v}_\alpha-\mathbf{v}_\kappa)-\mathbf{q}_\alpha-\mathbf{t}_\alpha\cdot\mathbf{v}_\alpha]\rangle_{\Omega_\kappa,\Omega}=\\&\quad-\sum_{\kappa\in\mathfrak{J}_{c\alpha}}\frac{E_{T\alpha}^{\overline{\overline{\kappa}}}}{\epsilon^\kappa\rho_\alpha^\kappa}\overset{\kappa\to\alpha}{M}\\&\quad+\sum_{\kappa\in\mathfrak{J}_{c\alpha}}\left\langle\mathbf{n}_\alpha\cdot\left(\frac{E_{T\alpha}}{\rho_\alpha}-\frac{E_{T\alpha}^{\overline{\overline{\kappa}}}}{\epsilon^\kappa\rho_\alpha^\kappa}\right)\rho_\alpha\left(\mathbf{v}_\alpha-\mathbf{v}_\kappa\right)-\mathbf{q}_\alpha-\mathbf{t}_\alpha\cdot\left[\mathbf{v}_\alpha^{\overline{\kappa}}+\left(\mathbf{v}_\alpha-\mathbf{v}_\alpha^{\overline{\kappa}}\right)\right]\right\rangle_{\Omega_\kappa,\Omega}\end{aligned} \tag{3.88}$$

Use the interface average of total energy in the expansion of the boundary terms. $E_{T\alpha}^{\overline{\overline{\kappa}}}$ is derived as follows:

$$E_{T\alpha}^{\overline{\overline{\kappa}}}=\langle E_{T\alpha}\rangle_{\Omega_\kappa,\Omega} \tag{3.89}$$

$$=\left\langle E_\alpha+\frac{1}{2}\rho_\alpha\mathbf{v}_\alpha\cdot\mathbf{v}_\alpha+\rho_\alpha\psi_\alpha\right\rangle_{\Omega_\kappa,\Omega} \tag{3.90}$$

$$=E_\alpha^{\overline{\overline{\kappa}}}+\left\langle\frac{1}{2}\rho_\alpha\mathbf{v}_\alpha\cdot\mathbf{v}_\alpha\right\rangle_{\Omega_\kappa,\Omega}+\epsilon^\kappa\rho_\alpha^\kappa\psi_\alpha^{\overline{\kappa}} \tag{3.91}$$

$$=E_\alpha^{\overline{\overline{\kappa}}}+\left\langle\frac{1}{2}\rho_\alpha\left(\mathbf{v}_\alpha^{\overline{\kappa}}+\mathbf{v}_\alpha-\mathbf{v}_\alpha^{\overline{\kappa}}\right)\cdot\left(\mathbf{v}_\alpha^{\overline{\kappa}}+\mathbf{v}_\alpha-\mathbf{v}_\alpha^{\overline{\kappa}}\right)\right\rangle_{\Omega_\kappa,\Omega}+\epsilon^\kappa\rho_\alpha^\kappa\psi_\alpha^{\overline{\kappa}} \tag{3.92}$$

$$\begin{aligned}&=E_\alpha^{\overline{\overline{\kappa}}}+\epsilon^\kappa\rho_\alpha^\kappa\psi_\alpha^{\overline{\kappa}}+\left\langle\frac{1}{2}\rho_\alpha\mathbf{v}_\alpha^{\overline{\kappa}}\cdot\mathbf{v}_\alpha^{\overline{\kappa}}\right\rangle_{\Omega_\kappa,\Omega}\\&\quad+\left\langle\rho_\alpha\mathbf{v}_\alpha^{\overline{\kappa}}\cdot\left(\mathbf{v}_\alpha-\mathbf{v}_\alpha^{\overline{\kappa}}\right)\right\rangle_{\Omega_\kappa,\Omega}+\left\langle\frac{1}{2}\rho_\alpha\left(\mathbf{v}_\alpha-\mathbf{v}_\alpha^{\overline{\kappa}}\right)\cdot\left(\mathbf{v}_\alpha-\mathbf{v}_\alpha^{\overline{\kappa}}\right)\right\rangle_{\Omega_\kappa,\Omega}\end{aligned} \tag{3.93}$$

$$= E_\alpha^{\overline{\overline{\kappa}}} + \epsilon^\alpha \rho_\alpha^\kappa \psi_\alpha^{\overline{\kappa}} + \rho_\alpha^\kappa \epsilon^\kappa \frac{\mathbf{v}_\alpha^{\overline{\kappa}} \cdot \mathbf{v}_\alpha^{\overline{\kappa}}}{2} + \left\langle \rho_\alpha \mathbf{v}_\alpha^{\overline{\kappa}} \cdot \left(\mathbf{v}_\alpha - \mathbf{v}_\alpha^{\overline{\kappa}} \right) \right\rangle_{\Omega_\kappa, \Omega}$$
$$+ \left\langle \frac{1}{2} \rho_\alpha \left(\mathbf{v}_\alpha - \mathbf{v}_\alpha^{\overline{\kappa}} \right) \cdot \left(\mathbf{v}_\alpha - \mathbf{v}_\alpha^{\overline{\kappa}} \right) \right\rangle_{\Omega_\kappa, \Omega} \tag{3.94}$$

The term $\langle \rho_\alpha \mathbf{v}_\alpha^{\overline{\kappa}} \cdot (\mathbf{v}_\alpha - \mathbf{v}_\alpha^{\overline{\kappa}}) \rangle_{\Omega_\kappa, \Omega}$ drops out as shown below:

$$\left\langle \rho_\alpha \mathbf{v}_\alpha^{\overline{\kappa}} \cdot \left(\mathbf{v}_\alpha - \mathbf{v}_\alpha^{\overline{\kappa}} \right) \right\rangle_{\Omega_\kappa, \Omega} = \mathbf{v}_\alpha^{\overline{\kappa}} \cdot \left\langle \rho_\alpha \left(\mathbf{v}_\alpha - \mathbf{v}_\alpha^{\overline{\kappa}} \right) \right\rangle_{\Omega_\kappa, \Omega} \tag{3.95}$$
$$= \mathbf{v}_\alpha^{\overline{\kappa}} \cdot \langle \rho_\alpha \mathbf{v}_\alpha \rangle_{\Omega_\kappa, \Omega} - \mathbf{v}_\alpha^{\overline{\kappa}} \cdot \mathbf{v}_\alpha^{\overline{\kappa}} \langle \rho_\alpha \rangle_{\Omega_\kappa, \Omega} \tag{3.96}$$
$$= \mathbf{v}_\alpha^{\overline{\kappa}} \cdot \mathbf{v}_\alpha^{\overline{\kappa}} \rho_\alpha^\kappa \epsilon^\kappa - \mathbf{v}_\alpha^{\overline{\kappa}} \cdot \mathbf{v}_\alpha^{\overline{\kappa}} \rho_\alpha^\kappa \epsilon^\kappa \tag{3.97}$$
$$= 0 \tag{3.98}$$

The term $\left\langle \frac{1}{2} \rho_\alpha (\mathbf{v}_\alpha - \mathbf{v}_\alpha^{\overline{\kappa}}) \cdot (\mathbf{v}_\alpha - \mathbf{v}_\alpha^{\overline{\kappa}}) \right\rangle_{\Omega_\kappa, \Omega}$ is defined as,

$$\left\langle \frac{1}{2} \rho_\alpha \left(\mathbf{v}_\alpha - \mathbf{v}_\alpha^{\overline{\kappa}} \right) \cdot \left(\mathbf{v}_\alpha - \mathbf{v}_\alpha^{\overline{\kappa}} \right) \right\rangle_{\Omega_\kappa, \Omega} = \rho_\alpha^\kappa \epsilon^\kappa K_{E\alpha}^{\overline{\overline{\kappa}}} \tag{3.99}$$

Thus leaving the following definition of $E_{T\alpha}^{\overline{\overline{\kappa}}}$:

$$E_{T\alpha}^{\overline{\overline{\kappa}}} = E_\alpha^{\overline{\overline{\kappa}}} + \frac{1}{2} \rho_\alpha^\kappa \epsilon^\kappa \mathbf{v}_\alpha^{\overline{\kappa}} \cdot \mathbf{v}_\alpha^{\overline{\kappa}} + \epsilon^\kappa \rho_\alpha^\kappa \psi_\alpha^{\overline{\kappa}} + \epsilon^\kappa \rho_\alpha^\kappa K_{E\alpha}^{\overline{\overline{\kappa}}} \tag{3.100}$$

The definitions for the micro- and macroscale total energies, $E_{T\alpha}$ and $E_{T\alpha}^{\overline{\overline{\kappa}}}$, can be substituted:

$$\sum_{\kappa \in \mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot [E_{T\alpha} (\mathbf{v}_\alpha - \mathbf{v}_\kappa) - \mathbf{q}_\alpha - \mathbf{t}_\alpha \cdot \mathbf{v}_\alpha] \rangle_{\Omega_\kappa, \Omega} = - \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \frac{E_{T\alpha}^{\overline{\overline{\kappa}}}}{\epsilon^\kappa \rho_\alpha^\kappa} \overset{\kappa \to \alpha}{M}$$
$$+ \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \left\langle \mathbf{n}_\alpha \cdot \left[\left(\frac{E_\alpha}{\rho_\alpha} + \frac{\mathbf{v}_\alpha \cdot \mathbf{v}_\alpha}{2} + \psi_\alpha \right) \rho_\alpha \left(\mathbf{v}_\alpha - \mathbf{v}_\kappa \right) \right] \right\rangle_{\Omega_\kappa, \Omega}$$
$$- \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \left\langle \mathbf{n}_\alpha \cdot \left[\left(\frac{E_\alpha^{\overline{\overline{\kappa}}}}{\epsilon^\kappa \rho_\alpha^\kappa} + \frac{\mathbf{v}_\alpha^{\overline{\kappa}} \cdot \mathbf{v}_\alpha^{\overline{\kappa}}}{2} + \psi^{\overline{\kappa}} + K_{E\alpha}^{\overline{\overline{\kappa}}} \right) \rho_\alpha \left(\mathbf{v}_\alpha - \mathbf{v}_\kappa \right) \right] \right\rangle_{\Omega_\kappa, \Omega}$$

$$- \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \left\langle \mathbf{n}_\alpha \cdot \left[\mathbf{q}_\alpha + \mathbf{t}_\alpha \cdot \left(\mathbf{v}_\alpha^{\overline{\kappa}} + \mathbf{v}_\alpha - \mathbf{v}_\alpha^{\overline{\kappa}} \right) \right] \right\rangle_{\Omega_\kappa, \Omega} \tag{3.101}$$

Further expand the microscale velocity dot product $\frac{\mathbf{v}_\alpha \cdot \mathbf{v}_\alpha}{2}$ by adding and subtracting $\mathbf{v}_\alpha^{\overline{\kappa}}$.

$$\begin{aligned}
\sum_{\kappa \in \mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot [E_{T\alpha}(\mathbf{v}_\alpha - \mathbf{v}_\kappa) - \mathbf{q}_\alpha - \mathbf{t}_\alpha \cdot \mathbf{v}_\alpha] \rangle_{\Omega_\kappa, \Omega} &= - \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \frac{E_{T\alpha}^{\overline{\overline{\kappa}}}}{\epsilon^\kappa \rho_\alpha^\kappa} \overset{\kappa \to \alpha}{M} \\
&+ \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \left\langle \mathbf{n}_\alpha \cdot \left[\left(\frac{E_\alpha}{\rho_\alpha} + \frac{(\mathbf{v}_\alpha^{\overline{\kappa}} + \mathbf{v}_\alpha - \mathbf{v}_\alpha^{\overline{\kappa}}) \cdot (\mathbf{v}_\alpha^{\overline{\kappa}} + \mathbf{v}_\alpha - \mathbf{v}_\alpha^{\overline{\kappa}})}{2} + \psi_\alpha \right) \rho_\alpha (\mathbf{v}_\alpha - \mathbf{v}_\kappa) \right] \right\rangle_{\Omega_\kappa, \Omega} \\
&- \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \left\langle \mathbf{n}_\alpha \cdot \left[\left(\frac{E_\alpha^{\overline{\overline{\kappa}}}}{\epsilon^\kappa \rho_\alpha^\kappa} + \frac{\mathbf{v}_\alpha^{\overline{\kappa}} \cdot \mathbf{v}_\alpha^{\overline{\kappa}}}{2} + \psi^{\overline{\kappa}} + K_{E\alpha}^{\overline{\overline{\kappa}}} \right) \rho_\alpha (\mathbf{v}_\alpha - \mathbf{v}_\kappa) \right] \right\rangle_{\Omega_\kappa, \Omega} \\
&- \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \left\langle \mathbf{n}_\alpha \cdot \left[\mathbf{q}_\alpha + \mathbf{t}_\alpha \cdot \left(\mathbf{v}_\alpha^{\overline{\kappa}} + \mathbf{v}_\alpha - \mathbf{v}_\alpha^{\overline{\kappa}} \right) \right] \right\rangle_{\Omega_\kappa, \Omega}
\end{aligned} \tag{3.102}$$

Rearrange.

$$\begin{aligned}
\sum_{\kappa \in \mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot [E_{T\alpha}(\mathbf{v}_\alpha - \mathbf{v}_\kappa) - \mathbf{q}_\alpha - \mathbf{t}_\alpha \cdot \mathbf{v}_\alpha] \rangle_{\Omega_\kappa, \Omega} &= - \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \frac{E_{T\alpha}^{\overline{\overline{\kappa}}}}{\epsilon^\kappa \rho_\alpha^\kappa} \overset{\kappa \to \alpha}{M} \\
&+ \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \left\langle \mathbf{n}_\alpha \cdot \left[\left(\frac{E_\alpha}{\rho_\alpha} + \psi_\alpha + \frac{\mathbf{v}_\alpha^{\overline{\kappa}} \cdot \mathbf{v}_\alpha^{\overline{\kappa}}}{2} + \mathbf{v}_\alpha^{\overline{\kappa}} \cdot (\mathbf{v}_\alpha - \mathbf{v}_\alpha^{\overline{\kappa}}) \right) \rho_\alpha (\mathbf{v}_\alpha - \mathbf{v}_\kappa) \right] \right\rangle_{\Omega_\kappa, \Omega} \\
&+ \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \left\langle \mathbf{n}_\alpha \cdot \left[\left(\frac{(\mathbf{v}_\alpha - \mathbf{v}_\alpha^{\overline{\kappa}}) \cdot (\mathbf{v}_\alpha - \mathbf{v}_\alpha^{\overline{\kappa}})}{2} \right) \rho_\alpha (\mathbf{v}_\alpha - \mathbf{v}_\kappa) \right] \right\rangle_{\Omega_\kappa, \Omega} \\
&- \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \left\langle \mathbf{n}_\alpha \cdot \left[\left(\frac{E_\alpha^{\overline{\overline{\kappa}}}}{\epsilon^\kappa \rho_\alpha^\kappa} + \frac{\mathbf{v}_\alpha^{\overline{\kappa}} \cdot \mathbf{v}_\alpha^{\overline{\kappa}}}{2} + K_{E\alpha}^{\overline{\overline{\kappa}}} + \psi_\alpha^{\overline{\kappa}} \right) \rho_\alpha (\mathbf{v}_\alpha - \mathbf{v}_\kappa) \right] \right\rangle_{\Omega_\kappa, \Omega} \\
&- \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \left\langle \mathbf{n}_\alpha \cdot \left[\mathbf{q}_\alpha + \mathbf{t}_\alpha \cdot \left(\mathbf{v}_\alpha^{\overline{\kappa}} + \mathbf{v}_\alpha - \mathbf{v}_\alpha^{\overline{\kappa}} \right) \right] \right\rangle_{\Omega_\kappa, \Omega}
\end{aligned} \tag{3.103}$$

The $\frac{\mathbf{v}_\alpha^{\overline{\kappa}} \cdot \mathbf{v}_\alpha^{\overline{\kappa}}}{2}$ terms cancel, leaving:

$$\sum_{\kappa \in \mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot [E_{T\alpha}(\mathbf{v}_\alpha - \mathbf{v}_\kappa) - \mathbf{q}_\alpha - \mathbf{t}_\alpha \cdot \mathbf{v}_\alpha] \rangle_{\Omega_\kappa, \Omega} = \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \frac{E_{T\alpha}^{\overline{\overline{\kappa}}}}{\epsilon^\kappa \rho_\alpha^\kappa} \overset{\kappa \to \alpha}{M}$$

$$+\sum_{\kappa\in\mathfrak{I}_{c\alpha}}\left\langle \mathbf{n}_\alpha\cdot\left[\left(\frac{E_\alpha}{\rho_\alpha}+\psi_\alpha\ +\mathbf{v}_\alpha^{\overline{\kappa}}\cdot\left(\mathbf{v}_\alpha-\mathbf{v}_\alpha^{\overline{\kappa}}\right)\right)\rho_\alpha\left(\mathbf{v}_\alpha-\mathbf{v}_\kappa\right)\right]\right\rangle_{\Omega_\kappa,\Omega}$$
$$+\sum_{\kappa\in\mathfrak{I}_{c\alpha}}\left\langle \mathbf{n}_\alpha\cdot\left[\left(\frac{(\mathbf{v}_\alpha-\mathbf{v}_\alpha^{\overline{\kappa}})\cdot(\mathbf{v}_\alpha-\mathbf{v}_\alpha^{\overline{\kappa}})}{2}\right)\rho_\alpha\left(\mathbf{v}_\alpha-\mathbf{v}_\kappa\right)\right]\right\rangle_{\Omega_\kappa,\Omega}$$
$$-\sum_{\kappa\in\mathfrak{I}_{c\alpha}}\left\langle \mathbf{n}_\alpha\cdot\left[\left(\frac{E_\alpha^{\overline{\overline{\kappa}}}}{\epsilon^\kappa\rho_\alpha^\kappa}+K_{E\alpha}^{\overline{\overline{\kappa}}}+\psi_\alpha^{\overline{\kappa}}\right)\rho_\alpha\left(\mathbf{v}_\alpha-\mathbf{v}_\kappa\right)\right]\right\rangle_{\Omega_\kappa,\Omega}$$
$$-\sum_{\kappa\in\mathfrak{I}_{c\alpha}}\left\langle \mathbf{n}_\alpha\cdot\left[\mathbf{q}_\alpha+\mathbf{t}_\alpha\cdot\left(\mathbf{v}_\alpha^{\overline{\kappa}}+\mathbf{v}_\alpha-\mathbf{v}_\alpha^{\overline{\kappa}}\right)\right]\right\rangle_{\Omega_\kappa,\Omega} \tag{3.104}$$

Group terms dotted with the macroscale velocity $\mathbf{v}_\alpha^{\overline{\kappa}}$ and remember the term for the transfer of momentum from the κ interface to the α phase.

$$\overset{\kappa\to\alpha}{\mathbf{T}}=\left\langle \mathbf{n}_\alpha\cdot\left[\rho_\alpha\left(\mathbf{v}_\alpha-\mathbf{v}_\alpha^{\overline{\kappa}}\right)\left(\mathbf{v}_\kappa-\mathbf{v}_\alpha\right)+\mathbf{t}_\alpha\right]\right\rangle_{\Omega_\kappa,\Omega} \tag{3.105}$$

Subsitituting this definition into the above, we obtain

$$\sum_{\kappa\in\mathfrak{I}_{c\alpha}}\left\langle \mathbf{n}_\alpha\cdot\left[E_{T\alpha}\left(\mathbf{v}_\alpha-\mathbf{v}_\kappa\right)-\mathbf{q}_\alpha-\mathbf{t}_\alpha\cdot\mathbf{v}_\alpha\right]\right\rangle_{\Omega_\kappa,\Omega}=-\sum_{\kappa\in\mathfrak{I}_{c\alpha}}E_{T\alpha}^{\overline{\overline{\kappa}}}\overset{\kappa\to\alpha}{M}-\sum_{\kappa\in\mathfrak{I}_{c\alpha}}\mathbf{v}_\alpha^{\overline{\kappa}}\cdot\overset{\kappa\to\alpha}{\mathbf{T}}$$
$$+\sum_{\kappa\in\mathfrak{I}_{c\alpha}}\left\langle \mathbf{n}_\alpha\cdot\left[\left(\frac{E_\alpha}{\rho_\alpha}+\psi_\alpha+\frac{(\mathbf{v}_\alpha-\mathbf{v}_\alpha^{\overline{\kappa}})\cdot(\mathbf{v}_\alpha-\mathbf{v}_\alpha^{\overline{\kappa}})}{2}\right)\rho_\alpha\left(\mathbf{v}_\alpha-\mathbf{v}_\kappa\right)\right]\right\rangle_{\Omega_\kappa,\Omega}$$
$$-\sum_{\kappa\in\mathfrak{I}_{c\alpha}}\left\langle \mathbf{n}_\alpha\cdot\left[\left(\frac{E_\alpha^{\overline{\overline{\kappa}}}}{\epsilon^\kappa\rho_\alpha^\kappa}+\psi_\alpha^{\overline{\kappa}}+K_{E\alpha}^{\overline{\overline{\kappa}}}\right)\rho_\alpha\left(\mathbf{v}_\alpha-\mathbf{v}_\kappa\right)\right]\right\rangle_{\Omega_\kappa,\Omega}$$
$$-\sum_{\kappa\in\mathfrak{I}_{c\alpha}}\left\langle \mathbf{n}_\alpha\cdot\left[\mathbf{q}_\alpha+\mathbf{t}_\alpha\cdot\left[\left(\mathbf{v}_\alpha-\mathbf{v}_\alpha^{\overline{\kappa}}\right)\right]\right]\right\rangle_{\Omega_\kappa,\Omega} \tag{3.106}$$

Define a heat transfer term.

$$\overset{\kappa\to\alpha}{Q}=$$
$$\left\langle \mathbf{n}_\alpha\cdot\left[\left(\frac{E_\alpha}{\rho_\alpha}-\frac{E_\alpha^{\overline{\overline{\kappa}}}}{\epsilon^\kappa\rho_\alpha^\kappa}+\frac{(\mathbf{v}_\alpha-\mathbf{v}_\alpha^{\overline{\kappa}})\cdot(\mathbf{v}_\alpha-\mathbf{v}_\alpha^{\overline{\kappa}})}{2}-K_{E\alpha}^{\overline{\overline{\kappa}}}\right)\rho_\alpha\left(\mathbf{v}_\alpha-\mathbf{v}_\kappa\right)\right]\right\rangle_{\Omega_\kappa,\Omega}$$
$$-\left\langle \mathbf{n}_\alpha\cdot\left[\mathbf{q}_\alpha+\mathbf{t}_\alpha\cdot\left(\mathbf{v}_\alpha-\mathbf{v}_\alpha^{\overline{\kappa}}\right)\right]\right\rangle_{\Omega_\kappa,\Omega} \tag{3.107}$$

Now substituting this into (3.106) gives:

$$\sum_{\kappa\in\mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha\cdot [E_{T\alpha}(\mathbf{v}_\alpha - \mathbf{v}_\kappa) - \mathbf{q}_\alpha - \mathbf{t}_\alpha\cdot\mathbf{v}_\alpha]\rangle_{\Omega_\kappa,\Omega}$$
$$= \sum_{\kappa\in\mathfrak{I}_{c\alpha}} \left[\frac{E_{T\alpha}^{\overline{\overline{\kappa}}}}{\epsilon^\alpha\rho_\alpha^\kappa}\overset{\kappa\to\alpha}{M} + \mathbf{v}_\alpha^{\overline{\kappa}}\cdot\overset{\kappa\to\alpha}{\mathbf{T}} + \overset{\kappa\to\alpha}{Q}\right]$$
$$+ \sum_{\kappa\in\mathfrak{I}_{c\alpha}} \left\langle \mathbf{n}_\alpha\rho_\alpha\cdot\left(\psi_\alpha - \psi_\alpha^{\overline{\kappa}}\right)(\mathbf{v}_\alpha - \mathbf{v}_\kappa)\right\rangle_{\Omega_\kappa,\Omega} \tag{3.108}$$

Reassemble the various parts of the macroscale total energy equation [(3.84), (3.108)] to obtain:

$$\boldsymbol{\mathcal{E}}^{\overline{\overline{\alpha}}} = \frac{\partial E_T^{\overline{\overline{\alpha}}}}{\partial t} + \nabla\cdot\left(E_T^{\overline{\overline{\alpha}}}\mathbf{v}^{\overline{\alpha}} - \epsilon^\alpha\mathbf{t}^{\overline{\overline{\alpha}}}\cdot\mathbf{v}^{\overline{\alpha}} - \epsilon^\alpha\mathbf{q}^{\overline{\overline{\alpha}}}\right) - \epsilon^\alpha h^{\overline{\overline{\alpha}}} - \left\langle\rho_\alpha\frac{\partial\psi_\alpha}{\partial t}\right\rangle_{\Omega_\alpha,\Omega}$$
$$- \sum_{\kappa\in\mathfrak{I}_{c\alpha}} \left[\frac{E_{T\alpha}^{\overline{\overline{\kappa}}}}{\epsilon^\alpha\rho_\alpha^\kappa}\overset{\kappa\to\alpha}{M} + \mathbf{v}_\alpha^{\overline{\kappa}}\cdot\overset{\kappa\to\alpha}{\mathbf{T}} + \overset{\kappa\to\alpha}{Q}\right]$$
$$+ \sum_{\kappa\in\mathfrak{I}_{c\alpha}} \left\langle \mathbf{n}_\alpha\rho_\alpha\cdot\left(\psi_\alpha - \psi_\alpha^{\overline{\kappa}}\right)(\mathbf{v}_\alpha - \mathbf{v}_\kappa)\right\rangle_{\Omega_\kappa,\Omega}$$
$$+ \nabla\cdot\left\langle\rho_\alpha\left(\psi_\alpha - \psi^{\overline{\alpha}}\right)\left(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}\right)\right\rangle_{\Omega_\alpha,\Omega} = 0 \tag{3.109}$$

Or with the total energy expanded,

$$\boldsymbol{\mathcal{E}}^{\overline{\overline{\alpha}}} = \frac{\partial\left(E^{\overline{\overline{\alpha}}} + \frac{1}{2}\epsilon^\alpha\rho^\alpha\mathbf{v}^{\overline{\alpha}}\cdot\mathbf{v}^{\overline{\alpha}} + \epsilon^\alpha\rho^\alpha\psi^{\overline{\alpha}} + \epsilon^\alpha\rho^\alpha K_E^{\overline{\overline{\alpha}}}\right)}{\partial t}$$
$$+ \nabla\cdot\left[\left(E^{\overline{\overline{\alpha}}} + \frac{1}{2}\epsilon^\alpha\rho^\alpha\mathbf{v}^{\overline{\alpha}}\cdot\mathbf{v}^{\overline{\alpha}} + \epsilon^\alpha\rho^\alpha\psi^{\overline{\alpha}} + \epsilon^\alpha\rho^\alpha K_E^{\overline{\overline{\alpha}}}\right)\mathbf{v}^{\overline{\alpha}} - \epsilon^\alpha\mathbf{t}^{\overline{\overline{\alpha}}}\cdot\mathbf{v}^{\overline{\alpha}} - \epsilon^\alpha\mathbf{q}^{\overline{\overline{\alpha}}}\right]$$
$$- \epsilon^\alpha h^{\overline{\overline{\alpha}}} - \left\langle\rho_\alpha\frac{\partial\psi_\alpha}{\partial t}\right\rangle_{\Omega_\alpha,\Omega}$$
$$- \sum_{\kappa\in\mathfrak{I}_{c\alpha}} \left[\left(\frac{1}{2}\mathbf{v}_\alpha^{\overline{\kappa}}\cdot\mathbf{v}_\alpha^{\overline{\kappa}} + \psi_\alpha^{\overline{\kappa}} + \frac{E_\alpha^{\overline{\overline{\kappa}}}}{\epsilon^\kappa\rho_\alpha^\kappa} + K_{E\alpha}^{\overline{\overline{\kappa}}}\right)\overset{\kappa\to\alpha}{M} + \mathbf{v}_\alpha^{\overline{\kappa}}\overset{\kappa\to\alpha}{\mathbf{T}} + \overset{\kappa\to\alpha}{Q}\right]$$
$$+ \sum_{\kappa\in\mathfrak{I}_{c\alpha}} \left\langle \mathbf{n}_\alpha\rho_\alpha\cdot\left(\psi_\alpha - \psi_\alpha^{\overline{\kappa}}\right)(\mathbf{v}_\alpha - \mathbf{v}_\kappa)\right\rangle_{\Omega_\kappa,\Omega}$$

$$+ \nabla \cdot \left\langle \rho_\alpha \left(\psi_\alpha - \psi^{\overline{\alpha}} \right) \left(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}} \right) \right\rangle_{\Omega_\alpha,\Omega} = 0 \tag{3.110}$$

3.6 Entropy

Microscale balance of entropy for a phase.

$$\frac{\partial \eta_\alpha}{\partial t} + \nabla \cdot (\mathbf{v}_\alpha \eta_\alpha) - b_\alpha - \nabla \cdot \boldsymbol{\varphi}_\alpha = \Lambda_\alpha \tag{3.111}$$

Average the microscale balance of entropy equation by applying the averaging operator to each term.

$$\left\langle \frac{\partial \eta_\alpha}{\partial t} \right\rangle_{\Omega_\alpha,\Omega} + \langle \nabla \cdot (\mathbf{v}_\alpha \eta_\alpha) \rangle_{\Omega_\alpha,\Omega} - \langle b_\alpha \rangle_{\Omega_\alpha,\Omega} - \langle \nabla \cdot \boldsymbol{\varphi}_\alpha \rangle_{\Omega_\alpha,\Omega} = \langle \Lambda_\alpha \rangle_{\Omega_\alpha,\Omega} \tag{3.112}$$

For ease in manipulation, each term will be evaluated separately.

Use **T[3,(3,0),0]** to remove the derivative from the averaging operator from the first term of (3.112).

$$\left\langle \frac{\partial \eta_\alpha}{\partial t} \right\rangle_{\Omega_\alpha,\Omega} = \frac{\partial}{\partial t} \langle \eta_\alpha \rangle_{\Omega_\alpha,\Omega} - \sum_{\kappa \in \mathfrak{J}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot \mathbf{v}_\kappa \eta_\alpha \rangle_{\Omega_\kappa,\Omega} \tag{3.113}$$

$$= \frac{\partial \eta^{\overline{\overline{\alpha}}}}{\partial t} - \sum_{\kappa \in \mathfrak{J}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot \mathbf{v}_\kappa \eta_\alpha \rangle_{\Omega_\kappa,\Omega} \tag{3.114}$$

$$\tag{3.115}$$

The boundary term in averaging operator form for manipulation later.

Use **D[3,(3,0),0]** to remove the divergence from inside the averaging operator in the second term of (3.112).

$$\langle \nabla\cdot (\mathbf{v}_\alpha \eta_\alpha)\rangle_{\Omega_\alpha,\Omega} = \nabla\cdot\langle \mathbf{v}_\alpha \eta_\alpha\rangle_{\Omega_\alpha,\Omega} + \sum_{\kappa\in\mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha\cdot\mathbf{v}_\alpha \eta_\alpha\rangle_{\Omega_\kappa,\Omega} \tag{3.116}$$

Since the average of velocity and entropy per volume cannot be evaluated directly, it is manipulated further by adding and subtracting $\mathbf{v}^\alpha$.

$$\nabla\cdot\langle \mathbf{v}_\alpha \eta_\alpha\rangle_{\Omega_\alpha,\Omega} = \nabla\cdot\langle \eta_\alpha[\mathbf{v}^\alpha + (\mathbf{v}_\alpha - \mathbf{v}^\alpha)]\rangle_{\Omega_\alpha,\Omega} \tag{3.117}$$

$$\nabla\cdot\langle \mathbf{v}^\alpha \eta_\alpha\rangle_{\Omega_\alpha,\Omega} + \nabla\cdot\langle \eta_\alpha(\mathbf{v}_\alpha - \mathbf{v}^\alpha)\rangle_{\Omega_\alpha,\Omega} = \nabla\cdot\mathbf{v}^\alpha\eta^\alpha + \nabla\cdot\langle \eta_\alpha(\mathbf{v}_\alpha - \mathbf{v}^\alpha)\rangle_{\Omega_\alpha,\Omega} \tag{3.118}$$

Leave the second term of (3.116) to be combined with other boundary terms.

The third term of (3.112) can be evaluated directly.

$$-\langle b\rangle_{\Omega_\alpha,\Omega} = -\epsilon^\alpha b^\alpha \tag{3.119}$$

For the fourth term of (3.112), theorem **D[3,(3,0),0]** is needed again.

$$-\langle \nabla\cdot\boldsymbol{\varphi}_\alpha\rangle_{\Omega_\alpha,\Omega} = -\nabla\cdot\langle \boldsymbol{\varphi}_\alpha\rangle_{\Omega_\alpha,\Omega} - \sum_{\kappa\in\mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha\cdot\boldsymbol{\varphi}_\alpha\rangle_{\Omega_\kappa,\Omega} \tag{3.120}$$

Add the boundary term from (3.116) to $\boldsymbol{\varphi}_\alpha$, according to the definition:

$$\boldsymbol{\varphi}^{\overline{\overline{\alpha}}} = \langle \boldsymbol{\varphi}_\alpha\rangle_{\Omega_\alpha,\Omega_\alpha} - \sum_{\kappa\in\mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha\cdot\mathbf{v}_\alpha \eta_\alpha\rangle_{\Omega_\alpha,\Omega_\alpha} \tag{3.121}$$

Therefore

$$-\langle \nabla\cdot\boldsymbol{\varphi}_\alpha\rangle_{\Omega_\alpha,\Omega} + \sum_{\kappa\in\mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha\cdot\mathbf{v}_\alpha \eta_\alpha\rangle_{\Omega_\alpha,\Omega_\alpha} = -\nabla\cdot\boldsymbol{\varphi}^{\overline{\overline{\alpha}}} - \sum_{\kappa\in\mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \boldsymbol{\varphi}_\alpha\rangle_{\Omega_\kappa,\Omega} \tag{3.122}$$

The macroscale generation of entropy term has a unique definition.

$$\langle \Lambda_\alpha \rangle_{\Omega_\alpha,\Omega} = \Lambda^{\overline{\overline{\alpha}}} \tag{3.123}$$

There are a number of boundary terms that remain in averaging operators. These can be combined.

$$\sum_{\kappa \in \mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot \mathbf{v}_\kappa \eta_\alpha \rangle_{\Omega_\kappa,\Omega} + \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot \mathbf{v}_\alpha \eta_\alpha \rangle_{\Omega_\kappa,\Omega} - \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot \boldsymbol{\varphi}_\alpha \rangle_{\Omega_\kappa,\Omega} \tag{3.124}$$

Combine them into one term and rearrange.

$$-\sum_{\kappa \in \mathfrak{I}_{c\alpha}} \langle \mathbf{n}_\alpha \cdot \left[\boldsymbol{\varphi}_\alpha - \eta_\alpha \left(\mathbf{v}_\alpha - \mathbf{v}_\kappa \right) \right] \rangle_{\Omega_\kappa,\Omega} \tag{3.125}$$

By definition, this term accounts for inter-phase transfer of entropy due to mass transfer, $\overset{\kappa\to\alpha}{M_\eta}$, and in the absence of mass transfer, $\overset{\kappa\to\alpha}{\Phi}$.

$$\overset{\kappa\to\alpha}{M_\eta} + \overset{\kappa\to\alpha}{\Phi} = \frac{\eta^{\overline{\overline{\alpha}}}}{\epsilon^\alpha \rho^\alpha} \overset{\kappa\to\alpha}{M} + \overset{\kappa\to\alpha}{\Phi} = \langle \mathbf{n}_\alpha \cdot \left[\boldsymbol{\varphi}_\alpha + \eta_\alpha \left(\mathbf{v}_\kappa - \mathbf{v}_\alpha \right) \right] \rangle_{\Omega_\kappa,\Omega} \tag{3.126}$$

By reassembling all the averaged terms, one gets the macroscale entropy inequality for a phase.

$$\frac{\partial \eta^\alpha}{\partial t} + \nabla \cdot \mathbf{v}^\alpha \eta^\alpha - \epsilon^\alpha b^\alpha - \nabla \cdot \epsilon^\alpha \boldsymbol{\phi} - \sum_{\kappa \in \mathfrak{I}_{c\alpha}} \left(\overset{\kappa\to\alpha}{M_\eta} + \overset{\kappa\to\alpha}{\Phi} \right) = \Lambda^{\overline{\overline{\alpha}}} \tag{3.127}$$

For a single phase, the generation of entropy may be positive or negative. However, if one sums the balance of entropy equation over all phases, then the generation term must be greater than or equal to zero because of the second law of thermodynamics.

3.7 Thermodynamics

In TCAT, classical irreversible thermodynamics (CIT) are used to constrain the set of mass, momentum, energy, and entropy equations. A macroscale thermodynamical equation is derived from the microscale using averaging operators, in the same manner as the conservation equations. The thermodynamic equation relates the derivative of internal energy to the other equations. With a full set of mass, momentum, energy, entropy, and thermodynamical equations at the macroscale, one can develop equilibrium conditions and relate forces and fluxes to close the system. See [32] and the references therein for more information.

Solid and fluid phases will be handled separately. Starting with the fluid phase, the intensive form of the internal energy function is a function of entropy per volume and mass per volume.

$$E = E(\eta, \rho) \tag{3.128}$$

The first differential of eq. (3.128) for a single-species, single fluid phase yields:

$$\mathrm{d}E_w = \theta_w \, \mathrm{d}\eta_w + \mu_w \, \mathrm{d}\rho_w \tag{3.129}$$

The definitions of θ_w and μ_w are:

$$\theta_w = \left(\frac{\partial E_w}{\partial \eta_w} \right)_{\rho_w} \tag{3.130}$$

$$\mu_w = \left(\frac{\partial E_w}{\partial \rho_w} \right)_{\eta_w} \tag{3.131}$$

Further standard mathematical manipulation of eq. (3.128) leads to the Euler form of the thermodynamic equation:

$$E_w = \eta_w \theta_w + \mu_w \rho_w - p_w \tag{3.132}$$

which can be differentiated:

$$\mathrm{d}E_w = \theta_w \,\mathrm{d}\eta_w + \eta_w \,\mathrm{d}\theta_w - \,\mathrm{d}p_w + \mu_w \,\mathrm{d}\rho_w + \rho_w \,\mathrm{d}\mu_w \tag{3.133}$$

Use of eqn (3.129) in eqn (3.133) reduces this equation to:

$$0 = \eta_w \,\mathrm{d}\theta_w - \,\mathrm{d}p_w + \rho_w \,\mathrm{d}\mu_w \tag{3.134}$$

Equation (3.134) is the microscale Gibbs-Duhem equation.

Average the microscale thermodynamic equation, eq. (3.132), to the macroscale:

$$E^{\overline{\overline{w}}} = \eta^{\overline{\overline{w}}} \theta^{\overline{\overline{w}}} + \rho^w \epsilon^w \mu^{\overline{w}} - \epsilon^w p^w \tag{3.135}$$

Take the material derivative of eq. (3.135) to obtain.

$$\begin{aligned} \frac{\mathrm{D}^{\overline{w}} E^{\overline{\overline{w}}}}{\mathrm{D}t} &= \theta^{\overline{\overline{w}}} \frac{\mathrm{D}^{\overline{w}} \eta^{\overline{\overline{w}}}}{\mathrm{D}t} + \eta^{\overline{\overline{w}}} \frac{\mathrm{D}^{\overline{w}} \theta^{\overline{\overline{w}}}}{\mathrm{D}t} + \mu^{\overline{w}} \frac{\mathrm{D}^{\overline{w}} \left(\rho^w \epsilon^w\right)}{\mathrm{D}t} \\ &+ \rho^w \epsilon^w \frac{\mathrm{D}^{\overline{w}} \mu^{\overline{w}}}{\mathrm{D}t} + p^w \frac{\mathrm{D}^{\overline{w}} \epsilon^w}{\mathrm{D}t} + \epsilon^w \frac{\mathrm{D}^{\overline{w}} p^w}{\mathrm{D}t} \end{aligned} \tag{3.136}$$

After some manipulation using the standard averaging approach, we obtain the following relation:

$$\mathcal{T}^w = \frac{\mathrm{D}^{\overline{w}} E^{\overline{\overline{w}}}}{\mathrm{D}t} - \theta^{\overline{\overline{w}}} \frac{\mathrm{D}^{\overline{w}} \eta^{\overline{\overline{w}}}}{\mathrm{D}t} - \mu^{\overline{w}} \frac{\mathrm{D}^{\overline{w}} \left(\rho^w \epsilon^w\right)}{\mathrm{D}t} + p^w \frac{\mathrm{D}^{\overline{w}} \epsilon^w}{\mathrm{D}t} \tag{3.137}$$

$$+ \left\langle \eta_w \frac{\mathrm{D}^{\overline{w}} \left(\theta_w - \theta^{\overline{\overline{w}}}\right)}{\mathrm{D}t} + \rho_w \frac{\mathrm{D}^{\overline{w}} \left(\mu_w - \mu^{\overline{w}}\right)}{\mathrm{D}t} - \frac{\mathrm{D}^{\overline{w}} p_w - p^w}{\mathrm{D}t} \right\rangle_{\Omega_w, \Omega} = 0 \tag{3.138}$$

For a solid phase, one must use a slightly different form of the internal energy relation since the internal energy of a solid phase depends not on the volume but rather on the strain tensor acting on a volume. At the megascale, one can define the functional thermodynamical relationship as:

$$\mathbb{E}_s = \mathbb{E}_s\left(\mathbb{S}_s, V_0\mathbf{C}_s, \mathbb{M}_s\right) \tag{3.139}$$

Now introduce Green's deformation tensor $\mathbf{C}_s$, which can be described as the solid deformation in reference coordinates $\mathbf{x}_s\left(\mathbf{X}_s, t\right)$. V_0 is the solid volume.

$$\mathbf{C}_s = \frac{\partial \mathbf{x}_s}{\partial \mathbf{X}_s} \cdot \frac{\partial \mathbf{x}_s}{\partial \mathbf{X}_s} \tag{3.140}$$

The stress tensor can now be defined as:

$$\boldsymbol{\sigma}_s = \frac{\partial \mathbb{E}_s}{\partial \left(V_0\mathbf{C}_s\right)}_{\mathbb{S}_s, \mathbb{M}_s} \tag{3.141}$$

The following expressions can be found for the energy per volume, the differential of the energy and for the Gibbs-Duhem equation for a solid,

$$E_s = \theta_s \eta_s + \mu_s \rho_s + \boldsymbol{\sigma}_s : \frac{\mathbf{C}_s}{j_s} \tag{3.142}$$

$$\mathrm{d}E_s = \theta_s \,\mathrm{d}\eta_s + \mu_s \,\mathrm{d}\rho_s + \boldsymbol{\sigma}_s : \mathrm{d}\left(\frac{\mathbf{C}_s}{j_s}\right) \tag{3.143}$$

$$0 = \eta_s \,\mathrm{d}\theta_s + \rho_s \,\mathrm{d}\mu_s + \frac{\mathbf{C}_s}{j_s} : \mathrm{d}\boldsymbol{\sigma}_s \tag{3.144}$$

where j_s is the microscale solid phase Jacobian.

Define the macroscale energy of the solid phase as the average energy E^s per averaging volume (REV):

$$E^{\overline{\overline{s}}} = \langle E_s \rangle_{\Omega_s,\Omega} = \left\langle \theta_s \eta_s + \mu_s \rho_s + \boldsymbol{\sigma}_s \mathbf{:} \frac{\mathbf{C}_s}{j_s} \right\rangle_{\Omega_s,\Omega} \tag{3.145}$$

Several macroscale averages of microscale quantities can be defined:

$$\eta^{\overline{\overline{s}}} = \langle \eta_s \rangle_{\Omega_s,\Omega} \tag{3.146}$$

$$\epsilon^s \rho^s = \langle \rho_s \rangle_{\Omega_s,\Omega} \tag{3.147}$$

$$\epsilon^s \frac{\mathbf{C}^s}{j^s} = \left\langle \frac{\mathbf{C}_s}{j_s} \right\rangle_{\Omega_{ps},\Omega} \tag{3.148}$$

Add and subtract the macroscale quantities into (3.145), to obtain:

$$\begin{aligned} E^{\overline{\overline{s}}} &= \mu^{\overline{s}} \epsilon^s \rho^s + \theta^{\overline{\overline{s}}} \epsilon^s + \epsilon^s \boldsymbol{\sigma}^s \mathbf{:} \frac{\mathbf{C}^s}{j^s} + \left\langle \left[\left(\mu_s - \mu^{\overline{s}} \right) \rho_s + \left(\theta_s - \theta^{\overline{\overline{s}}} \right) \eta_s \right] \right\rangle_{\Omega_s,\Omega} \\ &+ \left\langle \left(\boldsymbol{\sigma}_s - \boldsymbol{\sigma}^s \right) \mathbf{:} \frac{\mathbf{C}_s}{j_s} \right\rangle_{\Omega_s,\Omega} \end{aligned} \tag{3.149}$$

The definitions of macroscale quantities μ^s, θ^s, and $\boldsymbol{\sigma}^s$ are defined such that the remaining 3 integral quantities are equal to zero. Thus, one may write:

$$E^{\overline{\overline{s}}} = \mu^{\overline{s}} \epsilon^s \rho^s + \theta^{\overline{\overline{s}}} \eta^{\overline{\overline{s}}} + \epsilon^s \boldsymbol{\sigma}^s \mathbf{:} \frac{\mathbf{C}^s}{j^s} \tag{3.150}$$

The differential of 3.150 can be written:

$$\mathrm{d}E^{\overline{\overline{s}}} = \mu^{\overline{s}} \, \mathrm{d} \left(\epsilon^s \rho^s \right) + \theta^{\overline{\overline{s}}} \, \mathrm{d}\eta^{\overline{\overline{s}}} + \boldsymbol{\sigma}^s \mathbf{:} \, \mathrm{d} \left(\epsilon^s \frac{\mathbf{C}^s}{j^s} \right) + \epsilon^s \rho^s \, \mathrm{d}\mu^{\overline{s}} + \eta^{\overline{\overline{s}}} \, \mathrm{d}\theta^{\overline{\overline{s}}} + \epsilon^s \frac{\mathbf{C}^s}{j^s} \mathbf{:} \, \mathrm{d}\boldsymbol{\sigma}^s \tag{3.151}$$

This can also be expressed as a material derivative.

$$\frac{\mathrm{D}^{\bar{s}} E^{\bar{\bar{s}}}}{\mathrm{D}t} - \theta^{\bar{\bar{s}}} \frac{\mathrm{D}^{\bar{s}} \eta^{\bar{\bar{s}}}}{\mathrm{D}t} - \mu^{\bar{s}} \frac{\mathrm{D}^{\bar{s}} \left(\epsilon^s \rho^s\right)}{\mathrm{D}t} + \left\langle \rho_s \frac{\mathrm{D}^{\bar{s}} \left(\mu_s - \mu^{\bar{s}}\right)}{\mathrm{D}t} \right\rangle_{\Omega_s,\Omega} + \left\langle \eta_s \frac{\mathrm{D}^{\bar{s}} \left(\theta_s - \theta^{\bar{\bar{s}}}\right)}{\mathrm{D}t} \right\rangle_{\Omega_s,\Omega}$$
$$+ \left\langle \frac{\mathbf{C}_s}{j_s} : \frac{\mathrm{D}^{\bar{s}} \left(\boldsymbol{\sigma}_s - \boldsymbol{\sigma}^s\right)}{\mathrm{D}t} \right\rangle_{\Omega_s,\Omega} - \boldsymbol{\sigma}^s : \frac{\mathrm{D}^{\bar{s}}}{\mathrm{D}t} \left(\epsilon^s \frac{\mathbf{C}^s}{j^s}\right) = 0 \tag{3.152}$$

After some manipulation, one can arrive at the form of solid phase, macroscale thermodynamics used in the TCAT entropy inequalities.

$$\begin{aligned}
\mathcal{T}^{\bar{s}} = {} & \frac{\mathrm{D}^{\bar{s}} E^{\bar{\bar{s}}}}{\mathrm{D}t} - \theta^{\bar{\bar{s}}} \frac{\mathrm{D}^{\bar{s}} \eta^{\bar{\bar{s}}}}{\mathrm{D}t} - \mu^{\bar{s}} \frac{\mathrm{D}^{\bar{s}} \left(\epsilon^s \rho^s\right)}{\mathrm{D}t} + p^s \frac{\mathrm{D}^{\bar{s}} \epsilon^s}{\mathrm{D}t} \\
& + \left\langle \eta_s \frac{\mathrm{D}_s (\theta_s - \theta^{\bar{\bar{s}}})}{\mathrm{D}t} + \rho_s \frac{\mathrm{D}_s (\mu_s - \mu^{\bar{s}})}{\mathrm{D}t} \right\rangle_{\Omega_s,\Omega} \\
& - \left\langle \left(\frac{\mathbf{C}_s}{j_s} : \boldsymbol{\sigma}_s \right) \left(\mathbf{v}_{ws} - \mathbf{v}_s\right) \cdot \mathbf{n}_s \right\rangle_{\Omega_{ws},\Omega} \\
& - \left\langle \mathbf{n}_s \cdot \left[\frac{2}{j_s} \boldsymbol{\sigma}_s : \left(\nabla_X \mathbf{x} \nabla_X \mathbf{x}\right) \cdot \left(\mathbf{v}_s - \mathbf{v}^{\bar{s}}\right) \right] \right\rangle_{\Omega_{ws},\Omega} \\
& + \left\langle \left\{ \nabla \cdot \left[\frac{2}{j_s} \boldsymbol{\sigma} : \left(\nabla_X \mathbf{x} \nabla_X \mathbf{x}\right) \right] - \nabla \boldsymbol{\sigma}_s : \frac{\mathbf{C}_s}{j_s} \right\} \cdot \left(\mathbf{v}_s - \mathbf{v}^{\bar{s}}\right) \right\rangle_{\Omega_s,\Omega} \\
& + \epsilon^s \boldsymbol{\sigma}^s : \frac{\mathbf{C}^s}{j^s} \mathbf{I} : \mathbf{d}^{\bar{\bar{s}}} - \left\langle \frac{2}{j_s} \boldsymbol{\sigma}_s : \left(\nabla_X \mathbf{x} \nabla_X \mathbf{x}\right) \right\rangle_{\Omega_s,\Omega} : \mathbf{d}^{\bar{\bar{s}}} \\
& - \nabla \cdot \left\langle \left[\frac{2}{j_s} : \left(\nabla_X \mathbf{x} \nabla_X \mathbf{x}\right) - \boldsymbol{\sigma}_s : \frac{\mathbf{C}_s}{j_s} \mathbf{I} \right] \cdot \left(\mathbf{v}_s - \mathbf{v}^{\bar{s}}\right) \right\rangle_{\Omega_s,\Omega} = 0
\end{aligned} \tag{3.153}$$

3.8 Conclusion

To model systems of significant size, macroscale conservation equation are necessary due to limitations in computing power that prevent the solution of microscale equations for large domains. However, many models do not use rigorously derived macroscale equations. Such macroscale equations tend to be modeled after the microscale forms with ambiguous terms added to take account for sub-scale processes. Without a rigorous averaging procedure, there is no guarantee that the equations account for all possible terms. Formal and consistent definitions for macroscale quantities are also lacking. Though it may seem that the averaging process is complicated and creates many new terms that must be dealt with, formal averaging is essential to the careful formation of a macroscale model. The modeler may later choose to neglect terms in an averaged macroscale equation, thus reducing it to a form equivalent to conservation equations posited directly at the macroscale. The benefit of this approach is that such simplifications are done with full knowledge of what terms have been neglected so that they can be reexamined if the model fails to describe the system as expected. This mathematical transparency that averaged macroscale equations have is a stark contrast to their vague, informal counterparts. The entirety of this chapter has been devoted to understanding how microscale conservations equations are averaged to the macroscale. In the following chapter, each equation will be specified to represent the phases relevant to this model, referring back to the macroscale forms derived here.

Chapter 4

Equation Specification & Additional Hypotheses

This chapter will take the macroscale equations developed in chapter 3 and specify them for the phases included in this model. Explicit constitutive relations will be included for some equations, or discussed generally for others. The full closure procedure as used in the thermodynamically constrained averaging theory approach is not included here. The process of developing entropy inequalities is beyond the scope of this work, but some insights gained from this process and seen previously in the TCAT series of papers will be included in the discussion that follows. This chapter is divided into five sections: one each for mass, momentum, energy, entropy, and thermodynamic equations. The subsections are divided by phase (p, n, h, f, and b), or into broader categories of general solid and general fluid phases with subheadings for the individual phases. The goal of this chapter is to present the foundational equations for a simple yet carefully derived macroscale model of tumor growth.

4.1 Mass

General macroscale conservation of mass for a phase, derived in section 3.3.

$$\mathcal{M}^{\overline{\overline{\alpha}}} = \frac{\partial(\rho^\alpha \epsilon^\alpha)}{\partial t} + \nabla\cdot\left(\rho^\alpha \epsilon^\alpha \mathbf{v}^{\overline{\alpha}}\right) - \sum_{\kappa\in\mathfrak{I}_{c\alpha}} \overset{\kappa\to\alpha}{M} = 0 \tag{4.1}$$

General macroscale conservation of mass for a species (i) within a phase:

$$\frac{\partial(\epsilon^\alpha \rho^\alpha \omega^{i\alpha})}{\partial t} + \nabla\cdot\left(\epsilon^\alpha \rho^\alpha \omega^{i\alpha} \mathbf{v}^{\overline{i\alpha}}\right) - \epsilon^\alpha r^{i\alpha} - \sum_{\kappa\in\mathfrak{I}c\alpha} \overset{i\kappa\to i\alpha}{M} = 0 \tag{4.2}$$

4.1.1 Viable Tumor Tissue: p

The mass conservation equation for the viable, proliferative tumor solid phase includes accumulation, advection, and interphase mass transfer with the necrotic tumor solid phase and the interstitial fluid phase.

$$\frac{\partial(\rho^p \epsilon^p)}{\partial t} + \nabla\cdot\left(\rho^p \epsilon^p \mathbf{v}^{\overline{p}}\right) + \overset{p\to n}{M} - \overset{f\to p}{M} = 0 \tag{4.3}$$

The term $\overset{f\to p}{M}$ accounts for the transfer of mass from the fluid phase to the proliferative tumor tissue, which is equivalent to net production of tumor mass since the cells derive the nutrition they need from the surrounding fluid. This growth is dependent on a variety of nutrients and growth signals, but for this model there will be a single species (i), of key importance. The conceptual form of the species dependence in this model is based on glucose as the growth-limiting species. However, one could specify the constants in the constitutive equations in terms of a different nutrient thought to limit growth. One could also model the growth as dependent on multiple speciesl. The growth rate, and thus mass transfer from the interstitial fluid phase to the viable tumor phase, can be approximated using the Monod growth model. Mathematically, the Monod growth equation is similar to the equation for Michaelis-Menten kinetics that has been observed and used by other researchers ([70], [71], [25], [47]). However, the Michaelis-Menten equation is meant to represent reaction kinetics of an enzyme mediated reaction of a species within a phase. Since the desire here is to model cell population growth as a function of mass transfer, the conceptual basis of the Michaelis-Menten equation would have to be stretched to allow for the representation of growth due to mass transfer. Traditionally, the Monod growth and Michaelis-Menten equations are used to describe reactions within a phase, but in tumor modeling they are adapted to account for mass transfer.

By using the Monod growth equation, we are modeling the growth of cells as a mass transfer driven by the cellular growth rate as determined by the local nutrient concentration. The amount of mass transferred from the fluid phase to the proliferative tumor phase depends on the nutrient concentration at that point and population (mass) of the the proliferative cells. The nutrient concentration determines whether or not the cells undergo mitosis, which is the mechanism of growth of the proliferative tumor tissue solid phase. For a maximum nutrient concentration, when the cells are not nutrient-limited, we can assume that the existing mass of the p phase in the REV doubles after some number of hours by assuming that every cell doubles and becomes two cells with equal mass.

General Monod Growth Equation:

$$\mu^*_{obs} = \mu^*_{max} Y \left(\frac{C_s}{K_s + C_s} \right) \tag{4.4}$$

The Monod growth equation bases an observed growth rate (μ^*_{obs}) on a maximum growth rate (μ^*_{max}), the substrate concentration (C_s) and the Monod constant (K_s).

The coefficient Y represents the yield of cellular mass due to mass of substrate consumed. Its units are mass per mass. The phases and species of interest in this model can specified:

$$\mu_p^* = \mu_{max}^* Y \left(\frac{\epsilon^f \rho^f \omega^{i\overline{f}}}{K_s + \epsilon^f \rho^f \omega^{i\overline{f}}} \right) \tag{4.5}$$

In a porous medium system, the substrate concentration is expressed as the product of the volume fraction of phase f (ϵ^f), density of phase f (ρ^f), and mass fraction of species i within phase f ($\omega^{i\overline{f}}$). The observed proliferation rate is denoted μ_p. In order to translate this equation for the proliferative growth rate into a mass transfer term, the growth rate must be multiplied by the existing mass of proliferative cells in the REV to find the mass of new cells. Thus no growth, and no mass transfer, will occur if there is no mass of viable cells or if the concentration of nutrient i is zero ($\omega^{i\overline{f}} = 0$).

$$\overset{f\rightarrow p}{M} = \epsilon^p \rho^p \mu_p^* \tag{4.6}$$

$$= \epsilon^p \rho^p \mu_{max}^* Y \left(\frac{\epsilon^f \rho^f \omega^{i\overline{f}}}{K_s + \epsilon^f \rho^f \omega^{i\overline{f}}} \right) \tag{4.7}$$

This term represents the amount of mass that leaves the interstitial fluid phase (f) and is absorbed by the cells of the viable tumor phase (p) which then divide and create new cells. This model does not track the number of cells in the tumor, but instead the mass of the cells. However, one can calculate the approximate number of viable cells in the tumor by dividing the total mass of the p phase of the tumor by the average mass of a single cell.

The opposing mechanism to growth is cell death, which in this model is the creation of a necrotic region. The amount of mass becoming necrotic is represented by the other mass transfer term: $\overset{p\rightarrow n}{M}$. The mass transfer from the viable tumor phase to the necrotic tumor phase accounts for cell death due to necrosis, where R_d is the necrotic death rate.

$$\overset{p\to n}{M} = \epsilon^p \rho^p R_d \tag{4.8}$$

There is no term to account for cell death due to apoptosis because cancer cells tend to have a variety of mechanisms to avoid apoptosis. Evasion of apoptosis is such a common feature of cancer that it is was recognized as one of Hanahan and Weinberg's "Hallmarks of Cancer" [38, 39]. The mass transfer from viable to necrotic tissue accounts for non-apoptotic cell death that will be modeled as nutrient dependent. Essentially, tissue that does not receive enough nutrients (species i) from the interstitial fluid phase will starve and necrose. Necrosis can be described as cell death due to trauma, rather than part of the cell cycle. The critical nutrient concentration will be denoted as C_{crit}, and above this threshold concentration the necrotic death rate (R_d) is zero. Below the threshold, the rate of death is proportional to the nutrient deficit.

$$R_d = 0, \text{ when } C^{if} \geq C^{crit} \tag{4.9}$$

$$R_d = K_d \left(C^{crit} - C^{if} \right), \text{ when } C^{if} \leq C^{crit} \tag{4.10}$$

Or,

$$R_d = 0, \text{ when } \omega^{i\overline{f}} \geq \omega^{i\overline{f}}_{crit} \tag{4.11}$$

$$R_d = K_d \left(\epsilon^f \rho^f \omega^{i\overline{f}}_{crit} - \epsilon^f \rho^f \omega^{i\overline{f}} \right), \text{ when } \omega^{i\overline{f}} \leq \omega^{i\overline{f}}_{crit} \tag{4.12}$$

The mass conservation equation for the viable tumor tissue phase is complete after incorporating the constitutive equations for mass transfer due to growth and death.

$$\frac{\partial(\rho^p \epsilon^p)}{\partial t} + \nabla \cdot \left(\rho^p \epsilon^p \mathbf{v}^{\overline{p}} \right) + \epsilon^p \rho^p R_d - \epsilon^p \rho^p \mu^*_{max} Y \left(\frac{\epsilon^f \rho^f \omega^{i\overline{f}}}{K_s + \epsilon^f \rho^f \omega^{i\overline{f}}} \right) = 0 \tag{4.13}$$

The constants K_d, μ_{max}, Y, K_s, and $\omega_{crit}^{i\overline{f}}$ must be determined experimentally.

4.1.2 Necrotic Tumor Tissue: n

The conservation of mass equation for the necrotic tissue phase includes accumulation, advection, and mass transfer from the proliferative phase to the necrotic phase.

$$\frac{\partial(\rho^n \epsilon^n)}{\partial t} + \nabla\cdot\left(\rho^n \epsilon^n \mathbf{v}^{\overline{n}}\right) - \overset{p\to n}{M} = 0 \tag{4.14}$$

In this equation, $\overset{p\to n}{M}$ is a mass transfer term that accounts for the transfer of mass from the viable tumor cell phase to the necrotic tissue solid phase. (The direction of mass transfer is implied by the arrow). This is equal and opposite to the necrosis term in the viable tumor tissue equation.

$$\frac{\partial(\rho^n \epsilon^n)}{\partial t} + \nabla\cdot\left(\rho^n \epsilon^n \mathbf{v}^{\overline{n}}\right) - \epsilon^p \rho^p R_d = 0 \tag{4.15}$$

4.1.3 Host Tissue: h

Normal tissue has different morphology and physical properties than the tumor, and does not experience uncontrolled growth. The cells in this phase are not necessarily healthy because they may be experienced stress from the presence of the tumor. This phase can be called normal because the cells are non-cancerous. That is, they do not contain the genetic alterations of malignant cells and react normally to inter-/intracellular signals. For this model, the normal cells are assumed to be in homeostasis, meaning that there is no net proliferation and that number of cells and amount of mass is not dependent on nutrient transport. (This hypothesis is a very broad generalization, biologically speaking, but makes for a much simpler model.) The following equation is for conservation of mass of the normal tissue.

$$\frac{\partial\left(\epsilon^h\rho^h\right)}{\partial t} + \nabla\cdot\left(\epsilon^h\rho^h\mathbf{v}^{\overline{h}}\right) = 0 \tag{4.16}$$

There are no mass transfer terms in this conservation equation because of the assumption of homeostasis. This assumes that the growth and death rates of the normal tissue phase are equal, and eliminates the need to account for nutrient transfer and growth, or necrosis as was done in the tumor phase. This assumption is also similar to stating that the tumor and normal tissue are supplied by different vasculature, which is largely true once the tumor initiates angiogenesis. It is important to note that normal cells surrounding the tumor may have a negative net growth rate (indicating death) because of decreased pH or other microenvironmental factors, but this facet of tumor/host interaction is neglected here for simplicity.

4.1.4 Extravascular/Interstitial Fluid: f

The conservation of mass equation for the interstitial fluid phase includes terms for accumulation, advection, mass transfer to the proliferative tumor phase and mass transfer from the blood phase.

$$\frac{\partial\left(\rho^f\epsilon^f\right)}{\partial t} + \nabla\cdot\left(\rho^f\epsilon^f\mathbf{v}^{\overline{f}}\right) + \overset{f\to p}{M} - \overset{b\to f}{M} = 0 \tag{4.17}$$

The transfer of mass from the f to the p phase supplies the cells with nutrients required for growth, so $\overset{f\to p}{M}$ indicates growth, as discussed earlier. The nutrients in the interstitial fluid phase originate from the blood in the vasculature, accounted for by the $\overset{b\to f}{M}$ term. The mass transfer term from the interstitial fluid phase to the proliferative tumor phase is equal and opposite to the mass transfer seen in equation (4.3).

$$\frac{\partial\left(\rho^f \epsilon^f\right)}{\partial t} + \nabla\cdot \left(\rho^f \epsilon^f \mathbf{v}^{\overline{f}}\right) + \epsilon^p \rho^p \mu^*_{max} Y \left(\frac{\epsilon^f \rho^f \omega^{i\overline{f}}}{K_s + \epsilon^f \rho^f \omega^{i\overline{f}}}\right) - \overset{b\to f}{M} = 0 \tag{4.18}$$

One can also write a conservation of mass of species i in phase f by utilizing the species mass fraction, $\omega^{i\overline{f}}$. Terms included in the conservation equation are accumulation, flux (advective and diffusive), and transfer of species i to the p phase and from the blood (b) phase.

$$\frac{\partial\left(\rho^f \epsilon^f \omega^{i\overline{f}}\right)}{\partial t} + \nabla\cdot \left(\rho^f \epsilon^f \omega^{i\overline{f}} \mathbf{v}^{\overline{if}}\right) + \overset{if\to p}{M} - \overset{ib\to if}{M} = 0 \tag{4.19}$$

Since the phase equation has a term for mass transfer due to growth ($\overset{f\to p}{M}$), the mass of i transferred must be a fraction of the total mass transfer from the fluid phase. This scaling factor relating the mass of species i and total mass transferred to the proliferative phase is the yield coefficient (Y) seen previously in the Monod growth equation.

$$\overset{if\to p}{M} = \frac{\overset{f\to p}{M}}{Y} \tag{4.20}$$

$$\overset{if\to p}{M} = \frac{1}{Y} \epsilon^p \rho^p \mu^*_{max} Y \left(\frac{\epsilon^f \rho^f \omega^{i\overline{f}}}{K_s + \epsilon^f \rho^f \omega^{i\overline{f}}}\right) \tag{4.21}$$

The yield coefficients cancel.

$$\overset{if\to p}{M} = \epsilon^p \rho^p \mu^*_{max} \left(\frac{\epsilon^f \rho^f \omega^{i\overline{f}}}{K_s + \epsilon^f \rho^f \omega^{i\overline{f}}}\right) \tag{4.22}$$

Therefore, the conservation equation can be written as follows when one incorporates (4.20) and separate the species velocity into the sum of the phase velocity and the the diffusive velocity ($\mathbf{v}^{i\overline{f}} = \mathbf{v}^{\overline{f}} + \mathbf{u}^{\overline{\overline{if}}}$).

$$\frac{\partial\left(\rho^f \epsilon^f \omega^{i\overline{f}}\right)}{\partial t} + \nabla\cdot \left[\rho^f \epsilon^f \omega^{i\overline{f}} \left(\mathbf{v}^{\overline{f}} + \mathbf{u}^{\overline{\overline{if}}}\right)\right] + \epsilon^p \rho^p \mu^*_{max} \left(\frac{\epsilon^f \rho^f \omega^{i\overline{f}}}{K_s + \epsilon^f \rho^f \omega^{i\overline{f}}}\right) - \overset{ib\to if}{M} = 0 \quad (4.23)$$

Approximate the diffusive velocity using Fick's Law: $\rho^f \omega^{i\overline{f}} \mathbf{u}^{\overline{\overline{if}}} = -D^{if} \rho^f \nabla \omega^{i\overline{f}}$.

$$\frac{\partial\left(\rho^f \epsilon^f \omega^{i\overline{f}}\right)}{\partial t} + \nabla\cdot \left[\rho^f \epsilon^f \omega^{i\overline{f}} \mathbf{v}^{\overline{f}}\right] - \nabla\cdot \left(\epsilon^f \rho^f D^{if} \nabla \omega^{i\overline{f}}\right)$$
$$+\epsilon^p \rho^p \mu^*_{max} \left(\frac{\epsilon^f \rho^f \omega^{i\overline{f}}}{K_s + \epsilon^f \rho^f \omega^{i\overline{f}}}\right) - \overset{ib\to if}{M} = 0 \quad (4.24)$$

Additional closure will be needed for $\overset{ib\to if}{M}$, the extravasation of species i.

4.1.5 Intravascular Fluid (Blood): b

The mass conservation equation for the b phase includes accumulation, advection, and mass transfer.

$$\frac{\partial\left(\rho^b \epsilon^b\right)}{\partial t} + \nabla\cdot \left(\rho^b \epsilon^b \mathbf{v}^{\overline{b}}\right) + \overset{b\to f}{M} = 0 \quad (4.25)$$

The mass transfer term ($\overset{b\to f}{M}$) accounts for mass transferred from the blood, through the vessel walls, to the interstitial fluid. The species mass transfer and phase mass transfer are related by the same yield coefficient seen earlier.

$$\overset{b\to f}{M} = Y \overset{ib\to if}{M} \quad (4.26)$$

Therefore, the phase mass conservation equation can be rewritten using the yield coeffiecient and the species form of the mass transfer term, $\overset{ib\to if}{M}$.

$$\frac{\partial\left(\rho^b \epsilon^b\right)}{\partial t} + \nabla\cdot \left(\rho^b \epsilon^b \mathbf{v}^{\overline{b}}\right) + Y \overset{ib\to if}{M} = 0 \quad (4.27)$$

The species mass transfer term is seen without the yield coefficient in the mass conservation equation of species i in the b phase. The constitutive form of $\overset{ib\rightarrow if}{M}$ should be based on the surface area of the vessel (i.e. vessel radius) and other parameters. Such parameters that may influence extravasation of the nutrient species include nutrient concentration (passive diffusion), active transport by the epithelial cells of the vessel walls, blood flow rate, intravascular and extravascular pressure. However, most previous models have neglected these factors due to their complexity.

$$\frac{\partial\left(\rho^b\epsilon^b\omega^{i\overline{b}}\right)}{\partial t} + \nabla\cdot\left(\rho^b\epsilon^b\omega^{i\overline{b}}\mathbf{v}^{\overline{ib}}\right) + \overset{ib\rightarrow if}{M} = 0 \tag{4.28}$$

Incorporate Fick's Law to approximate the diffusive velocity, and this is the final form of the conservation of mass for species i in the b phase.

$$\frac{\partial\left(\rho^b\epsilon^b\omega^{i\overline{b}}\right)}{\partial t} + \nabla\cdot\left(\rho^b\epsilon^b\mathbf{v}^{\overline{b}}\right) - \nabla\cdot\left(\rho^b\epsilon^b D^{ib}\nabla\omega^{i\overline{b}}\right) + \overset{ib\rightarrow if}{M} = 0 \tag{4.29}$$

The approximations made for Fick's law and the mass transfer equations that represent growth and death are part of the constitutive relations needed to close the model. However, additional closure is needed to mathematically represent the transfer of mass from the blood phase to the interstitial fluid phase.

4.2 Momentum

General macroscale conservation of momentum for a phase, derived in section 3.4.

$$\boldsymbol{\mathcal{P}}^{\overline{\overline{\alpha}}} = \frac{\partial(\rho^\alpha\epsilon^\alpha\mathbf{v}^{\overline{\alpha}})}{\partial t} + \nabla\cdot\left(\rho^\alpha\epsilon^\alpha\mathbf{v}^{\overline{\alpha}}\mathbf{v}^{\overline{\alpha}}\right) - \nabla\cdot\left(\epsilon^\alpha\mathbf{t}^{\overline{\overline{\alpha}}}\right) - \rho^\alpha\epsilon^\alpha\mathbf{g}^{\overline{\alpha}} - \sum_{\kappa\in\mathfrak{I}c\alpha}\left[\mathbf{v}^{\overline{\alpha}}\overset{\kappa\rightarrow\alpha}{M} + \overset{\kappa\rightarrow\alpha}{\mathbf{T}}\right] = 0 \tag{4.30}$$

Like mass,the momentum conservation equation has terms for accumulation and advection. However, it also includes momentum from body sources that act on the entire volume ($\rho^{\alpha}\epsilon^{\alpha}\mathbf{g}^{\overline{\alpha}}$) and from non-flux sources ($\nabla\boldsymbol{\cdot}(\epsilon^{\alpha}\mathbf{t}^{\overline{\overline{\alpha}}})$) that act on the surface. The inter-phase transfer terms include momentum gained due to mass transfer ($\mathbf{v}^{\overline{\alpha}}\overset{\kappa\to\alpha}{M}$) and momentum gained due to mechanical interaction ($\overset{\kappa\to\alpha}{\mathbf{T}}$).

4.2.1 Solid phases: p, n, h

In this model, it will be assumed that the solid phases have the same velocity, which will be denoted as $\mathbf{v}^{\overline{s}}$, the macroscale solid phase velocity. This assumption is common to many of the continuum models discussed in chapter 1.

$$\mathbf{v}^{\overline{p}} = \mathbf{v}^{\overline{n}} = \mathbf{v}^{\overline{h}} = \mathbf{v}^{\overline{s}} \tag{4.31}$$

We can write a general momentum equation that applies to the three solid phases using the solid phase velocity $\mathbf{v}^{\overline{s}}$ and leaving other quantities as general phase α that can stand for p, n, or h.

$$\frac{\partial(\rho^{\alpha}\epsilon^{\alpha}\mathbf{v}^{\overline{s}})}{\partial t} + \nabla\boldsymbol{\cdot}\left(\rho^{\alpha}\epsilon^{\alpha}\mathbf{v}^{\overline{s}}\mathbf{v}^{\overline{s}}\right) - \nabla\boldsymbol{\cdot}\left(\epsilon^{\alpha}\mathbf{t}^{\overline{\overline{\alpha}}}\right) - \rho^{\alpha}\epsilon^{\alpha}\mathbf{g}^{\overline{\alpha}} - \sum_{\kappa\in\mathfrak{I}c\alpha}\left[\mathbf{v}^{\overline{\alpha}}\overset{\kappa\to\alpha}{M} + \overset{\kappa\to\alpha}{\mathbf{T}}\right] = 0 \tag{4.32}$$

In biological systems, hygro-thermal phenomena are slow, so inertial forces can be neglected. This means that the first two terms, accumulation and advection, are removed from the equation.

$$-\nabla\boldsymbol{\cdot}\left(\epsilon^{\alpha}\mathbf{t}^{\overline{\overline{\alpha}}}\right) - \rho^{\alpha}\epsilon^{\alpha}\mathbf{g}^{\overline{\alpha}} - \sum_{\kappa\in\mathfrak{I}c\alpha}\left[\mathbf{v}^{\overline{\alpha}}\overset{\kappa\to\alpha}{M} + \overset{\kappa\to\alpha}{\mathbf{T}}\right] = 0 \tag{4.33}$$

Also assume that momentum due to mass transfer is negligible. Neglect inertial terms to get the following.

$$-\nabla\cdot\left(\epsilon^{\alpha}\mathbf{t}^{\overline{\overline{\alpha}}}\right)-\rho^{\alpha}\epsilon^{\alpha}\mathbf{g}^{\overline{\alpha}}-\sum_{\kappa\in\mathfrak{I}c\alpha}\overset{\kappa\to\alpha}{\mathbf{T}}=0 \tag{4.34}$$

The analysis of multiple solid phases is not included here. However, from closure relations developed in TCAT, it is known that

$$\mathbf{t}^{\overline{\overline{\alpha}}}=\mathbf{t}^{\alpha},\ \text{When } \alpha \text{ is a solid.} \tag{4.35}$$

Incorporate $\mathbf{t}^{\alpha}$.

$$-\nabla\cdot\left(\epsilon^{\alpha}\mathbf{t}^{s}\right)-\rho^{\alpha}\epsilon^{\alpha}\mathbf{g}^{\overline{\alpha}}-\sum_{\kappa\in\mathfrak{I}c\alpha}\overset{\kappa\to\alpha}{\mathbf{T}}=0 \tag{4.36}$$

This equation can be specified to each of the solid phases.

Viable Tumor Tissue: p

$$-\nabla\cdot\left(\epsilon^{p}\mathbf{t}^{p}\right)-\rho^{p}\epsilon^{p}\mathbf{g}^{\overline{p}}-\sum_{\kappa\in\mathfrak{I}cp}\overset{\kappa\to p}{\mathbf{T}}=0 \tag{4.37}$$

Necrotic Tumor Tissue: n

$$-\nabla\cdot\left(\epsilon^{n}\mathbf{t}^{n}\right)-\rho^{n}\epsilon^{n}\mathbf{g}^{\overline{n}}-\sum_{\kappa\in\mathfrak{I}cn}\overset{\kappa\to n}{\mathbf{T}}=0 \tag{4.38}$$

Host Tissue: h

$$-\nabla\cdot\left(\epsilon^{h}\mathbf{t}^{h}\right)-\rho^{h}\epsilon^{h}\mathbf{g}^{\overline{h}}-\sum_{\kappa\in\mathfrak{I}ch}\overset{\kappa\to h}{\mathbf{T}}=0 \tag{4.39}$$

The form of the momentum equation for the solid phases still needs closure approximations for the stress tensor and for the transfer of momentum term. The constitutive form of the solid phase stress tensor will depend on the type of deformation that is assumed. The simplest choice is an incompressible solid phase, but most modern tumor models are representing the solid phases as elastic or viscoelastic solids. These constitutive forms vary based on the mathematical form that represents the deformation of the solid. Solid stress can be separated into normal stress, also called pressure, and tangential stress which can stretch, twist, and bend the solid out of shape. Solid mechanics are considerably more complex than fluid mechanics because of the dependence on the original configuration of the solid, which is not important in fluid mechanics.

The momentum transfer term, $\overset{\kappa\to s}{\mathbf{T}}$, must also be specified for each phase. It represents the transfer of momentum between phases that is not due to the exchange of mass. Since the κ qualifier stands for the interfaces that are connected to the phase, this model must consider three general types of interfaces: solid-solid, solid-fluid, and fluid-fluid. The solid-solid momentum transfer terms can be neglected because the solids are moving with one velocity, $\mathbf{v}^{\overline{s}}$. The fluid-fluid term will also be neglected because the blood phase and interstitial phase are separated by the blood vessel walls. Therefore no momentum can transfer without exchange of mass between the fluids because they are not in direct contact. However, the solid-fluid interface can transfer momentum and constitutive relations are necessary to close the model. As the fluid flows in contact with the solid, it may transfer momentum due to friction, and this should be accounted for in the model.

4.2.2 Fluid Phases: f, b

The general conservation of momentum for the fluid phase will be denoted using the letter w as a qualifier. Later the w will be specified as either f or b.

$$\frac{\partial(\rho^w\epsilon^w\mathbf{v}^{\overline{w}})}{\partial t}+\nabla\cdot\left(\rho^w\epsilon^w\mathbf{v}^{\overline{w}}\mathbf{v}^{\overline{w}}\right)-\nabla\cdot\left(\epsilon^w\mathbf{t}^{\overline{\overline{w}}}\right)-\rho^w\epsilon^w\mathbf{g}^{\overline{w}}-\sum_{\kappa\in\mathfrak{I}cw}\left[\mathbf{v}^{\overline{w}}\overset{\kappa\to w}{M}+\overset{\kappa\to w}{\mathbf{T}}\right]=0 \quad (4.40)$$

Neglect inertial (accumulation and advection) terms.

$$\frac{\partial(\rho^w \epsilon^w \mathbf{v}^{\overline{w}})}{\partial t} + \nabla\cdot \left(\rho^f \epsilon^w \mathbf{v}^{\overline{w}} \mathbf{v}^{\overline{w}}\right) \approx 0 \tag{4.41}$$

This leaves the following simplified momentum equation.

$$-\nabla\cdot \left(\epsilon^w \mathbf{t}^{\overline{\overline{w}}}\right) - \epsilon^w \rho^w \mathbf{g}^{\overline{w}} - \sum_{\kappa \in \mathfrak{I}cw} \left[\mathbf{v}^{\overline{w}} \overset{\kappa\to w}{M} + \overset{\kappa\to w}{\mathbf{T}}\right] = 0 \tag{4.42}$$

The momentum due to mass transfer ($\mathbf{v}^{\overline{w}} \overset{\kappa\to w}{M}$) is small because only species i and other nutrients are transported between phases and one may assume that the system is dilute. Therefore this term can be neglected.

$$-\nabla\cdot \left(\epsilon^w \mathbf{t}^{\overline{\overline{w}}}\right) - \epsilon^w \rho^w \mathbf{g}^{\overline{w}} - \sum_{\kappa \in \mathfrak{I}cw} \overset{\kappa\to w}{\mathbf{T}} = 0 \tag{4.43}$$

The TCAT method of closure involves arranging terms into force-flux pairs. According to thermodynamics, at equilibrium the forces and fluxes are zero. This relationship between forces and fluxes at equilibrium can help guide closure. From TCAT the flux-force term including $\overset{\kappa\to w}{\mathbf{T}}$ is as follows.

$$-\frac{1}{\theta^{\overline{\overline{w}}}} \left(\epsilon^w \rho^w \mathbf{g}^{\overline{w}} + \epsilon^w \rho^w \nabla \left(\psi^{\overline{w}} + \mu^{\overline{w}}\right) - \nabla \left(\epsilon^w p^w\right) + \sum_{\kappa \in \mathfrak{I}cw} \overset{\kappa\to w}{\mathbf{T}}\right) \cdot \left(\mathbf{v}^{\overline{w}} - \mathbf{v}^{\overline{s}}\right) = 0 \tag{4.44}$$

In this equation, $\theta^{\overline{\overline{w}}}$ stands for the temperature of the w phase, $\psi^{\overline{w}}$ is the gravitational potential, $\mu^{\overline{w}}$ is the chemical potential, p^w is the fluid pressure, and $\mathbf{v}^{\overline{s}}$ is the velocity of the solid phase

To further simplify $\overset{\kappa\to w}{\mathbf{T}}$, assume the system has uniform composition and isothermal conditions. By assuming uniform composition, $-\nabla\psi = g$, and those terms cancel. The isothermal assumption means that $\epsilon^w \rho^w \nabla \mu^{\overline{w}} = \epsilon^w \nabla p^w$. Therefore, the force-flux pair reduces to the following.

$$\left(-p^w \nabla \epsilon^w + \sum_{\kappa \in \mathfrak{I}cw} \overset{\kappa \to w}{\mathbf{T}}\right) \cdot \left(\mathbf{v}^{\overline{w}} - \mathbf{v}^{\overline{s}}\right) = 0 \tag{4.45}$$

Because this is a force-flux relation, it can be generalized as follows, giving the form seen in Darcy's law.

$$\sum_{\kappa \in \mathfrak{I}cw} \overset{\kappa \to w}{\mathbf{T}} = p^w \nabla \epsilon^w - \mathbf{K}^w \cdot \left(\mathbf{v}^{\overline{w}} - \mathbf{v}^{\overline{s}}\right) \tag{4.46}$$

Where $\mathbf{K}^w$ is the hydraulic conductivity of solid phase to the w phase.

The stress tensor can also be simplified by examining the force-flux pairs, to lead to the following simplification.

$$\mathbf{t}^{\overline{\overline{f}}} = -p^f \mathbf{I} \tag{4.47}$$

Therefore,

$$-\nabla \cdot \left(\epsilon^w \mathbf{t}^{\overline{\overline{w}}}\right) = \nabla \left(\epsilon^w p^w\right) \tag{4.48}$$

Incorporating these simplifications gives the following momentum equation.

$$\nabla \left(\epsilon^w p^w\right) - \epsilon^w \rho^w \mathbf{g}^{\overline{w}} - \left[p^w \nabla \epsilon^w - \mathbf{K}^w \cdot \left(\mathbf{v}^{\overline{w}} - \mathbf{v}^{\overline{s}}\right)\right] = 0 \tag{4.49}$$

Combine the pressure terms to get the following equation for conservation of momentum for a general fluid phase in its simplest form.

$$-\epsilon^w \rho^w \mathbf{g}^{\overline{w}} + \epsilon^w \nabla p^w + \mathbf{K}^w \cdot \left(\mathbf{v}^{\overline{w}} - \mathbf{v}^{\overline{s}}\right) = 0 \tag{4.50}$$

This equation applies to the f and b phases in this model and can be written for each one.

Interstitial fluid: f

$$-\epsilon^f \rho^f \mathbf{g}^{\overline{f}} + \epsilon^f \nabla p^f + \mathbf{K}^f \cdot \left(\mathbf{v}^{\overline{f}} - \mathbf{v}^{\overline{s}} \right) = 0 \tag{4.51}$$

Blood: b

$$-\epsilon^b \rho^b \mathbf{g}^{\overline{b}} + \epsilon^b \nabla p^b + \mathbf{K}^b \cdot \left(\mathbf{v}^{\overline{b}} - \mathbf{v}^{\overline{s}} \right) = 0 \tag{4.52}$$

The hydraulic conductivity parameter, $\mathbf{K}$, depends on both the fluid and the solid porous material through which it is flowing. The properties of the solid media that influence flow are important in determining the hydraulic conductivity of the cellular solid phases include the cell size distribution, shape of the cells, tortuosity of passages, specific surface area, and porosity (the sum of the fluid volume fractions). It also depends on the density and viscosity of the fluid.[6]

4.3 Energy

This model assumes an isothermal system since the solid tissues and fluids stay at normal body temperature for all intents and purposes. Any temperature changes that occur naturally will be small and occur gradually compared with the time scale of flow and nutrient transfer. For an isothermal system, it is not necessary to define and close the energy equation. However, the goal of this work is to be transferable to situations outside the simplifications assumed here. For example, thermal ablation is one therapeutic treatment designed to eliminate tumors by using heat to kill the malignant cells. Therefore, it might be of interest to model heat transfer in a tumor using the model system detailed in this document. The remainder of this section develops general energy equations for each phase and will discuss a few likely simplifications after all equations have been presented.

General macroscale conservation of total energy for a phase, derived in section 3.5:

$$\begin{aligned}
\boldsymbol{\mathcal{E}}^{\overline{\overline{\alpha}}} = & \frac{\partial}{\partial t}\left(E^{\overline{\overline{\alpha}}} + \frac{1}{2}\epsilon^\alpha\rho^\alpha\mathbf{v}^{\overline{\alpha}}\cdot\mathbf{v}^{\overline{\alpha}} + \epsilon^\alpha\rho^\alpha\psi^{\overline{\alpha}} + \epsilon^\alpha\rho^\alpha K_E^{\overline{\overline{\alpha}}}\right) \\
& + \nabla\cdot\left[\left(E^{\overline{\overline{\alpha}}} + \frac{1}{2}\epsilon^\alpha\rho^\alpha\mathbf{v}^{\overline{\alpha}}\cdot\mathbf{v}^{\overline{\alpha}} + \epsilon^\alpha\rho^\alpha\psi^{\overline{\alpha}} + \epsilon^\alpha\rho^\alpha K_E^{\overline{\overline{\alpha}}}\right)\mathbf{v}^{\overline{\alpha}}\right] \\
& - \nabla\cdot\left(\epsilon^\alpha\mathbf{t}^{\overline{\overline{\alpha}}}\cdot\mathbf{v}^{\overline{\alpha}} + \epsilon^\alpha\mathbf{q}^{\overline{\overline{\alpha}}}\right) - \epsilon^\alpha h^{\overline{\overline{\alpha}}} - \left\langle\rho_\alpha\frac{\partial\psi_\alpha}{\partial t}\right\rangle_{\Omega_\alpha,\Omega} \\
& - \sum_{\kappa\in\mathfrak{I}_{c\alpha}}\left[\left(\frac{1}{2}\mathbf{v}_\alpha^{\overline{\kappa}}\cdot\mathbf{v}_\alpha^{\overline{\kappa}} + \psi_\alpha^{\overline{\kappa}} + \frac{E_\alpha^{\overline{\overline{\kappa}}}}{\epsilon^\kappa\rho_\alpha^\kappa} + K_{E\alpha}^{\overline{\overline{\kappa}}}\right)\overset{\kappa\to\alpha}{M} + \mathbf{v}_\alpha^{\overline{\kappa}}\cdot\overset{\kappa\to\alpha}{\mathbf{T}} + \overset{\kappa\to\alpha}{Q}\right] \\
& + \sum_{\kappa\in\mathfrak{I}_{c\alpha}}\left\langle\mathbf{n}_\alpha\rho_\alpha\cdot\left(\psi_\alpha - \psi_\alpha^{\overline{\kappa}}\right)\left(\mathbf{v}_\alpha - \mathbf{v}_\kappa\right)\right\rangle_{\Omega_\kappa,\Omega} \\
& + \nabla\cdot\left\langle\rho_\alpha\left(\psi_\alpha - \psi^{\overline{\alpha}}\right)\left(\mathbf{v}_\alpha - \mathbf{v}^{\overline{\alpha}}\right)\right\rangle_{\Omega_\alpha,\Omega} = 0
\end{aligned} \tag{4.53}$$

4.3.1 Viable Tumor Tissue: p

General conservation of energy, specified for the p phase:

$$\begin{aligned}
& \frac{\partial}{\partial t}\left(E^{\overline{\overline{p}}} + \frac{1}{2}\epsilon^p\rho^p\mathbf{v}^{\overline{p}}\cdot\mathbf{v}^{\overline{p}} + \epsilon^p\rho^p\psi^{\overline{p}} + \epsilon^p\rho^p K_E^{\overline{\overline{p}}}\right) \\
& + \nabla\cdot\left[\left(E^{\overline{\overline{p}}} + \frac{1}{2}\epsilon^p\rho^p\mathbf{v}^{\overline{p}}\cdot\mathbf{v}^{\overline{p}} + \epsilon^p\rho^p\psi^{\overline{p}} + \epsilon^p\rho^p K_E^{\overline{\overline{p}}}\right)\mathbf{v}^{\overline{p}}\right] \\
& - \nabla\cdot\left(\epsilon^p\mathbf{t}^{\overline{\overline{p}}}\cdot\mathbf{v}^{\overline{p}} + \epsilon^p\mathbf{q}^{\overline{\overline{p}}}\right) - \epsilon^p h^{\overline{\overline{p}}} - \left\langle\rho_p\frac{\partial\psi_p}{\partial t}\right\rangle_{\Omega_p,\Omega} \\
& - \sum_{\kappa\in\mathfrak{I}cp}\left[\left(\frac{1}{2}\mathbf{v}_p^{\overline{\kappa}}\cdot\mathbf{v}_p^{\overline{\kappa}} + \psi_p^{\overline{\kappa}} + \frac{E_p^{\overline{\overline{\kappa}}}}{\epsilon^\kappa\rho_p^{\overline{\kappa}}} + K_{Ep}^{\overline{\overline{\kappa}}}\right)\overset{\kappa\to p}{M} + \mathbf{v}_p^{\overline{\kappa}}\cdot\overset{\kappa\to p}{\mathbf{T}} + \overset{\kappa\to p}{Q}\right] \\
& + \sum_{\kappa\in\mathfrak{I}cp}\left\langle\mathbf{n}_p\rho_p\cdot\left(\psi_p - \psi_p^{\overline{\kappa}}\right)\left(\mathbf{v}_p - \mathbf{v}_\kappa\right)\right\rangle_{\Omega_\kappa,\Omega} \\
& + \nabla\cdot\left\langle\rho_p\left(\psi_p - \psi^{\overline{p}}\right)\left(\mathbf{v}_p - \mathbf{v}^{\overline{p}}\right)\right\rangle_{\Omega_p,\Omega} = 0
\end{aligned} \tag{4.54}$$

Input the solid velocity ($\mathbf{v}_s$ and $\mathbf{v}^{\overline{s}}$) for the velocity of the p phase.

$$\begin{aligned}
&\frac{\partial}{\partial t}\left(E^{\overline{\overline{p}}}+\frac{1}{2}\epsilon^p\rho^p\mathbf{v}^{\overline{s}}\cdot\mathbf{v}^{\overline{s}}+\epsilon^p\rho^p\psi^{\overline{p}}+\epsilon^p\rho^p K_E^{\overline{\overline{p}}}\right)\\
&\quad+\nabla\cdot\left[\left(E^{\overline{\overline{p}}}+\frac{1}{2}\epsilon^p\rho^p\mathbf{v}^{\overline{s}}\cdot\mathbf{v}^{\overline{s}}+\epsilon^p\rho^p\psi^{\overline{p}}+\epsilon^p\rho^p K_E^{\overline{\overline{p}}}\right)\mathbf{v}^{\overline{s}}\right]\\
&\quad-\nabla\cdot\left(\epsilon^p\mathbf{t}^{\overline{\overline{p}}}\cdot\mathbf{v}^{\overline{s}}+\epsilon^p\mathbf{q}^{\overline{\overline{p}}}\right)-\epsilon^p h^{\overline{\overline{p}}}-\left\langle\rho_p\frac{\partial\psi_p}{\partial t}\right\rangle_{\Omega_p,\Omega}\\
&\quad-\sum_{\kappa\in\mathfrak{I}cp}\left[\left(\frac{1}{2}\mathbf{v}_s^{\overline{\kappa}}\cdot\mathbf{v}_s^{\overline{\kappa}}+\psi_p^{\overline{\kappa}}+\frac{E_p^{\overline{\overline{\kappa}}}}{\epsilon^\kappa\rho_p^{\overline{\kappa}}}+K_{Ep}^{\overline{\overline{\kappa}}}\right)\overset{\kappa\to p}{M}+\mathbf{v}_s^{\overline{\kappa}}\cdot\overset{\kappa\to p}{\mathbf{T}}+\overset{\kappa\to p}{Q}\right]\\
&\quad+\sum_{\kappa\in\mathfrak{I}cp}\left\langle\mathbf{n}_p\rho_p\cdot\left(\psi_p-\psi_p^{\overline{\kappa}}\right)\left(\mathbf{v}_s-\mathbf{v}_\kappa\right)\right\rangle_{\Omega_\kappa,\Omega}\\
&\quad+\nabla\cdot\left\langle\rho_p\left(\psi_p-\psi^{\overline{p}}\right)\left(\mathbf{v}_s-\mathbf{v}^{\overline{s}}\right)\right\rangle_{\Omega_p,\Omega}=0
\end{aligned}\tag{4.55}$$

Two mass transfer terms involving the p phase have been defined. Recall:

$$\overset{n\to p}{M}=-\epsilon^p\rho^p R_d \tag{4.56}$$

$$\overset{f\to p}{M}=\epsilon^p\rho^p\mu^*_{max}Y\left(\frac{\epsilon^f\rho^f\omega^{i\overline{f}}}{K_s+\epsilon^f\rho^f\omega^{i\overline{f}}}\right) \tag{4.57}$$

Input these definitions into the energy equation and substitute the constitutive form of the solid stress tensor ($\mathbf{t}^{\overline{\overline{p}}}=\mathbf{t}^p$).

$$\begin{aligned}
&\frac{\partial}{\partial t}\left(E^{\overline{\overline{p}}}+\frac{1}{2}\epsilon^p\rho^p\mathbf{v}^{\overline{s}}\cdot\mathbf{v}^{\overline{s}}+\epsilon^p\rho^p\psi^{\overline{p}}+\epsilon^p\rho^p K_E^{\overline{\overline{p}}}\right)\\
&\quad+\nabla\cdot\left[\left(E^{\overline{\overline{p}}}+\frac{1}{2}\epsilon^p\rho^p\mathbf{v}^{\overline{s}}\cdot\mathbf{v}^{\overline{s}}+\epsilon^p\rho^p\psi^{\overline{p}}+\epsilon^p\rho^p K_E^{\overline{\overline{p}}}\right)\mathbf{v}^{\overline{s}}\right]\\
&\quad-\nabla\cdot\left(\epsilon^p\mathbf{t}^p\cdot\mathbf{v}^{\overline{s}}+\epsilon^p\mathbf{q}^{\overline{\overline{p}}}\right)-\epsilon^p h^{\overline{\overline{p}}}-\left\langle\rho_p\frac{\partial\psi_p}{\partial t}\right\rangle_{\Omega_p,\Omega}\\
&\quad-\left(\frac{1}{2}\mathbf{v}_s^{\overline{fp}}\cdot\mathbf{v}_s^{\overline{fp}}+\psi_p^{\overline{fp}}+\frac{E_p^{\overline{\overline{fp}}}}{\epsilon^{fp}\rho_p^{\overline{fp}}}+K_{Ep}^{\overline{\overline{fp}}}\right)\left(\epsilon^p\rho^p\mu^*_{max}Y\left(\frac{\epsilon^f\rho^f\omega^{i\overline{f}}}{K_s+\epsilon^f\rho^f\omega^{i\overline{f}}}\right)\right)\\
&\quad+\left(\frac{1}{2}\mathbf{v}_s^{\overline{np}}\cdot\mathbf{v}_s^{\overline{np}}+\psi_p^{\overline{np}}+\frac{E_p^{\overline{\overline{np}}}}{\epsilon^{np}\rho_p^{\overline{np}}}+K_{Ep}^{\overline{\overline{np}}}\right)\left(\epsilon^p\rho^p R_d\right)
\end{aligned}$$

$$
-\sum_{\kappa\in\mathfrak{I}cp}\left[\mathbf{v}_s^{\overline{\kappa}}\cdot\overset{\kappa\to p}{\mathbf{T}}+\overset{\kappa\to p}{Q}\right]
$$

$$
+\sum_{\kappa\in\mathfrak{I}cp}\left\langle\mathbf{n}_p\rho_p\cdot\left(\psi_p-\psi_p^{\overline{\kappa}}\right)\left(\mathbf{v}_s-\mathbf{v}_\kappa\right)\right\rangle_{\Omega_\kappa,\Omega}=0 \tag{4.58}
$$

4.3.2 Necrotic Tumor Tissue: n

The conservation of total energy equation, specified for the necrotic tumor phase:

$$
\begin{aligned}
&\frac{\partial}{\partial t}\left(E^{\overline{\overline{n}}}+\frac{1}{2}\epsilon^n\rho^n\mathbf{v}^{\overline{n}}\cdot\mathbf{v}^{\overline{n}}+\epsilon^n\rho^n\psi^{\overline{n}}+\epsilon^n\rho^n K_E^{\overline{\overline{n}}}\right)\\
&\quad+\nabla\cdot\left[\left(E^{\overline{\overline{n}}}+\frac{1}{2}\epsilon^n\rho^n\mathbf{v}^{\overline{n}}\cdot\mathbf{v}^{\overline{n}}+\epsilon^n\rho^n\psi^{\overline{n}}+\epsilon^n\rho^n K_E^{\overline{\overline{n}}}\right)\mathbf{v}^{\overline{n}}\right]\\
&\quad-\nabla\cdot\left(\epsilon^n\mathbf{t}^{\overline{\overline{n}}}\cdot\mathbf{v}^{\overline{n}}+\epsilon^n\mathbf{q}^{\overline{\overline{n}}}\right)-\epsilon^n h^{\overline{\overline{n}}}-\left\langle\rho_n\frac{\partial\psi_n}{\partial t}\right\rangle_{\Omega_n,\Omega}\\
&\quad-\sum_{\kappa\in\mathfrak{I}cn}\left[\left(\frac{1}{2}\mathbf{v}_n^{\overline{\kappa}}\cdot\mathbf{v}_n^{\overline{\kappa}}+\psi_n^{\overline{\kappa}}+\frac{E_n^{\overline{\overline{\kappa}}}}{\epsilon^\kappa\rho_n^{\overline{\kappa}}}+K_{En}^{\overline{\overline{\kappa}}}\right)\overset{\kappa\to n}{M}+\mathbf{v}_n^{\overline{\kappa}}\cdot\overset{\kappa\to n}{\mathbf{T}}+\overset{\kappa\to n}{Q}\right]\\
&\quad+\sum_{\kappa\in\mathfrak{I}cn}\left\langle\mathbf{n}_n\rho_n\cdot\left(\psi_n-\psi_n^{\overline{\kappa}}\right)\left(\mathbf{v}_n-\mathbf{v}_\kappa\right)\right\rangle_{\Omega_\kappa,\Omega}\\
&\quad+\nabla\cdot\left\langle\rho_n\left(\psi_n-\psi^{\overline{n}}\right)\left(\mathbf{v}_n-\mathbf{v}^{\overline{n}}\right)\right\rangle_{\Omega_n,\Omega}=0
\end{aligned} \tag{4.59}
$$

Substitute $\mathbf{v}^{\overline{s}}$ for $\mathbf{v}^{\overline{n}}$.

$$
\begin{aligned}
&\frac{\partial}{\partial t}\left(E^{\overline{\overline{n}}}+\frac{1}{2}\epsilon^n\rho^n\mathbf{v}^{\overline{s}}\cdot\mathbf{v}^{\overline{s}}+\epsilon^n\rho^n\psi^{\overline{n}}+\epsilon^n\rho^n K_E^{\overline{\overline{n}}}\right)\\
&\quad+\nabla\cdot\left[\left(E^{\overline{\overline{n}}}+\frac{1}{2}\epsilon^n\rho^n\mathbf{v}^{\overline{s}}\cdot\mathbf{v}^{\overline{s}}+\epsilon^n\rho^n\psi^{\overline{n}}+\epsilon^n\rho^n K_E^{\overline{\overline{n}}}\right)\mathbf{v}^{\overline{s}}\right]\\
&\quad-\nabla\cdot\left(\epsilon^n\mathbf{t}^{\overline{\overline{n}}}\cdot\mathbf{v}^{\overline{s}}+\epsilon^n\mathbf{q}^{\overline{\overline{n}}}\right)-\epsilon^n h^{\overline{\overline{n}}}-\left\langle\rho_n\frac{\partial\psi_n}{\partial t}\right\rangle_{\Omega_n,\Omega}\\
&\quad-\sum_{\kappa\in\mathfrak{I}cn}\left[\left(\frac{1}{2}\mathbf{v}_s^{\overline{\kappa}}\cdot\mathbf{v}_s^{\overline{\kappa}}+\psi_n^{\overline{\kappa}}+\frac{E_n^{\overline{\overline{\kappa}}}}{\epsilon^\kappa\rho_n^{\overline{\kappa}}}+K_{En}^{\overline{\overline{\kappa}}}\right)\overset{\kappa\to n}{M}+\mathbf{v}_s^{\overline{\kappa}}\cdot\overset{\kappa\to n}{\mathbf{T}}+\overset{\kappa\to n}{Q}\right]\\
&\quad+\sum_{\kappa\in\mathfrak{I}cn}\left\langle\mathbf{n}_n\rho_n\cdot\left(\psi_n-\psi_n^{\overline{\kappa}}\right)\left(\mathbf{v}_s-\mathbf{v}_\kappa\right)\right\rangle_{\Omega_\kappa,\Omega}\\
&\quad+\nabla\cdot\left\langle\rho_n\left(\psi_n-\psi^{\overline{n}}\right)\left(\mathbf{v}_s-\mathbf{v}^{\overline{s}}\right)\right\rangle_{\Omega_n,\Omega}=0
\end{aligned} \tag{4.60}
$$

Insert the constitutive relations for mass transfer $\left(\overset{p\to n}{M} = \epsilon^p \rho^p R_d\right)$ and the stress tensor $\left(\mathbf{t}^{\overline{\overline{n}}} = \mathbf{t}^n\right)$.

$$
\begin{aligned}
&\frac{\partial}{\partial t}\left(E^{\overline{\overline{n}}} + \frac{1}{2}\epsilon^n \rho^n \mathbf{v}^{\overline{s}}\cdot\mathbf{v}^{\overline{s}} + \epsilon^n \rho^n \psi^{\overline{n}} + \epsilon^n \rho^n K_E^{\overline{\overline{n}}}\right) \\
&\quad + \nabla\cdot\left[\left(E^{\overline{\overline{p}}} + \frac{1}{2}\epsilon^p \rho^p \mathbf{v}^{\overline{s}}\cdot\mathbf{v}^{\overline{s}} + \epsilon^p \rho^p \psi^{\overline{p}} + \epsilon^p \rho^p K_E^{\overline{\overline{p}}}\right)\mathbf{v}^{\overline{s}}\right] \\
&\quad - \nabla\cdot\left(\epsilon^n \mathbf{t}^n\cdot\mathbf{v}^{\overline{n}} + \epsilon^n \mathbf{q}^{\overline{\overline{n}}}\right) - \epsilon^n h^{\overline{\overline{n}}} - \left\langle \rho_n \frac{\partial \psi_n}{\partial t}\right\rangle_{\Omega_n,\Omega} \\
&\quad - \left(\frac{1}{2}\mathbf{v}_s^{\overline{np}}\cdot\mathbf{v}_s^{\overline{np}} + \psi_n^{\overline{np}} + \frac{E_p^{\overline{\overline{np}}}}{\epsilon^{np}\rho_n^{\overline{\overline{np}}}} + K_{En}^{\overline{\overline{np}}}\right)\left(\epsilon^p \rho^p R_d\right) \\
&\quad - \sum_{\kappa\in\Im cn}\left[\mathbf{v}_n^{\overline{\kappa}}\cdot\overset{\kappa\to n}{\mathbf{T}} + \overset{\kappa\to n}{Q}\right] \\
&\quad + \sum_{\kappa\in\Im cn}\left\langle \mathbf{n}_n \rho_n\cdot\left(\psi_n - \psi_n^{\overline{\kappa}}\right)\left(\mathbf{v}_s - \mathbf{v}_\kappa\right)\right\rangle_{\Omega_\kappa,\Omega} = 0
\end{aligned}
\tag{4.61}
$$

4.3.3 Host Tissue: h

General conservation of mass for phase h:

$$
\begin{aligned}
&\frac{\partial}{\partial t}\left(E^{\overline{\overline{h}}} + \frac{1}{2}\epsilon^h \rho^h \mathbf{v}^{\overline{h}}\cdot\mathbf{v}^{\overline{h}} + \epsilon^h \rho^h \psi^{\overline{h}} + \epsilon^h \rho^h K_E^{\overline{\overline{h}}}\right) \\
&\quad + \nabla\cdot\left[\left(E^{\overline{\overline{h}}} + \frac{1}{2}\epsilon^h \rho^h \mathbf{v}^{\overline{h}}\cdot\mathbf{v}^{\overline{h}} + \epsilon^h \rho^h \psi^{\overline{h}} + \epsilon^h \rho^h K_E^{\overline{\overline{h}}}\right)\mathbf{v}^{\overline{h}}\right] \\
&\quad - \nabla\cdot\left(\epsilon^h \mathbf{t}^{\overline{\overline{h}}}\cdot\mathbf{v}^{\overline{h}} + \epsilon^h \mathbf{q}^{\overline{\overline{h}}}\right) - \epsilon^h h^{\overline{\overline{h}}} - \left\langle \rho_h \frac{\partial \psi_h}{\partial t}\right\rangle_{\Omega_h,\Omega} \\
&\quad - \sum_{\kappa\in\Im ch}\left[\left(\frac{1}{2}\mathbf{v}_h^{\overline{\kappa}}\cdot\mathbf{v}_h^{\overline{\kappa}} + \psi_h^{\overline{\kappa}} + \frac{E_h^{\overline{\overline{\kappa}}}}{\epsilon^{\kappa}\rho_h^{\overline{\overline{\kappa}}}} + K_{Eh}^{\overline{\overline{\kappa}}}\right)\overset{\kappa\to h}{M} + \mathbf{v}_h^{\overline{\kappa}}\cdot\overset{\kappa\to h}{\mathbf{T}} + \overset{\kappa\to h}{Q}\right] \\
&\quad + \sum_{\kappa\in\Im ch}\left\langle \mathbf{n}_h \rho_h\cdot\left(\psi_h - \psi_h^{\overline{\kappa}}\right)\left(\mathbf{v}_h - \mathbf{v}_\kappa\right)\right\rangle_{\Omega_\kappa,\Omega} \\
&\quad + \nabla\cdot\left\langle \rho_h\left(\psi_h - \psi^{\overline{h}}\right)\left(\mathbf{v}_h - \mathbf{v}^{\overline{h}}\right)\right\rangle_{\Omega_h,\Omega} = 0
\end{aligned}
\tag{4.62}
$$

Substitute the solid velocity for the velocity of the host tissue phase.

$$
\begin{aligned}
&\frac{\partial}{\partial t}\left(E^{\overline{\overline{h}}} + \frac{1}{2}\epsilon^h\rho^h\mathbf{v}^{\overline{s}}\cdot\mathbf{v}^{\overline{s}} + \epsilon^h\rho^h\psi^{\overline{h}} + \epsilon^h\rho^h K_E^{\overline{\overline{h}}}\right) \\
&\quad + \nabla\cdot\left[\left(E^{\overline{\overline{h}}} + \frac{1}{2}\epsilon^h\rho^h\mathbf{v}^{\overline{s}}\cdot\mathbf{v}^{\overline{s}} + \epsilon^h\rho^h\psi^{\overline{h}} + \epsilon^h\rho^h K_E^{\overline{\overline{h}}}\right)\mathbf{v}^{\overline{s}}\right] \\
&\quad - \nabla\cdot\left(\epsilon^h\mathbf{t}^{\overline{\overline{h}}}\cdot\mathbf{v}^{\overline{s}} + \epsilon^h\mathbf{q}^{\overline{\overline{h}}}\right) - \epsilon^h h^{\overline{\overline{h}}} - \left\langle\rho_h\frac{\partial\psi_h}{\partial t}\right\rangle_{\Omega_h,\Omega} \\
&\quad - \sum_{\kappa\in\Im ch}\left[\left(\frac{1}{2}\mathbf{v}_s^{\overline{\kappa}}\cdot\mathbf{v}_s^{\overline{\kappa}} + \psi_h^{\overline{\kappa}} + \frac{E_h^{\overline{\overline{\kappa}}}}{\epsilon^\kappa\rho_h^{\overline{\kappa}}} + K_{Eh}^{\overline{\overline{\kappa}}}\right)\overset{\kappa\to h}{M} + \mathbf{v}_s^{\overline{\kappa}}\cdot\overset{\kappa\to h}{\mathbf{T}} + \overset{\kappa\to h}{Q}\right] \\
&\quad + \sum_{\kappa\in\Im ch}\left\langle\mathbf{n}_h\rho_h\cdot\left(\psi_h - \psi_h^{\overline{\kappa}}\right)\left(\mathbf{v}_s - \mathbf{v}_\kappa\right)\right\rangle_{\Omega_\kappa,\Omega} \\
&\quad + \nabla\cdot\left\langle\rho_h\left(\psi_h - \psi^{\overline{h}}\right)\left(\mathbf{v}_s - \mathbf{v}^{\overline{s}}\right)\right\rangle_{\Omega_h,\Omega} = 0
\end{aligned}
\tag{4.63}
$$

There are no mass transfers to or from the host tissue phase, so that term can be dropped. Also substitute $\mathbf{t}^h$ for $\mathbf{t}^{\overline{\overline{h}}}$.

$$
\begin{aligned}
&\frac{\partial}{\partial t}\left(E^{\overline{\overline{h}}} + \frac{1}{2}\epsilon^h\rho^h\mathbf{v}^{\overline{s}}\cdot\mathbf{v}^{\overline{s}} + \epsilon^h\rho^h\psi^{\overline{h}} + \epsilon^h\rho^h K_E^{\overline{\overline{h}}}\right) \\
&\quad + \nabla\cdot\left[\left(E^{\overline{\overline{h}}} + \frac{1}{2}\epsilon^h\rho^h\mathbf{v}^{\overline{s}}\cdot\mathbf{v}^{\overline{s}} + \epsilon^h\rho^h\psi^{\overline{h}} + \epsilon^h\rho^h K_E^{\overline{\overline{h}}}\right)\mathbf{v}^{\overline{s}}\right] \\
&\quad - \nabla\cdot\left(\epsilon^h\mathbf{t}^h\cdot\mathbf{v}^{\overline{s}} + \epsilon^h\mathbf{q}^{\overline{\overline{h}}}\right) - \epsilon^h h^{\overline{\overline{h}}} - \left\langle\rho_h\frac{\partial\psi_h}{\partial t}\right\rangle_{\Omega_h,\Omega} \\
&\quad - \sum_{\kappa\in\Im ch}\left[\mathbf{v}_h^{\overline{\kappa}}\cdot\overset{\kappa\to h}{\mathbf{T}} + \overset{\kappa\to h}{Q}\right] \\
&\quad + \sum_{\kappa\in\Im ch}\left\langle\mathbf{n}_h\rho_h\cdot\left(\psi_h - \psi_h^{\overline{\kappa}}\right)\left(\mathbf{v}_h - \mathbf{v}_\kappa\right)\right\rangle_{\Omega_\kappa,\Omega} = 0
\end{aligned}
\tag{4.64}
$$

4.3.4 Interstitial Fluid: f

General conservation of total energy for the f phase.

$$
\frac{\partial}{\partial t}\left(E^{\overline{\overline{f}}} + \frac{1}{2}\epsilon^f\rho^f\mathbf{v}^{\overline{f}}\cdot\mathbf{v}^{\overline{f}} + \epsilon^f\rho^f\psi^{\overline{f}} + \epsilon^f\rho^f K_E^{\overline{\overline{f}}}\right)
$$

$$
\begin{aligned}
&+ \nabla\cdot \left[\left(E^{\overline{\overline{f}}} + \frac{1}{2}\epsilon^f \rho^f \mathbf{v}^{\overline{f}}\cdot\mathbf{v}^{\overline{f}} + \epsilon^f \rho^f \psi^{\overline{f}} + \epsilon^f \rho^f K_E^{\overline{\overline{f}}} \right) \mathbf{v}^{\overline{f}} \right] \\
&- \nabla\cdot \left(\epsilon^f \mathbf{t}^{\overline{\overline{f}}}\cdot\mathbf{v}^{\overline{f}} + \epsilon^f \mathbf{q}^{\overline{\overline{f}}} \right) - \epsilon^f h^{\overline{\overline{f}}} - \left\langle \rho_f \frac{\partial \psi_f}{\partial t} \right\rangle_{\Omega_f,\Omega} \\
&- \sum_{\kappa\in\Im cf} \left[\left(\frac{1}{2}\mathbf{v}_f^{\overline{\kappa}}\cdot\mathbf{v}_f^{\overline{\kappa}} + \psi_f^{\overline{\kappa}} + \frac{E_f^{\overline{\overline{\kappa}}}}{\epsilon^\kappa \rho_f^{\overline{\kappa}}} + K_{Ef}^{\overline{\overline{\kappa}}} \right) \overset{\kappa\to f}{M} + \mathbf{v}_f^{\overline{\kappa}}\cdot \overset{\kappa\to f}{\mathbf{T}} + \overset{\kappa\to f}{Q} \right] \\
&+ \sum_{\kappa\in\Im cf} \left\langle \mathbf{n}_f \rho_f \cdot \left(\psi_f - \psi_f^{\overline{\kappa}} \right) \left(\mathbf{v}_f - \mathbf{v}_\kappa \right) \right\rangle_{\Omega_\kappa,\Omega} \\
&+ \nabla\cdot \left\langle \rho_f \left(\psi_f - \psi^{\overline{f}} \right) \left(\mathbf{v}_f - \mathbf{v}^{\overline{f}} \right) \right\rangle_{\Omega_f,\Omega} = 0
\end{aligned} \tag{4.65}
$$

Recall that the constitutive form of the stress tensor is $\mathbf{t}^{\overline{\overline{f}}} = -p^f \mathsf{I}$. This can be put into the stress tensor divergence term.

$$
-\nabla\cdot \left(\epsilon^f \mathbf{t}^{\overline{\overline{f}}}\cdot\mathbf{v}^{\overline{f}} \right) = \nabla\cdot \left(\epsilon^f p^f \mathsf{I}\cdot\mathbf{v}^{\overline{f}} \right) \tag{4.66}
$$

$$
= \nabla\cdot \left(\epsilon^f p^f \mathbf{v}^{\overline{f}} \right) \tag{4.67}
$$

One can also use the constitutive form of $\overset{\kappa\to f}{\mathbf{T}}$.

$$
\sum_{\kappa\in\Im cw} \overset{\kappa\to w}{\mathbf{T}} = p^w \nabla \epsilon^w - \mathsf{K}\cdot \left(\mathbf{v}^{\overline{w}} - \mathbf{v}^{\overline{s}} \right) \tag{4.68}
$$

$$
\sum_{\kappa\in\Im cf} \mathbf{v}_f^{\overline{\kappa}} \overset{\kappa\to f}{\mathbf{T}} = \mathbf{v}_f^{\overline{\kappa}}\cdot \left[p^f \nabla \epsilon^f - \mathsf{K}\cdot \left(\mathbf{v}^{\overline{f}} - \mathbf{v}^{\overline{s}} \right) \right] \tag{4.69}
$$

Insert these simplifications into the equation.

$$
\begin{aligned}
&\frac{\partial}{\partial t} \left(E^{\overline{\overline{f}}} + \frac{1}{2}\epsilon^f \rho^f \mathbf{v}^{\overline{f}}\cdot\mathbf{v}^{\overline{f}} + \epsilon^f \rho^f \psi^{\overline{f}} + \epsilon^f \rho^f K_E^{\overline{\overline{f}}} \right) \\
&\quad + \nabla\cdot \left[\left(E^{\overline{\overline{f}}} + \frac{1}{2}\epsilon^f \rho^f \mathbf{v}^{\overline{f}}\cdot\mathbf{v}^{\overline{f}} + \epsilon^f \rho^f \psi^{\overline{f}} + \epsilon^f \rho^f K_E^{\overline{\overline{f}}} \right) \mathbf{v}^{\overline{f}} \right] \\
&\quad - \nabla\cdot \left(\epsilon^f p^f \mathbf{v}^{\overline{f}} + \epsilon^f \mathbf{q}^{\overline{\overline{f}}} \right) - \epsilon^f h^{\overline{\overline{f}}} - \left\langle \rho_f \frac{\partial \psi_f}{\partial t} \right\rangle_{\Omega_f,\Omega}
\end{aligned}
$$

$$
\begin{aligned}
&- \sum_{\kappa \in \Im c f} \left[\left(\frac{1}{2} \mathbf{v}_f^{\overline{\kappa}} \cdot \mathbf{v}_f^{\overline{\kappa}} + \psi_f^{\overline{\kappa}} + \frac{E_f{}^{\overline{\overline{\kappa}}}}{\epsilon^\kappa \rho_f^\kappa} + K_{Ef}^{\overline{\overline{\kappa}}} \right) \overset{\kappa \to f}{M} \right] \\
&- \sum_{\kappa \in \Im c f} \left(\mathbf{v}_f^{\overline{fs}} \cdot \left[p^f \nabla \epsilon^f - \mathsf{K} \cdot \left(\mathbf{v}^{\overline{f}} - \mathbf{v}^{\overline{s}} \right) \right] + \overset{\kappa \to f}{Q} \right) \\
&+ \sum_{\kappa \in \Im c f} \left\langle \mathbf{n}_f \rho_f \cdot \left(\psi_f - \psi_f^{\overline{\kappa}} \right) \left(\mathbf{v}_f - \mathbf{v}_\kappa \right) \right\rangle_{\Omega_\kappa, \Omega} \\
&+ \nabla \cdot \left\langle \rho_f \left(\psi_f - \psi^{\overline{f}} \right) \left(\mathbf{v}_f - \mathbf{v}^{\overline{f}} \right) \right\rangle_{\Omega_b, \Omega} = 0
\end{aligned} \tag{4.70}
$$

Also input the previously established mass transfer terms: $\overset{b \to f}{M}$ and $\overset{p \to f}{M}$.

$$
\overset{b \to f}{M} = Y \overset{ib \to if}{M} \tag{4.71}
$$

$$
\overset{p \to f}{M} = - \overset{f \to p}{M} = - \epsilon^p \rho^p \mu^*_{max} Y \left(\frac{\epsilon^f \rho^f \omega^{i\overline{f}}}{K_s + \epsilon^f \rho^f \omega^{i\overline{f}}} \right) \tag{4.72}
$$

$$
\begin{aligned}
&\frac{\partial}{\partial t} \left(E^{\overline{\overline{f}}} + \frac{1}{2} \epsilon^f \rho^f \mathbf{v}^{\overline{f}} \cdot \mathbf{v}^{\overline{f}} + \epsilon^f \rho^f \psi^{\overline{f}} + \epsilon^f \rho^f K_E^{\overline{\overline{f}}} \right) \\
&\quad + \nabla \cdot \left[\left(E^{\overline{\overline{f}}} + \frac{1}{2} \epsilon^f \rho^f \mathbf{v}^{\overline{f}} \cdot \mathbf{v}^{\overline{f}} + \epsilon^f \rho^f \psi^{\overline{f}} + \epsilon^f \rho^f K_E^{\overline{\overline{f}}} \right) \mathbf{v}^{\overline{f}} \right] \\
&\quad - \nabla \cdot \left(\epsilon^f p^f \mathbf{v}^{\overline{f}} + \epsilon^f \mathbf{q}^{\overline{\overline{f}}} \right) - \epsilon^f h^{\overline{\overline{f}}} - \left\langle \rho_f \frac{\partial \psi_f}{\partial t} \right\rangle_{\Omega_f, \Omega} \\
&\quad + \sum_{\kappa \in \Im c f} \left[\left(\frac{1}{2} \mathbf{v}_f^{\overline{\kappa}} \cdot \mathbf{v}_f^{\overline{\kappa}} + \psi_f^{\overline{\kappa}} + \frac{E_f{}^{\overline{\overline{\kappa}}}}{\epsilon^\kappa \rho_f^\kappa} + K_{Ef}^{\overline{\overline{\kappa}}} \right) \epsilon^p \rho^p \mu^*_{max} Y \left(\frac{\epsilon^f \rho^f \omega^{i\overline{f}}}{K_s + \epsilon^f \rho^f \omega^{i\overline{f}}} \right) \right] \\
&\quad - \sum_{\kappa \in \Im c f} \left[\left(\frac{1}{2} \mathbf{v}_f^{\overline{\kappa}} \cdot \mathbf{v}_f^{\overline{\kappa}} + \psi_f^{\overline{\kappa}} + \frac{E_f{}^{\overline{\overline{\kappa}}}}{\epsilon^\kappa \rho_f^\kappa} + K_{Ef}^{\overline{\overline{\kappa}}} \right) \left(Y \overset{ib \to if}{M} \right) \right] \\
&\quad - \sum_{\kappa \in \Im c f} \left(\mathbf{v}_f^{\overline{fs}} \cdot \left[p^f \nabla \epsilon^f - \mathsf{K} \cdot \left(\mathbf{v}^{\overline{f}} - \mathbf{v}^{\overline{s}} \right) \right] + \overset{\kappa \to f}{Q} \right) \\
&\quad + \sum_{\kappa \in \Im c f} \left\langle \mathbf{n}_f \rho_f \cdot \left(\psi_f - \psi_f^{\overline{\kappa}} \right) \left(\mathbf{v}_f - \mathbf{v}_\kappa \right) \right\rangle_{\Omega_\kappa, \Omega} \\
&\quad + \nabla \cdot \left\langle \rho_f \left(\psi_f - \psi^{\overline{f}} \right) \left(\mathbf{v}_f - \mathbf{v}^{\overline{f}} \right) \right\rangle_{\Omega_b, \Omega} = 0
\end{aligned} \tag{4.73}
$$

4.3.5 Blood: b

General conservation of total energy for the b phase.

$$\begin{aligned}
&\frac{\partial}{\partial t}\left(E^{\overline{\overline{b}}} + \frac{1}{2}\epsilon^b\rho^b\mathbf{v}^{\overline{b}}\cdot\mathbf{v}^{\overline{b}} + \epsilon^b\rho^b\psi^{\overline{b}} + \epsilon^b\rho^b K_E^{\overline{\overline{b}}}\right)\\
&\quad + \nabla\cdot\left[\left(E^{\overline{\overline{b}}} + \frac{1}{2}\epsilon^b\rho^b\mathbf{v}^{\overline{b}}\cdot\mathbf{v}^{\overline{b}} + \epsilon^b\rho^b\psi^{\overline{b}} + \epsilon^b\rho^b K_E^{\overline{\overline{b}}}\right)\mathbf{v}^{\overline{b}}\right]\\
&\quad - \nabla\cdot\left(\epsilon^b\mathbf{t}^{\overline{\overline{b}}}\cdot\mathbf{v}^{\overline{b}} + \epsilon^b\mathbf{q}^{\overline{\overline{b}}}\right) - \epsilon^b h^{\overline{\overline{b}}} - \left\langle \rho_b\frac{\partial\psi_b}{\partial t}\right\rangle_{\Omega_b,\Omega}\\
&\quad - \sum_{\kappa\in\mathfrak{I}cb}\left[\left(\frac{1}{2}\mathbf{v}_b^{\overline{\kappa}}\cdot\mathbf{v}_b^{\overline{\kappa}} + \psi_b^{\overline{\kappa}} + \frac{E_b^{\overline{\overline{\kappa}}}}{\epsilon^\kappa\rho_b^{\overline{\kappa}}} + K_{Eb}^{\overline{\overline{\kappa}}}\right)\overset{\kappa\to b}{M} + \mathbf{v}_b^{\overline{\kappa}}\cdot\overset{\kappa\to b}{\mathbf{T}} + \overset{\kappa\to b}{Q}\right]\\
&\quad + \sum_{\kappa\in\mathfrak{I}cb}\left\langle \mathbf{n}_b\rho_b\cdot\left(\psi_b - \psi_b^{\overline{\kappa}}\right)\left(\mathbf{v}_b - \mathbf{v}_\kappa\right)\right\rangle_{\Omega_\kappa,\Omega}\\
&\quad + \nabla\cdot\left\langle \rho_b\left(\psi_b - \psi^{\overline{b}}\right)\left(\mathbf{v}_b - \mathbf{v}^{\overline{b}}\right)\right\rangle_{\Omega_b,\Omega} = 0
\end{aligned} \tag{4.74}$$

The constitutive form of the stress tensor $\left(\mathbf{t}^{\overline{\overline{b}}} = -p^b\mathbf{I}\right)$ can be put into the stress tensor divergence term.

$$-\nabla\cdot\left(\epsilon^b\mathbf{t}^{\overline{\overline{b}}}\cdot\mathbf{v}^{\overline{b}}\right) = \nabla\cdot\left(\epsilon^b p^b\mathbf{v}^{\overline{b}}\right) \tag{4.75}$$

The constitutive form of $\overset{\kappa\to b}{\mathbf{T}}$ can also be used.

$$\sum_{\kappa\in\mathfrak{I}cb}\mathbf{v}_f^{\overline{\kappa}}\overset{\kappa\to b}{\mathbf{T}} = \mathbf{v}_b^{\overline{\kappa}}\cdot\left[p^b\nabla\epsilon^b - \mathbf{K}\cdot\left(\mathbf{v}^{\overline{b}} - \mathbf{v}^{\overline{s}}\right)\right] \tag{4.76}$$

Insert these simplifications into the equation.

$$\begin{aligned}
&\frac{\partial}{\partial t}\left(E^{\overline{\overline{b}}} + \frac{1}{2}\epsilon^b\rho^b\mathbf{v}^{\overline{b}}\cdot\mathbf{v}^{\overline{b}} + \epsilon^b\rho^b\psi^{\overline{b}} + \epsilon^b\rho^b K_E^{\overline{\overline{b}}}\right)\\
&\quad + \nabla\cdot\left[\left(E^{\overline{\overline{b}}} + \frac{1}{2}\epsilon^b\rho^b\mathbf{v}^{\overline{b}}\cdot\mathbf{v}^{\overline{b}} + \epsilon^b\rho^b\psi^{\overline{b}} + \epsilon^b\rho^b K_E^{\overline{\overline{b}}}\right)\mathbf{v}^{\overline{b}}\right]\\
&\quad - \nabla\cdot\left(\epsilon^b p^b\mathbf{v}^{\overline{b}} + \epsilon^b\mathbf{q}^{\overline{\overline{b}}}\right) - \epsilon^b h^{\overline{\overline{b}}} - \left\langle \rho_b\frac{\partial\psi_b}{\partial t}\right\rangle_{\Omega_b,\Omega}
\end{aligned}$$

$$
\begin{aligned}
&- \sum_{\kappa \in \Im cb} \left[\left(\frac{1}{2} \mathbf{v}_b^{\overline{\kappa}} \cdot \mathbf{v}_b^{\overline{\kappa}} + \psi_b^{\overline{\kappa}} + \frac{E_b^{\overline{\overline{\kappa}}}}{\epsilon^\kappa \rho_b^\kappa} + K_{Eb}^{\overline{\overline{\kappa}}} \right) \overset{\kappa \to b}{M} \right] \\
&- \sum_{\kappa \in \Im cb} \left(\mathbf{v}_b^{\overline{bs}} \cdot \left[p^b \nabla \epsilon^b - \mathsf{K} \cdot \left(\mathbf{v}^{\overline{b}} - \mathbf{v}^{\overline{s}} \right) \right] + \overset{\kappa \to b}{Q} \right) \\
&+ \sum_{\kappa \in \Im cb} \left\langle \mathbf{n}_b \rho_b \cdot \left(\psi_b - \psi_b^{\overline{\kappa}} \right) \left(\mathbf{v}_b - \mathbf{v}_\kappa \right) \right\rangle_{\Omega_\kappa, \Omega} \\
&+ \nabla \cdot \left\langle \rho_b \left(\psi_b - \psi^{\overline{b}} \right) \left(\mathbf{v}_b - \mathbf{v}^{\overline{b}} \right) \right\rangle_{\Omega_b, \Omega} = 0
\end{aligned}
\tag{4.77}
$$

Finally, specify the mass transfer term as $-Y \overset{ib \to if}{M}$.

$$
\begin{aligned}
&\frac{\partial}{\partial t} \left(E^{\overline{\overline{b}}} + \frac{1}{2} \epsilon^b \rho^b \mathbf{v}^{\overline{b}} \cdot \mathbf{v}^{\overline{b}} + \epsilon^b \rho^b \psi^{\overline{b}} + \epsilon^b \rho^b K_E^{\overline{\overline{b}}} \right) \\
&\quad + \nabla \cdot \left[\left(E^{\overline{\overline{b}}} + \frac{1}{2} \epsilon^b \rho^b \mathbf{v}^{\overline{b}} \cdot \mathbf{v}^{\overline{b}} + \epsilon^b \rho^b \psi^{\overline{b}} + \epsilon^b \rho^b K_E^{\overline{\overline{b}}} \right) \mathbf{v}^{\overline{b}} \right] \\
&\quad - \nabla \cdot \left(\epsilon^b p^b \mathbf{v}^{\overline{b}} + \epsilon^b \mathbf{q}^{\overline{\overline{b}}} \right) - \epsilon^b h^{\overline{\overline{b}}} - \left\langle \rho_b \frac{\partial \psi_b}{\partial t} \right\rangle_{\Omega_b, \Omega} \\
&\quad + \left[\left(\frac{1}{2} \mathbf{v}_b^{\overline{bf}} \cdot \mathbf{v}_b^{\overline{bf}} + \psi_b^{\overline{bf}} + \frac{E_b^{\overline{\overline{bf}}}}{\epsilon^{bf} \rho_b^{bf}} + K_{Eb}^{\overline{\overline{bf}}} \right) Y \overset{ib \to if}{M} \right] \\
&\quad - \sum_{\kappa \in \Im cb} \left(\mathbf{v}_b^{\overline{bs}} \cdot \left[p^b \nabla \epsilon^b - \mathsf{K} \cdot \left(\mathbf{v}^{\overline{b}} - \mathbf{v}^{\overline{s}} \right) \right] + \overset{\kappa \to b}{Q} \right) \\
&\quad + \sum_{\kappa \in \Im cb} \left\langle \mathbf{n}_b \rho_b \cdot \left(\psi_b - \psi_b^{\overline{\kappa}} \right) \left(\mathbf{v}_b - \mathbf{v}_\kappa \right) \right\rangle_{\Omega_\kappa, \Omega} \\
&\quad + \nabla \cdot \left\langle \rho_b \left(\psi_b - \psi^{\overline{b}} \right) \left(\mathbf{v}_b - \mathbf{v}^{\overline{b}} \right) \right\rangle_{\Omega_b, \Omega} = 0
\end{aligned}
\tag{4.78}
$$

It is likely that, for the solid phase equations (equations (4.58), (4.61), (4.64)) the kinetic energy terms will be negligible compared to the potential and internal energy terms. Therefore, the terms including kinetic energy, $\frac{1}{2} \epsilon^s \rho^s \mathbf{v}^{\overline{s}} \cdot \mathbf{v}^{\overline{s}}$ and $\epsilon^s \rho^s K_E^{\overline{\overline{p}}}$, could be neglected. Another term likely to be small is energy transferred due to transfer of momentum $\left(\mathbf{v}_s^{\overline{s}} \overset{\kappa \to s}{\mathbf{T}} \right)$ so this term could also be neglected. Additionally, the last two terms where averaging operators remain are often assumed to be very small and are not included either the solid phases or fluid phases.

4.4 Entropy

Entropy is integral to the TCAT approach because it is used to constrain the conservation equations. Consider the general macroscale balance of entropy for a phase, derived in section 3.6.

$$\boldsymbol{\mathcal{S}}^{\overline{\overline{\alpha}}} = \frac{\partial \eta^{\overline{\overline{\alpha}}}}{\partial t} + \nabla\boldsymbol{\cdot} \left(\eta^{\overline{\overline{\alpha}}}\mathbf{v}^{\overline{\alpha}}\right) - \nabla\boldsymbol{\cdot} \left(\epsilon^{\alpha}\boldsymbol{\varphi}^{\overline{\overline{\alpha}}}\right) - \epsilon^{\alpha} b^{\alpha} - \sum_{\kappa\in\mathfrak{I}_{c\alpha}} \left(\overset{\kappa\to\alpha}{M}\frac{\eta^{\overline{\overline{\alpha}}}}{\epsilon^{\alpha}\rho^{\alpha}} + \overset{\kappa\to\alpha}{\Phi}\right) = \Lambda^{\overline{\overline{\alpha}}} \tag{4.79}$$

The balance of entropy equation includes terms for rate of accumulation $\left(\frac{\partial \eta^{\overline{\overline{\alpha}}}}{\partial t}\right)$, advection $\left(\nabla\boldsymbol{\cdot}\left(\eta^{\overline{\overline{\alpha}}}\mathbf{v}^{\overline{\alpha}}\right)\right)$, non-advective entropy flux $\left(\nabla\boldsymbol{\cdot}\left(\epsilon^{\alpha}\boldsymbol{\varphi}^{\overline{\overline{\alpha}}}\right)\right)$, body sources $(\epsilon^{\alpha}b^{\alpha})$, inter-phase transfer $\left(\sum_{\kappa\in\mathfrak{I}_{c\alpha}}\left(\overset{\kappa\to\alpha}{M}\frac{\eta^{\overline{\overline{\alpha}}}}{\epsilon^{\alpha}\rho^{\alpha}} + \overset{\kappa\to\alpha}{\Phi}\right)\right)$, and generation $\left(\Lambda^{\overline{\overline{\alpha}}}\right)$.

4.4.1 Viable Tumor Tissue: p

The balance of entropy equation for the p phase.

$$\frac{\partial \eta^{\overline{\overline{p}}}}{\partial t} + \nabla\boldsymbol{\cdot} \left(\eta^{\overline{\overline{p}}}\mathbf{v}^{\overline{p}}\right) - \nabla\boldsymbol{\cdot} \left(\epsilon^{p}\boldsymbol{\varphi}^{\overline{\overline{p}}}\right) - \epsilon^{p} b^{p} - \sum_{\kappa\in\mathfrak{I}cp} \left(\overset{\kappa\to p}{M}\frac{\eta^{\overline{\overline{p}}}}{\epsilon^{p}\rho^{p}} + \overset{\kappa\to p}{\Phi}\right) = \Lambda^{\overline{\overline{p}}} \tag{4.80}$$

The phases that transfer mass with the p phase are the n and f phases. Recall the definitions of the two mass transfer terms:

$$\overset{n\to p}{M} = -\epsilon^{p}\rho^{p}R_d \tag{4.81}$$

$$\overset{f\to p}{M} = \epsilon^{p}\rho^{p}\mu^{*}_{max}Y\left(\frac{\epsilon^{f}\rho^{f}\omega^{i\overline{f}}}{K_s + \epsilon^{f}\rho^{f}\omega^{i\overline{f}}}\right) \tag{4.82}$$

Therefore the entropy transfer terms can be rewritten as follows.

$$
\begin{aligned}
-\sum_{\kappa \in \mathfrak{I}cp} \left(\overset{\kappa \to p}{M} \frac{\eta^{\overline{\overline{p}}}}{\epsilon^p \rho^p} + \overset{\kappa \to p}{\Phi} \right) &= - \left(\frac{\eta^{\overline{\overline{p}}}}{\epsilon^p \rho^p} \right) \left(\overset{n \to p}{M} + \overset{f \to p}{M} \right) - \sum_{\kappa \in \mathfrak{I}cp} \overset{\kappa \to p}{\Phi} \\
&= - \left[\epsilon^p \rho^p \mu^*_{max} Y \left(\frac{\epsilon^f \rho^f \omega^{i\overline{f}}}{K_s + \epsilon^f \rho^f \omega^{i\overline{f}}} \right) \right] \left(\frac{\eta^{\overline{\overline{\alpha}}}}{\epsilon^\alpha \rho^\alpha} \right) \\
&\quad + \epsilon^p \rho^p R_d \left(\frac{\eta^{\overline{\overline{\alpha}}}}{\epsilon^\alpha \rho^\alpha} \right) - \sum_{\kappa \in \mathfrak{I}cp} \overset{\kappa \to p}{\Phi} \qquad (4.83)
\end{aligned}
$$

Using these definitions for the mass transfer terms, one can rewrite the balance of entropy equation for the viable tumor tissue phase.

$$
\begin{aligned}
\frac{\partial \eta^{\overline{\overline{p}}}}{\partial t} + \nabla\cdot \left(\eta^{\overline{\overline{p}}} \mathbf{v}^{\overline{p}} \right) - \nabla\cdot \left(\epsilon^p \boldsymbol{\varphi}^{\overline{\overline{p}}} \right) - \epsilon^p b^p \\
- \left[\epsilon^p \rho^p \mu^*_{max} Y \left(\frac{\epsilon^f \rho^f \omega^{i\overline{f}}}{K_s + \epsilon^f \rho^f \omega^{i\overline{f}}} \right) \right] \left(\frac{\eta^{\overline{\overline{\alpha}}}}{\epsilon^\alpha \rho^\alpha} \right) \\
+ \epsilon^p \rho^p R_d \left(\frac{\eta^{\overline{\overline{\alpha}}}}{\epsilon^\alpha \rho^\alpha} \right) - \sum_{\kappa \in \mathfrak{I}cp} \overset{\kappa \to p}{\Phi} = \Lambda^{\overline{\overline{\alpha}}} \qquad (4.84)
\end{aligned}
$$

And substitute the solid velocity, $\mathbf{v}^{\overline{s}}$, for $\mathbf{v}^{\overline{p}}$.

$$
\begin{aligned}
\frac{\partial \eta^{\overline{\overline{p}}}}{\partial t} + \nabla\cdot \left(\eta^{\overline{\overline{p}}} \mathbf{v}^{\overline{s}} \right) - \nabla\cdot \left(\epsilon^p \boldsymbol{\varphi}^{\overline{\overline{p}}} \right) - \epsilon^p b^p \\
- \left[\epsilon^p \rho^p \mu^*_{max} Y \left(\frac{\epsilon^f \rho^f \omega^{i\overline{f}}}{K_s + \epsilon^f \rho^f \omega^{i\overline{f}}} \right) \right] \left(\frac{\eta^{\overline{\overline{\alpha}}}}{\epsilon^\alpha \rho^\alpha} \right) \\
+ \epsilon^p \rho^p R_d \left(\frac{\eta^{\overline{\overline{\alpha}}}}{\epsilon^\alpha \rho^\alpha} \right) - \sum_{\kappa \in \mathfrak{I}cp} \overset{\kappa \to p}{\Phi} = \Lambda^{\overline{\overline{\alpha}}} \qquad (4.85)
\end{aligned}
$$

4.4.2 Necrotic Tumor Tissue: n

The balance of entropy equation for the n phase.

$$
\frac{\partial \eta^{\overline{\overline{n}}}}{\partial t} + \nabla\cdot \left(\eta^{\overline{\overline{n}}} \mathbf{v}^{\overline{n}} \right) - \nabla\cdot \left(\epsilon^n \boldsymbol{\varphi}^{\overline{\overline{n}}} \right) - \epsilon^n b^n
$$

$$- \sum_{\kappa \in \mathfrak{I}cn} \left(\overset{\kappa \to n}{M} \frac{\eta^{\overline{\overline{n}}}}{\epsilon^n \rho^n} + \overset{\kappa \to n}{\Phi} \right) = \Lambda^{\overline{\overline{n}}} \tag{4.86}$$

The only phase that transfers mass to the n phase is p:

$$\overset{p \to n}{M} = - \overset{n \to p}{M} = \epsilon^p \rho^p R_d \tag{4.87}$$

Substitute this definition and the solid phase velocity into the equation.

$$\begin{aligned} \frac{\partial \eta^{\overline{\overline{n}}}}{\partial t} + \nabla \cdot \left(\eta^{\overline{\overline{n}}} \mathbf{v}^{\overline{s}} \right) - \nabla \cdot \left(\epsilon^n \boldsymbol{\varphi}^{\overline{\overline{n}}} \right) - \epsilon^n b^n \\ - \epsilon^p \rho^p R_d \left(\frac{\eta^{\overline{\overline{\alpha}}}}{\epsilon^\alpha \rho^\alpha} \right) - \sum_{\kappa \in \mathfrak{I}cp} \overset{\kappa \to p}{\Phi} = \Lambda^{\overline{\overline{n}}} \end{aligned} \tag{4.88}$$

4.4.3 Host Tissue: h

The balance of entropy equation for the h phase.

$$\begin{aligned} \frac{\partial \eta^{\overline{\overline{h}}}}{\partial t} + \nabla \cdot \left(\eta^{\overline{\overline{h}}} \mathbf{v}^{\overline{h}} \right) - \nabla \cdot \left(\epsilon^h \boldsymbol{\varphi}^{\overline{\overline{h}}} \right) - \epsilon^h b^h \\ - \sum_{\kappa \in \mathfrak{I}ch} \left(\overset{\kappa \to h}{M} \frac{\eta^{\overline{\overline{h}}}}{\epsilon^h \rho^h} + \overset{\kappa \to h}{\Phi} \right) = \Lambda^{\overline{\overline{h}}} \end{aligned} \tag{4.89}$$

There are no transfer of mass terms including the h phase so the entropy due to mass transfer term can be dropped out of the equation.

$$\frac{\partial \eta^{\overline{\overline{h}}}}{\partial t} + \nabla \cdot \left(\eta^{\overline{\overline{h}}} \mathbf{v}^{\overline{h}} \right) - \nabla \cdot \left(\epsilon^h \boldsymbol{\varphi}^{\overline{\overline{h}}} \right) - \epsilon^h b^h - \sum_{\kappa \in \mathfrak{I}ch} \overset{\kappa \to h}{\Phi} = \Lambda^{\overline{\overline{h}}} \tag{4.90}$$

Substitute $\mathbf{v}^{\overline{s}}$ for $\mathbf{v}^{\overline{h}}$.

$$\frac{\partial \eta^{\overline{\overline{h}}}}{\partial t} + \nabla \cdot \left(\eta^{\overline{\overline{h}}} \mathbf{v}^{\overline{s}} \right) - \nabla \cdot \left(\epsilon^h \boldsymbol{\varphi}^{\overline{\overline{h}}} \right) - \epsilon^h b^h - \sum_{\kappa \in \mathfrak{I}ch} \overset{\kappa \to h}{\Phi} = \Lambda^{\overline{\overline{h}}} \tag{4.91}$$

4.4.4 Interstitial Fluid: f

The balance of entropy equation for the f phase.

$$\frac{\partial \eta^{\overline{\overline{f}}}}{\partial t} + \nabla\cdot\left(\eta^{\overline{\overline{f}}}\mathbf{v}^{\overline{f}}\right) - \nabla\cdot\left(\epsilon^f \boldsymbol{\varphi}^{\overline{\overline{f}}}\right) - \epsilon^f b^f - \sum_{\kappa\in\mathfrak{I}cf}\left(\overset{\kappa\to f}{M}\frac{\eta^{\overline{\overline{f}}}}{\epsilon^f\rho^f} + \overset{\kappa\to f}{\Phi}\right) = \Lambda^{\overline{\overline{f}}} \tag{4.92}$$

Inter-phase mass transfers involving the interstitial fluid phase include $\overset{p\to f}{M}$ and $\overset{b\to f}{M}$.

$$\overset{p\to f}{M} = -\overset{f\to p}{M} = -\epsilon^p\rho^p\mu^*_{max}Y\left(\frac{\epsilon^f\rho^f\omega^{i\overline{f}}}{K_s + \epsilon^f\rho^f\omega^{i\overline{f}}}\right) \tag{4.93}$$

$$\overset{b\to f}{M} = Y\overset{ib\to if}{M} \tag{4.94}$$

Substitute these definitions into the balance of entropy equation.

$$\frac{\partial \eta^{\overline{\overline{f}}}}{\partial t} + \nabla\cdot\left(\eta^{\overline{\overline{f}}}\mathbf{v}^{\overline{f}}\right) - \nabla\cdot\left(\epsilon^f \boldsymbol{\varphi}^{\overline{\overline{f}}}\right) - \epsilon^f b^f + \left[\epsilon^p\rho^p\mu^*_{max}Y\left(\frac{\epsilon^f\rho^f\omega^{i\overline{f}}}{K_s + \epsilon^f\rho^f\omega^{i\overline{f}}}\right)\right]\left(\frac{\eta^{\overline{\overline{f}}}}{\epsilon^f\rho^f}\right) - Y\overset{ib\to if}{M}\left(\frac{\eta^{\overline{\overline{f}}}}{\epsilon^f\rho^f}\right) - \sum_{\kappa\in\mathfrak{I}cf}\overset{\kappa\to b}{\Phi} = \Lambda^{\overline{\overline{f}}} \tag{4.95}$$

4.4.5 Blood: b

The balance of entropy equation for the b phase.

$$\frac{\partial \eta^{\overline{\overline{b}}}}{\partial t} + \nabla\cdot\left(\eta^{\overline{\overline{b}}}\mathbf{v}^{\overline{b}}\right) - \nabla\cdot\left(\epsilon^b \boldsymbol{\varphi}^{\overline{\overline{b}}}\right) - \epsilon^b b^b - \sum_{\kappa\in\mathfrak{I}cb}\left(\overset{\kappa\to b}{M}\frac{\eta^{\overline{\overline{b}}}}{\epsilon^b\rho^b} + \overset{\kappa\to b}{\Phi}\right) = \Lambda^{\overline{\overline{b}}} \tag{4.96}$$

The balance of entropy equation for the b phase must include mass transfer between the b and f phases, $\overset{f\rightarrow b}{M}$.

$$\overset{f\rightarrow b}{M} = -Y \overset{ib\rightarrow if}{M} \tag{4.97}$$

This definition can be inserted for the mass transfer term.

$$\begin{aligned} &\frac{\partial \eta^{\overline{\overline{b}}}}{\partial t} + \nabla\cdot \left(\eta^{\overline{\overline{b}}}\mathbf{v}^{\overline{b}}\right) - \nabla\cdot \left(\epsilon^b \boldsymbol{\varphi}^{\overline{\overline{b}}}\right) - \epsilon^b b^b \\ &+Y \overset{ib\rightarrow if}{M} \frac{\eta^{\overline{\overline{b}}}}{\epsilon^b \rho^b} - \sum_{\kappa\in\mathfrak{I}cb} \overset{\kappa\rightarrow b}{\Phi} = \Lambda^{\overline{\overline{b}}} \end{aligned} \tag{4.98}$$

The sum of the entropy equations over all the phases results in the total generation of entropy term to be greater than or equal to zero, in accordance with the the second law of thermodynamics. Therefore the entropy inequality can be added to the conservation of mass, momentum, and energy equations resulting in a single equation containing all the model variables, that is greater than or equal to zero. This is the constraint provided by the entropy equation. However, thermodynamic expressions are also required to tie everything together in the TCAT method.

4.5 Thermodynamics

The general forms of macroscale thermodynamic equations were derived in section 3.7. This section is divided into subsections of general solid and general fluid phases because they have different thermodynamic forms. Full closure of the thermodynamic equations is not part of this project, but these equations are included because of their use in the TCAT closure procedure using a constrained entropy inequality. Thermodynamic equations are used because the entropy equation used to constrain the system of equations does not share variables with the other conservation equations. Therefore, thermodynamics are used to link the conservation equations and balance of entropy together. Therefore, the purpose of this section is to present macroscale thermodynamic equations for each phase as a reference for creating a constrained entropy inequality.

4.5.1 Solid phases: p, n, h

General solid phase classical irreversible thermodynamic expression (using s as the general qualifier for the solid phase, and w as the general qualifier for the fluid phase).

$$
\begin{aligned}
\mathcal{T}^{\overline{s}} = & \frac{\mathrm{D}^{\overline{s}} E^{\overline{\overline{s}}}}{\mathrm{D}t} - \theta^{\overline{\overline{s}}} \frac{\mathrm{D}^{\overline{s}} \eta^{\overline{\overline{s}}}}{\mathrm{D}t} - \mu^{\overline{s}} \frac{\mathrm{D}^{\overline{s}} \left(\epsilon^s \rho^s\right)}{\mathrm{D}t} + p^s \frac{\mathrm{D}^{\overline{s}} \epsilon^s}{\mathrm{D}t} \\
& + \left\langle \eta_s \frac{\mathrm{D}_s(\theta_s - \theta^{\overline{\overline{s}}})}{\mathrm{D}t} + \rho_s \frac{\mathrm{D}_s(\mu_s - \mu^{\overline{s}})}{\mathrm{D}t} \right\rangle_{\Omega_s,\Omega} \\
& - \left\langle \left(\frac{\mathbf{C}_s}{j_s} \mathbf{:} \boldsymbol{\sigma}_s \right) \left(\mathbf{v}_{ws} - \mathbf{v}_s\right) \boldsymbol{\cdot} \mathbf{n}_s \right\rangle_{\Omega_{ws},\Omega} \\
& - \left\langle \mathbf{n}_s \boldsymbol{\cdot} \left[\frac{2}{j_s} \boldsymbol{\sigma}_s \mathbf{:} \left(\nabla_X \mathbf{x} \nabla_X \mathbf{x}\right) \boldsymbol{\cdot} \left(\mathbf{v}_s - \mathbf{v}^{\overline{s}}\right) \right] \right\rangle_{\Omega_{ws},\Omega} \\
& + \left\langle \left\{ \nabla \boldsymbol{\cdot} \left[\frac{2}{j_s} \boldsymbol{\sigma} \mathbf{:} \left(\nabla_X \mathbf{x} \nabla_X \mathbf{x}\right) \right] - \nabla \boldsymbol{\sigma}_s \mathbf{:} \frac{\mathbf{C}_s}{j_s} \right\} \boldsymbol{\cdot} \left(\mathbf{v}_s - \mathbf{v}^{\overline{s}}\right) \right\rangle_{\Omega_s,\Omega} \\
& + \epsilon^s \boldsymbol{\sigma}^s \mathbf{:} \frac{\mathbf{C}^s}{j^s} \mathbf{I} \mathbf{:} \mathbf{d}^{\overline{\overline{s}}} - \left\langle \frac{2}{j_s} \boldsymbol{\sigma}_s \mathbf{:} \left(\nabla_X \mathbf{x} \nabla_X \mathbf{x}\right) \right\rangle_{\Omega_s,\Omega} \mathbf{:} \mathbf{d}^{\overline{\overline{s}}} \\
& - \nabla \boldsymbol{\cdot} \left\langle \left[\frac{2}{j_s} \mathbf{:} \left(\nabla_X \mathbf{x} \nabla_X \mathbf{x}\right) - \boldsymbol{\sigma}_s \mathbf{:} \frac{\mathbf{C}_s}{j_s} \mathbf{I} \right] \boldsymbol{\cdot} \left(\mathbf{v}_s - \mathbf{v}^{\overline{s}}\right) \right\rangle_{\Omega_s,\Omega} = 0 \qquad (4.99)
\end{aligned}
$$

Because it has already been assumed that the solid phases move with the same velocity, the material derivatives, rate of strain tensors, and velocities will be left as referenced the the generic solid phase s.

Proliferative Tumor Tissue: p

$$
\frac{\mathrm{D}^{\overline{s}} E^{\overline{\overline{p}}}}{\mathrm{D}t} - \theta^{\overline{\overline{p}}} \frac{\mathrm{D}^{\overline{s}} \eta^{\overline{\overline{p}}}}{\mathrm{D}t} - \mu^{\overline{p}} \frac{\mathrm{D}^{\overline{s}} \left(\epsilon^p \rho^p\right)}{\mathrm{D}t} + p^p \frac{\mathrm{D}^{\overline{s}} \epsilon^p}{\mathrm{D}t}
$$

$$+\left\langle \eta_p \frac{\mathrm{D}_s(\theta_p - \theta^{\overline{\overline{p}}})}{\mathrm{D}t} + \rho_p \frac{\mathrm{D}_s(\mu_p - \mu^{\overline{p}})}{\mathrm{D}t} \right\rangle_{\Omega_p,\Omega}$$

$$-\left\langle \left(\frac{\mathbf{C}_p}{j_p} \boldsymbol{:} \boldsymbol{\sigma}_p \right) (\mathbf{v}_{wp} - \mathbf{v}_s) \boldsymbol{\cdot} \mathbf{n}_p \right\rangle_{\Omega_{wp},\Omega}$$

$$-\left\langle \mathbf{n}_p \boldsymbol{\cdot} \left[\frac{2}{j_p} \boldsymbol{\sigma}_p \boldsymbol{:} (\nabla_X \mathbf{x} \nabla_X \mathbf{x}) \boldsymbol{\cdot} \left(\mathbf{v}_s - \mathbf{v}^{\overline{s}} \right) \right] \right\rangle_{\Omega_{wp},\Omega}$$

$$+\left\langle \left\{ \nabla \boldsymbol{\cdot} \left[\frac{2}{j_p} \boldsymbol{\sigma}_p \boldsymbol{:} (\nabla_X \mathbf{x} \nabla_X \mathbf{x}) \right] - \nabla \boldsymbol{\sigma}_p \boldsymbol{:} \frac{\mathbf{C}_p}{j_p} \right\} \boldsymbol{\cdot} \left(\mathbf{v}_s - \mathbf{v}^{\overline{s}} \right) \right\rangle_{\Omega_p,\Omega}$$

$$+ \epsilon^p \boldsymbol{\sigma}^p \boldsymbol{:} \frac{\mathbf{C}^p}{j^p} \mathbf{I} \boldsymbol{:} \mathbf{d}^{\overline{\overline{s}}} - \left\langle \frac{2}{j_p} \boldsymbol{\sigma}_p \boldsymbol{:} (\nabla_X \mathbf{x} \nabla_X \mathbf{x}) \right\rangle_{\Omega_p,\Omega} \boldsymbol{:} \mathbf{d}^{\overline{\overline{s}}}$$

$$- \nabla \boldsymbol{\cdot} \left\langle \left[\frac{2}{j_p} \boldsymbol{:} (\nabla_X \mathbf{x} \nabla_X \mathbf{x}) - \boldsymbol{\sigma}_p \boldsymbol{:} \frac{\mathbf{C}^p}{j_p} \mathbf{I} \right] \boldsymbol{\cdot} \left(\mathbf{v}_s - \mathbf{v}^{\overline{s}} \right) \right\rangle_{\Omega_p,\Omega} = 0 \qquad (4.100)$$

Necrotic Tissue: n

$$\frac{\mathrm{D}^{\overline{s}} E^{\overline{\overline{n}}}}{\mathrm{D}t} - \theta^{\overline{\overline{n}}} \frac{\mathrm{D}^{\overline{s}} \eta^{\overline{\overline{n}}}}{\mathrm{D}t} - \mu^{\overline{n}} \frac{\mathrm{D}^{\overline{s}} \left(\epsilon^n \rho^n \right)}{\mathrm{D}t} + p^n \frac{\mathrm{D}^{\overline{s}} \epsilon^n}{\mathrm{D}t}$$

$$+\left\langle \eta_n \frac{\mathrm{D}_s(\theta_n - \theta^{\overline{\overline{n}}})}{\mathrm{D}t} + \rho_s \frac{\mathrm{D}_s(\mu_n - \mu^{\overline{n}})}{\mathrm{D}t} \right\rangle_{\Omega_n,\Omega}$$

$$-\left\langle \left(\frac{\mathbf{C}_n}{j_n} \boldsymbol{:} \boldsymbol{\sigma}_n \right) (\mathbf{v}_{wn} - \mathbf{v}_s) \boldsymbol{\cdot} \mathbf{n}_n \right\rangle_{\Omega_{wn},\Omega}$$

$$-\left\langle \mathbf{n}_n \boldsymbol{\cdot} \left[\frac{2}{j_n} \boldsymbol{\sigma}_n \boldsymbol{:} (\nabla_X \mathbf{x} \nabla_X \mathbf{x}) \boldsymbol{\cdot} \left(\mathbf{v}_s - \mathbf{v}^{\overline{s}} \right) \right] \right\rangle_{\Omega_{wn},\Omega}$$

$$+\left\langle \left\{ \nabla \boldsymbol{\cdot} \left[\frac{2}{j_n} \boldsymbol{\sigma}_n \boldsymbol{:} (\nabla_X \mathbf{x} \nabla_X \mathbf{x}) \right] - \nabla \boldsymbol{\sigma}_n \boldsymbol{:} \frac{\mathbf{C}_n}{j_n} \right\} \boldsymbol{\cdot} \left(\mathbf{v}_s - \mathbf{v}^{\overline{s}} \right) \right\rangle_{\Omega_n,\Omega}$$

$$+ \epsilon^n \boldsymbol{\sigma}^n \boldsymbol{:} \frac{\mathbf{C}^n}{j^n} \mathbf{I} \boldsymbol{:} \mathbf{d}^{\overline{\overline{s}}} - \left\langle \frac{2}{j_n} \boldsymbol{\sigma} n \boldsymbol{:} (\nabla_X \mathbf{x} \nabla_X \mathbf{x}) \right\rangle_{\Omega_n,\Omega} \boldsymbol{:} \mathbf{d}^{\overline{\overline{s}}}$$

$$- \nabla \boldsymbol{\cdot} \left\langle \left[\frac{2}{j_n} \boldsymbol{:} (\nabla_X \mathbf{x} \nabla_X \mathbf{x}) - \boldsymbol{\sigma}_n \boldsymbol{:} \frac{\mathbf{C}_n}{j_n} \mathbf{I} \right] \boldsymbol{\cdot} \left(\mathbf{v}_s - \mathbf{v}^{\overline{s}} \right) \right\rangle_{\Omega_s,\Omega} = 0 \qquad (4.101)$$

Host Tissue: h

$$\frac{\mathrm{D}^{\overline{s}} E^{\overline{\overline{h}}}}{\mathrm{D}t} - \theta^{\overline{\overline{h}}} \frac{\mathrm{D}^{\overline{s}} \eta^{\overline{\overline{h}}}}{\mathrm{D}t} - \mu^{\overline{h}} \frac{\mathrm{D}^{\overline{s}} \left(\epsilon^h \rho^h \right)}{\mathrm{D}t} + p^h \frac{\mathrm{D}^{\overline{s}} \epsilon^h}{\mathrm{D}t}$$

$$+\left\langle \eta_h \frac{\mathrm{D}_s(\theta_h - \theta^{\overline{\overline{h}}})}{\mathrm{D}t} + \rho_h \frac{\mathrm{D}_s(\mu_h - \mu^{\overline{h}})}{\mathrm{D}t} \right\rangle_{\Omega_h,\Omega}$$

$$-\left\langle \left(\frac{\mathbf{C}_h}{j_h} \mathbf{:} \boldsymbol{\sigma}_h \right) (\mathbf{v}_{wh} - \mathbf{v}_s) \boldsymbol{\cdot} \mathbf{n}_h \right\rangle_{\Omega_{wh},\Omega}$$

$$-\left\langle \mathbf{n}_h \boldsymbol{\cdot} \left[\frac{2}{j_h} \boldsymbol{\sigma}_h \mathbf{:} (\nabla_X \mathbf{x} \nabla_X \mathbf{x}) \boldsymbol{\cdot} \left(\mathbf{v}_s - \mathbf{v}^{\overline{s}} \right) \right] \right\rangle_{\Omega_{wh},\Omega}$$

$$+\left\langle \left\{ \nabla \boldsymbol{\cdot} \left[\frac{2}{j_h} \boldsymbol{\sigma}_h \mathbf{:} (\nabla_X \mathbf{x} \nabla_X \mathbf{x}) \right] - \nabla \boldsymbol{\sigma}_h \mathbf{:} \frac{\mathbf{C}_h}{j_h} \right\} \boldsymbol{\cdot} \left(\mathbf{v}_s - \mathbf{v}^{\overline{s}} \right) \right\rangle_{\Omega_h,\Omega}$$

$$+ \epsilon^h \boldsymbol{\sigma}^h \mathbf{:} \frac{\mathbf{C}^h}{j^h} \mathbf{I} \mathbf{:} \mathbf{d}^{\overline{\overline{s}}} - \left\langle \frac{2}{j_h} \boldsymbol{\sigma}_h \mathbf{:} (\nabla_X \mathbf{x} \nabla_X \mathbf{x}) \right\rangle_{\Omega_h,\Omega} \mathbf{:} \mathbf{d}^{\overline{\overline{s}}}$$

$$- \nabla \boldsymbol{\cdot} \left\langle \left[\frac{2}{j_h} \mathbf{:} (\nabla_X \mathbf{x} \nabla_X \mathbf{x}) - \boldsymbol{\sigma}_h \mathbf{:} \frac{\mathbf{C}^h}{j_h} \mathbf{I} \right] \boldsymbol{\cdot} \left(\mathbf{v}_s - \mathbf{v}^{\overline{s}} \right) \right\rangle_{\Omega_h,\Omega} = 0 \tag{4.102}$$

4.5.2 Fluid Phases: f, b

General fluid phase thermodynamic expression using the material derivative.

$$\mathcal{T}^{\overline{w}} = \frac{\mathrm{D}^{\overline{w}} E^{\overline{\overline{w}}}}{\mathrm{D}t} - \theta^{\overline{\overline{w}}} \frac{\mathrm{D}^{\overline{w}} \eta^{\overline{\overline{w}}}}{\mathrm{D}t} - \mu^{\overline{w}} \frac{\mathrm{D}^{\overline{w}} \left(\epsilon^w \rho^w \right)}{\mathrm{D}t} + p^w \frac{\mathrm{D}^{\overline{w}} \epsilon^w}{\mathrm{D}t}$$
$$+ \left\langle \eta_w \frac{\mathrm{D}_w(\theta_w - \theta^{\overline{\overline{w}}})}{\mathrm{D}t} + \rho_w \frac{\mathrm{D}_w \left(\mu_w - \mu^{\overline{w}} \right)}{\mathrm{D}t} - \frac{\mathrm{D}^{\overline{w}} \left(p_w - p^w \right)}{\mathrm{D}t} \right\rangle_{\Omega_w,\Omega} = 0 \tag{4.103}$$

Interstitial Fluid: f

$$\frac{\mathrm{D}^{\overline{f}} E^{\overline{\overline{f}}}}{\mathrm{D}t} - \theta^{\overline{\overline{f}}} \frac{\mathrm{D}^{\overline{f}} \eta^{\overline{\overline{f}}}}{\mathrm{D}t} - \mu^{\overline{f}} \frac{\mathrm{D}^{\overline{f}} \left(\epsilon^f \rho^f \right)}{\mathrm{D}t} + p^w \frac{\mathrm{D}^{\overline{f}} \epsilon^f}{\mathrm{D}t}$$
$$+ \left\langle \eta_f \frac{\mathrm{D}_f(\theta_f - \theta^{\overline{\overline{f}}})}{\mathrm{D}t} + \rho_f \frac{\mathrm{D}_f \left(\mu_f - \mu^{\overline{f}} \right)}{\mathrm{D}t} - \frac{\mathrm{D}^{\overline{f}} \left(p_f - p^f \right)}{\mathrm{D}t} \right\rangle_{\Omega_f,\Omega} = 0 \tag{4.104}$$

Blood: b

$$\frac{\mathrm{D}^{\overline{b}} E^{\overline{\overline{b}}}}{\mathrm{D}t} - \theta^{\overline{\overline{b}}} \frac{\mathrm{D}^{\overline{b}} \eta^{\overline{\overline{b}}}}{\mathrm{D}t} - \mu^{\overline{b}} \frac{\mathrm{D}^{\overline{b}} \left(\epsilon^b \rho^b \right)}{\mathrm{D}t} + p^b \frac{\mathrm{D}^{\overline{b}} \epsilon^b}{\mathrm{D}t}$$

$$+\left\langle \eta_b \frac{\mathrm{D}_b(\theta_b - \theta^{\bar{\bar{b}}})}{\mathrm{D}t} + \rho_b \frac{\mathrm{D}_b\left(\mu_b - \mu^{\bar{b}}\right)}{\mathrm{D}t} - \frac{\mathrm{D}^{\bar{b}}\left(p_b - p^b\right)}{\mathrm{D}t} \right\rangle_{\Omega_b,\Omega} = 0 \qquad (4.105)$$

These preceding five thermodynamic equations, (4.100), (4.101), (4.102), (4.104), and (4.105), are those which would be combined with the mass, momentum, energy, and entropy equations to form a constrained entropy inequality.

4.6 Concluding Remarks

This document has covered a wide range of topics, all the way from cancer biology to macroscale conservation equations. It is the author's wish to have connected these topics in a way that is approachable to readers from the field of cancer biology or from engineering. The level of detail and use of specific terminology is likely to be formidable to readers from both sides, but was designed to introduce both "camps" to their opposite fields. Meaningful biological modeling is only possible if researchers from different disciplines and backgrounds can come together, learn to speak one another's language, and begin to understand the important tenants of both areas of study. Specifically, this document is designed to present the important discoveries made about the biology of cancer, growth mechanisms, genetic mutation, and biological interactions to an scientific, yet uninitiated reader- the engineer. It also aims to to describe to the biologist how the engineers conceptualize the physical regions, the simplifications that must occur to render a biological system amenable to modeling, and the mathematics involved in developing such a model.

Further motivation is for the advancement of current continuum tumor modeling. Existing models are flawed in a number of ways and are generally vague and inconsistent in their mathematical representations of the macroscale. This document presents a simple, yet complete, form of a tumor model that includes all the system descriptions and equations needed to graduate to a more complicated model. More importantly, all macroscale equations were derived using a rigorous, formal averaging theory to translate the microscale to the macroscale in a complete and transparent manner. Furthermore, any closure relations imposed on the macroscale equations included clear statements of the assumptions made.

Another benefit of this type of model development is its flexibility. The model presented in this chapter could be extended to include multiple species such as glucose, oxygen, and a variety of growth factors. It could also be altered to include additional dependencies regarding necrosis like pressure-induced necrosis, or the release of pro-inflammatory and similar biochemical signals due to necrosis. Hypoxia, pH, and oncotic pressure are other microenvironmental conditions of interest that could be the focus of the model. One improvement to the model which would greatly increase its realism is the incorporation of angiogenesis as a systematic increase in the volume fraction of the blood phase. Constitutive relations will have to be developed carefully in collaboration with biologists to produce meaningful equations. The model could also be used to test treatment therapies including the transport of chemotherapeutics, which is already an area of study in cancer modeling. Lifting the assumption of isothermal conditions would also allow treatment by thermal ablation to be modeled. Though the lay-person often assumes the only value of a model is its "predictiveness", this project does not include any numerical simulations. Instead the focus is on carefully developing an understanding of the biology of cancer and the mathematical equations to describe it. The author encourages the audience to value this journey undertaken to connect the two, and not simply the destination.

Bibliography

[1] A. R. Anderson. A hybrid mathematical model of solid tumour invasion: the importance of cell adhesion. *Math Med Biol*, 22:163–186, Jun 2005.

[2] A. R. Anderson and M. A. Chaplain. Continuous and discrete mathematical models of tumor-induced angiogenesis. *Bull. Math. Biol.*, 60:857–899, Sep 1998.

[3] R.P. Araujo and L.S. McElwain. A history of the study of solid tumor growth: the contribution of mathematical modelling. *Bulletin of Math. Biology*, 66:1039–1091, 2004.

[4] Bruce P. Ayati, Glenn F. Webb, and Alexander R. A. Anderson. Computational methods and results for structured multiscale models of tumor invasion. *Multiscale Modeling & Simulation*, 5(1):1 – 20, 2006.

[5] I. D. Bassukas and B. Maurer-Schultze. The recursion formula of the Gompertz function: a simple method for the estimation and comparison of tumor growth curves. *Growth Dev Aging*, 52:113–122, 1988.

[6] J. Bear. *Hydraulics of Groundwater*. McGraw-Hill, New York, 1979.

[7] E. L. Bearer, J. S. Lowengrub, H. B. Frieboes, Y. L. Chuang, F. Jin, S. M. Wise, M. Ferrari, D. B. Agus, and V. Cristini. Multiparameter computational modeling of tumor invasion. *Cancer Res.*, 69:4493–4501, May 2009.

[8] H Begg, AC andJanssen, D Sprong, I Hofland, G Blommestijn, JA Raleigh, M Varia, A Balm, L van Velthuyzen, P Delaere, R Sciot, and KMG Haustermans. Hypoxia and perfusion measurements in human tumors-initial experience with pimonidazole and IUdR. *Acta Oncol*, 40:924–928, 2001.

[9] Y. Boucher and R. K. Jain. Microvascular pressure is the principal driving force for interstitial hypertension in solid tumors: implications for vascular collapse. *Cancer Res.*, 52:5110–5114, Sep 1992.

[10] A. C. Burton. Rate of growth of solid tumours as a problem of diffusion. *Growth*, 30:157–176, Jun 1966.

[11] H. Byrne and L. Preziosi. Modelling solid tumour growth using the theory of mixtures. *Math Med Biol*, 20:341–366, Dec 2003.

[12] AE Casey. The experimental alteration of malignancy with an homologous mammalian tumor material-i. *Am. J. Cancer*, 21:760–775, 1934.

[13] M. A. Chaplain. Mathematical modelling of angiogenesis. *J. Neurooncol.*, 50:37–51, 2000.

[14] M. A. Chaplain, L. Graziano, and L. Preziosi. Mathematical modelling of the loss of tissue compression responsiveness and its role in solid tumour development. *Math Med Biol*, 23:197–229, Sep 2006.

[15] M. A. Chaplain and B. D. Sleeman. Modelling the growth of solid tumours and incorporating a method for their classification using nonlinear elasticity theory. *J Math Biol*, 31:431–473, 1993.

[16] V. Cristini, H. B. Frieboes, R. Gatenby, S. Caserta, M. Ferrari, and J. Sinek. Morphologic instability and cancer invasion. *Clin. Cancer Res.*, 11:6772–6779, Oct 2005.

[17] V. Cristini, J. Lowengrub, and Q. Nie. Nonlinear simulation of tumor growth. *J Math Biol*, 46:191–224, Mar 2003.

[18] Vittorio Cristini, Xiangrong Li, John S. Lowengrub, and Steven M. Wise. Nonlinear simulations of solid tumor growth using a mixture model: invasion and branching. *Journal of Mathematical Biology*, 58(4/5):723 – 763, 2009.

[19] T. S. Deisboeck, Z. Wang, P. Macklin, and V. Cristini. Multiscale Cancer Modeling. *Annu Rev Biomed Eng*, Jul 2010.

[20] Karin Maria Erbertseder. Modeling the spatial and temporal distribution of therapeutic agents in tumor tissues (a continuum approach). Master's thesis, University of Stuttgart, 2008.

[21] H. B. Frieboes, M. E. Edgerton, J. P. Fruehauf, F. R. Rose, L. K. Worrall, R. A. Gatenby, M. Ferrari, and V. Cristini. Prediction of drug response in breast cancer using integrative experimental/computational modeling. *Cancer Res.*, 69:4484–4492, May 2009.

[22] H. B. Frieboes, X. Zheng, C. H. Sun, B. Tromberg, R. Gatenby, and V. Cristini. An integrated computational/experimental model of tumor invasion. *Cancer Res.*, 66:1597–1604, Feb 2006.

[23] Hermann B. Frieboes, Fang Jin, Yao-Li Chuang, Steven M. Wise, John S. Lowengrub, and Vittorio Cristini. Three-dimensional multispecies nonlinear tumor growthii: Tumor invasion and angiogenesis. *Journal of Theoretical Biology*, 264(4):1254 – 1278, 2010.

[24] Hermann B. Frieboes, John S. Lowengrub, S. Wise, X. Zheng, Paul Macklin, Elaine L. Bearer, and Vittorio Cristini. Computer simulation of glioma growth and morphology. *NeuroImage*, 37:S59 – S70, 2007.

[25] J. Kleinerman G. M. Saidel, L.A. Liotta. System dynamics of a metastatic process from an implanted tumor. *J. Theor. Biol.*, 56:417–434, 1976.

[26] P. Gerlee and A. R. Anderson. An evolutionary hybrid cellular automaton model of solid tumour growth. *J. Theor. Biol.*, 246:583–603, Jun 2007.

[27] P. Gerlee and A. R. Anderson. Diffusion-limited tumour growth: simulations and analysis. *Math Biosci Eng*, 7:385–400, Apr 2010.

[28] P. Gerlee and A.R.A. Anderson. Evolution of cell motility in an individual-based model of tumour growth. *Journal of Theoretical Biology*, 259(1):67 – 83, 2009.

[29] W. G. Gray and C. T. Miller. Thermodynamically Constrained Averaging Theory Approach for Modeling Flow and Transport Phenomena in Porous Medium Systems: 7. Single-Phase Megascale Flow Models. *Adv Water Resour*, 32:1121–1142, Aug 2009.

[30] W. G. Gray and C. T. Miller. Thermodynamically Constrained Averaging Theory Approach for Modeling Flow and Transport Phenomena in Porous Medium Systems: 8. Interface and Common Curve Dynamics. *Adv Water Resour*, 33:1427–1443, Dec 2010.

[31] William G. Gray, Anton Leijnse, Randall L Kolar, and Cheryl A. Blain. *Mathematical Tools for Changing Scale in the Analysis of Physical Systems*. CRC Press, 1993.

[32] William G. Gray and Cass T. Miller. Thermodynamically constrained averaging theory approach for modeling flow and transport phenomena in porous medium systems: 1. motivation and overview. *Advances in Water Resources*, 28(2):161 – 180, 2005.

[33] William G. Gray and Cass T. Miller. Thermodynamically constrained averaging theory approach for modeling flow and transport phenomena in porous medium systems: 3. single-fluid-phase flow. *Advances in Water Resources*, 29(11):1745 – 1765, 2006.

[34] William G. Gray and Cass T. Miller. Thermodynamically constrained averaging theory approach for heat transport in single-fluid-phase porous medium systems. *Journal of Heat Transfer*, 131(10):4, 2009.

[35] William G. Gray and Cass T. Miller. Thermodynamically constrained averaging theory approach for modeling flow and transport phenomena in porous medium systems: 5. single-fluid-phase transport. *Advances in Water Resources*, 32(5):681 – 711, 2009.

[36] H.P. Greenspan. Models for the growth of a solid tumour by diffusion. *Stud. Appl. Math.*, 51:317–340, 1972.

[37] M. Gyllenberg and G. F. Webb. Quiescence as an explanation of Gompertzian tumor growth. *Growth Dev Aging*, 53:25–33, 1989.

[38] D. Hanahan and R. A. Weinberg. The hallmarks of cancer. *Cell*, 100:57–70, Jan 2000.

[39] D. Hanahan and R. A. Weinberg. Hallmarks of cancer: the next generation. *Cell*, 144:646–674, Mar 2011.

[40] Ian R. Hart. Biology of cancer. *Cancer Biology*, 32:1–4, Mar 2004.

[41] G. Helmlinger, P. A. Netti, H. C. Lichtenbeld, R. J. Melder, and R. K. Jain. Solid stress inhibits the growth of multicellular tumor spheroids. *Nat. Biotechnol.*, 15:778–783, Aug 1997.

[42] Osborne J. M. A hybrid approach to multi-scale modelling of cancer. *Philosophical Transactions of the Royal Society A: Mathematical, Physical & Engineering Sciences*, 368(1930):5013 – 5028, 2010.

[43] Amber S. Jackson, Cass T. Miller, and William G. Gray. Thermodynamically constrained averaging theory approach for modeling flow and transport phenomena in porous medium systems: 6. two-fluid-phase flow. *Advances in Water Resources*, 32(6):779 – 795, 2009.

[44] A. F. Jones, H. M. Byrne, J. S. Gibson, and J. W. Dold. A mathematical model of the stress induced during avascular tumour growth. *J Math Biol*, 40:473–499, Jun 2000.

[45] R.J.B. King and M.W. Robins. *Cancer Biology*. Pearson Education Limited, Edinburgh Gate, U.K., 2006.

[46] Margaret Knowles and Peter Selby, editors. *Introduction to the Cellular and Molecular Biology of Cancer*. Oxford University Press, fourth edition, 2005.

[47] G.M. Saidel L.A. Liotta, J. Kleinerman. Quantitative relationshiops of intravascular tumor cells, tumor vessels, and pulmonary metastases following tumor implantation. *Cancer Research*, 34:997–1004, 1974.

[48] M. Leunig, F. Yuan, M. D. Menger, Y. Boucher, A. E. Goetz, K. Messmer, and R. K. Jain. Angiogenesis, microvascular architecture, microhemodynamics, and interstitial fluid pressure during early growth of human adenocarcinoma LS174T in SCID mice. *Cancer Res.*, 52:6553–6560, Dec 1992.

[49] L. A. Liotta, G. M. Saidel, and J. Kleinerman. Stochastic model of metastases formation. *Biometrics*, 32:535–550, Sep 1976.

[50] J. S. Lowengrub, H. B. Frieboes, F. Jin, Y. L. Chuang, X. Li, P. Macklin, S. M. Wise, and V. Cristini. Nonlinear modelling of cancer: bridging the gap between cells and tumours. *Nonlinearity*, 23:R1–R9, 2010.

[51] P. Macklin and J. Lowengrub. Nonlinear simulation of the effect of microenvironment on tumor growth. *J. Theor. Biol.*, 245:677–704, Apr 2007.

[52] P. Macklin and J. S. Lowengrub. A New Ghost Cell/Level Set Method for Moving Boundary Problems: Application to Tumor Growth. *J Sci Comput*, 35:266–299, Jun 2008.

[53] P. Macklin, S. McDougall, A. R. Anderson, M. A. Chaplain, V. Cristini, and J. Lowengrub. Multiscale modelling and nonlinear simulation of vascular tumour growth. *J Math Biol*, 58:765–798, Apr 2009.

[54] S. R. McDougall, A. R. Anderson, and M. A. Chaplain. Mathematical modelling of dynamic adaptive tumour-induced angiogenesis: clinical implications and therapeutic targeting strategies. *J. Theor. Biol.*, 241:564–589, Aug 2006.

[55] C. T. Miller and W. G. Gray. Thermodynamically Constrained Averaging Theory Approach for Modeling Flow and Transport Phenomena in Porous Medium Systems: 4. Species Transport Fundamentals. *Adv Water Resour*, 31:577–597, Mar 2008.

[56] Cass T. Miller and William G. Gray. Thermodynamically constrained averaging theory approach for modeling flow and transport phenomena in porous medium systems: 2. foundation. *Advances in Water Resources*, 28(2):181 – 202, 2005.

[57] P. C. Nowell. Tumor progression: a brief historical perspective. *Semin. Cancer Biol.*, 12:261–266, Aug 2002.

[58] J.T. Oden, A. Hawkins, and S. Prudhomme. General diffuse-interface theories and an approach to predictive tumor growth modeling. *Mathematical Models & Methods in Applied Sciences*, 20(3):477 – 517, 2010.

[59] M. E. Orme and M. A. Chaplain. A mathematical model of the first steps of tumour-related angiogenesis: capillary sprout formation and secondary branching. *IMA J Math Appl Med Biol*, 13:73–98, Jun 1996.

[60] K. Pham, H. B. Frieboes, V. Cristini, and J. Lowengrub. Predictions of tumour morphological stability and evaluation against experimental observations. *J R Soc Interface*, 8:16–29, Jan 2011.

[61] C.P. Please, G.J. Pettet, and D.L.S. McElwain. A new approach to modelling the formation of necrotic regions in tumours. *Appl. Math. Lett.*, 11:89–94, 1998.

[62] Vito Quaranta, Alissa M. Weaver, Peter T. Cummings, and Alexander R.A. Anderson. Mathematical modeling of cancer: The future of prognosis and treatment. *Clinica Chimica Acta*, 357(2):173 – 179, 2005.

[63] I. Ramis-Conde, M. A. Chaplain, A. R. Anderson, and D. Drasdo. Multi-scale modelling of cancer cell intravasation: the role of cadherins in metastasis. *Phys Biol*, 6:016008, 2009.

[64] Tiina Roose, S. Jonathan Chapman, and Philip K. Maini. Mathematical models of avascular tumor growth. *SIAM Review*, 49(2):179 – 208, 2007.

[65] Sandeep Sanga, Hermann B. Frieboes, Xiaoming Zheng, Robert Gatenby, Elaine L. Bearer, and Vittorio Cristini. Predictive oncology: A review of multidisciplinary, multiscale in silico modeling linking phenotype, morphology and growth. *NeuroImage*, 37:S120 – S134, 2007.

[66] J. P. Sinek, S. Sanga, X. Zheng, H. B. Frieboes, M. Ferrari, and V. Cristini. Predicting drug pharmacokinetics and effect in vascularized tumors using computer simulation. *J Math Biol*, 58:485–510, Apr 2009.

[67] M. Stohrer, Y. Boucher, M. Stangassinger, and R. K. Jain. Oncotic pressure in solid tumors is elevated. *Cancer Res.*, 60:4251–4255, Aug 2000.

[68] R. H. Thomlinson and L. H. Gray. The histological structure of some human lung cancers and the possible implications for radiotherapy. *Br. J. Cancer*, 9:539–549, Dec 1955.

[69] V. G. Vaidya and F. J. Alexandro. Evaluation of some mathematical models for tumor growth. *Int. J. Biomed. Comput.*, 13:19–36, Jan 1982.

[70] J. P. Ward and J. R. King. Mathematical modelling of avascular-tumour growth. *IMA J Math Appl Med Biol*, 14:39–69, Mar 1997.

[71] J. P. Ward and J. R. King. Mathematical modelling of avascular-tumour growth. II: Modelling growth saturation. *IMA J Math Appl Med Biol*, 16:171–211, Jun 1999.

[72] J. P. Ward and J. R. King. Mathematical modelling of th eeffects of mitotic inhibitors on avascular tumour growth. *J. Theor. Med.*, 1:287–311, 1999.

[73] J. P. Ward and J. R. King. Modelling the effect of cell shedding on avascular tumour growth. *J. Theor. Med.*, 2:155–174, 2000.

[74] J. P. Ward and J. R. King. Mathematical modelling of drug transport in tumour multicell spheroids and monolayer cultures. *Math Biosci*, 181:177–207, Feb 2003.

[75] S. M. Wise, J. S. Lowengrub, H. B. Frieboes, and V. Cristini. Three-dimensional multispecies nonlinear tumor growth–I Model and numerical method. *J. Theor. Biol.*, 253:524–543, Aug 2008.

[76] S.M. Wise, J.S. Lowengrub, and V. Cristini. An adaptive multigrid algorithm for simulating solid tumor growth using mixture models. *Mathematical & Computer Modelling*, 53(1/2):1 – 20, 2011.

[77] X. Zheng, S. M. Wise, and V. Cristini. Nonlinear simulation of tumor necrosis, neo-vascularization and tissue invasion via an adaptive finite-element/level-set method. *Bull. Math. Biol.*, 67:211–259, Mar 2005.