A MIXTURE THEORY FOR THE GENESIS OF RESIDUAL STRESSES IN GROWING TISSUES I: A GENERAL FORMULATION*

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Abstract. In this paper a theoretical framework for the study of residual stresses in growing tissues is presented using the theory of mixtures. Such a formulation must necessarily be a solid-multiphase model, comprising at least one phase with solid characteristics, owing to the fundamental role played by the incompatibility of strains in generating residual stresses. Since biological growth involves mass exchange between cellular and extracellular phases, field equations are presented for individual phases and for the mixture as a whole which incorporate this phenomenon. Appropriate constitutive equations are then deduced from first principles, appealing to the second law of thermodynamics.

The analysis shows that the distinguishing feature of multiphase models involving mass exchange is the necessity to propose an additional constitutive postulate between the variables in the mass-balance equation in order to close the model. In particular, the defining characteristic of a solid-multiphase model which describes biological growth is a constitutive postulate which relates the process of interphase mass exchange (cell proliferation/cell death) with the expansion or contraction of the solid phase. Thus, the framework presented here represents a new class of mathematical models which extends the concepts of poroelasticity to accommodate continuous volumetric growth. A set of modelling equations is then proposed for the simplest case of a solid-multiphase model, being a biphasic mixture of a linear-elastic solid and an inviscid fluid.

Key words. tissue growth, mixture theory, residual stresses, continuum mechanics, constitutive equations, porous media

AMS subject classifications. 70S99, 74A, 74F, 74L15, 76S05

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1. Introduction. The evolution and spatial distribution of tissue stresses is of fundamental importance in a number of physiological phenomena. The experimentally observed phenomenon of vascular collapse in tumors, for example, which has been attributed to the elevated tissue stresses resulting from confined proliferation of tumor cells [5, 9], represents a significant barrier to the delivery of blood-borne therapeutic drugs. Such stresses are *residual* in nature, arising in the tissue when it is free of external loads, and result from the incompatibility of growth strains [21, 38, 40].

Fung [20] further notes the existence of residual stresses in living organs and highlights the importance of such stresses to physiological functions, asserting that "in a living organism, the function of its organs depends on the levels of their internal stress and strain."

Hence continuum models of growing tissues would provide a theoretical framework for a wide range of studies in biology, ranging from tumor biology and anticancer therapies [23, 38] to studies in embryology [7, 34], developmental biology, and plant physiology [18], in addition to providing tools for prediction and analysis for a wide range of projects in the rapidly growing field of tissue engineering [31].

Nevertheless, the underlying phenomenological determinants of residual stresses, as well as their purpose and implications in both normal tissue development and

various pathological conditions, are poorly understood since there is a paucity of mathematical models to elucidate these phenomena.

Gatenby [22] explains that "recent research in tumour biology, particularly that using new techniques from molecular biology, has produced information at an explosive pace. Yet a conceptual framework within which all these new (and old) data can be fitted is lacking." Gatenby and Maini [23] add that "clinical oncologists and tumour biologists possess virtually no comprehensive theoretical model to serve as a framework for understanding, organizing and applying these data," noting the necessity to "(develop) mechanistic models that provide real insights into critical parameters that control system dynamics." Murray [32] concurs, arguing that "the goal is to develop models which capture the essence of various interactions allowing their outcome to be more fully understood."

Indeed, while experimental approaches may attest to the *existence* of residual stresses and provide information about their distribution in tissues, the underlying mechanisms governing their genesis cannot be fully elucidated in the absence of mathematical modeling owing to the fundamental role played by the incompatibility of growth strains in their formation [40]. Mathematical analysis provides the key to identifying incompatible growth and represents a tool for investigating the roles of a variety of phenomenological aspects of growing tissues—distribution of nutrients, growth-related density changes, stress modulated cell-proliferation and apoptosis, geometric effects—in promoting incompatibilities and the associated residual stresses.

An important consideration in the mathematical modelling of tissue growth is the choice between single-phase mechanics and mixture theory [2]. The former, which appeals to an analogy with thermal expansion, incorporates a *source term* in the balance of mass, with the phase or phases responsible for the mass source remaining implicit to the model. While Skalak [39] claims that volumetric growth is analogous to thermal expansion—an analogy which forms the basis of the tissue growth models by Shannon and Rubinsky [38], Jones et al. [26], and Araujo and McElwain [4]—it does not consider all the processes which determine the stresses induced during biological tissue growth. Indeed, Araujo and McElwain [4] note that the single-constituent framework does not take into account the net fluid movement associated with the growth process and the Darcy-like drag terms in the equilibrium of forces—a consideration which may be significant when the elastic (residual) stresses are small.

Multiphase models, on the other hand, which are based on mixture theory, clarify the nature of any mass sources, and consider the role of interstitial fluid in the growth process. While several *fluid* multiphase models of growing tissues have been proposed recently [15, 16, 28], it is essential to recognize that these models provide no basis for examining the genesis of *residual* stresses in tissues, which requires a consideration of the tissue's *solid* characteristics.

Hence, a theoretical framework which enables the growth process and the associated development of tissue stresses to be modeled naturally, without recourse to an analogy with thermal expansion, is lacking.

This paper is the first in a series of papers which elaborate a mixture theory for the genesis of residual stresses in growing soft tissues, based on field equations which incorporate interphase mass exchange. This paper presents a general formulation for deducing thermodynamically appropriate constitutive equations relevant to the study of biological growth. In section 2, the field equations are presented, being adapted from the classical field theories developed by Truesdell and Toupin [42] and the theory of mixtures developed by Bowen [12] and manipulated into the forms most useful to further exploration of the problem at hand. In sections 3 and 4, these classical

theories are used as a guide to developing a particular form of the second axiom of thermodynamics from which the relevant constitutive equations may be deduced most readily, neglecting the influence of possible density changes associated with a change of phase. Constitutive assumptions for a general mixture of n phases are then outlined in section 5, following the pioneering work on constitutive modeling by Coleman and Noll [17], Ehlers [19], and Bowen [12].

In sections 6 through 8, a simple two-phase mixture of an elastic solid and an inviscid fluid is considered in detail. Since this solid-biphasic mixture must be able to exhibit continuous volumetric expansion to model the process of biological growth and an associated evolution of residual stresses, this paper stands alone in the mathematical literature pertaining to solid tumor growth, enucleating the very essence of the closure problem relevant to continuous growth of a tissue with solid characteristics. The solutions to these biphasic equations will be presented in the next paper in the series.

1.1. Differentiation conventions and index of symbols. The following conventions will be adopted throughout this paper.

If $\hat{\alpha}_i$ and $\boldsymbol{\alpha}_i$ are scalar and vector/tensor properties of the ith constituent, respectively, then $\boldsymbol{\nabla}\hat{\alpha}_i$ and $\boldsymbol{\nabla}.\boldsymbol{\alpha}_i$ denote the gradient and the divergence, respectively, with respect to *spatial* coordinates. (Note that in many references and texts in continuum mechanics these symbols are used to denote partial differentiation with respect to the *reference configuration*.) The symbols $\mathbf{Grad}\hat{\alpha}_i$ and $\mathbf{Div}\boldsymbol{\alpha}_i$ will denote the gradient and divergence, respectively, with respect to the *reference configuration*.

In addition, the symbol $\frac{D^i}{Dt}$ denotes the material derivative following the motion defined by $\mathbf{v}_i$, the velocity of the ith constituent. The symbol $\frac{D}{Dt}$, on the other hand, represents the material derivative following the motion defined by $\mathbf{v}_m$, the velocity of the mixture as a whole.

Table 1.1 gives a summary of the nomenclature adopted in this paper, along with the equation in which each symbol first appears. Each quantity is given a more complete description when it is first introduced in the text.

2. Constituent field equations. The balances of mass, linear momentum, angular momentum, and energy for the ith constituent of an n-phase mixture are summarized below. The equations incorporate a mass exchange term, so that the mass of the ith constituent may increase (or decrease) at the expense of other constituents. All constituents are equipresent at each spatial point.

2.1. Balance of mass. The balance of mass for the ith constituent, or *phase*, of an n-phase mixture is given by

$$(2.1) \qquad \frac{D^i(\phi_i\rho_i)}{Dt} + (\phi_i\rho_i)\boldsymbol{\nabla} \cdot \mathbf{v}_i = \Gamma_i,$$

or, equivalently,

$$(2.2) \qquad \frac{\partial(\phi_i\rho_i)}{\partial t} + \boldsymbol{\nabla}.(\phi_i\rho_i\mathbf{v}_i) = \Gamma_i,$$

where ϕ_i and ρ_i are the volume fraction and density, respectively, of the ith phase and Γ_i is the mass supplied to the ith phase per unit time per unit mixture volume. Truesdell and Toupin's [42] rule for differentiating a determinant gives the identity

$$\frac{D^i}{Dt}(\det\mathbf{F}_i) = (\det\mathbf{F}_i)\boldsymbol{\nabla} \cdot \mathbf{v}_i,$$

TABLE 1.1
Symbols.

Symbol	Description	Equation of first occurrence
ϕ	Volume fraction	(2.1)
ρ	True density	(2.1)
Γ	Mass supply	(2.1)
$\mathbf{F}$	Deformation Gradient	(2.3)
$\mathbf{v}$	Velocity	(2.1)
$\boldsymbol{\sigma}$	Partial Cauchy stress tensor	(2.7)
$\boldsymbol{\sigma}_I$	*Inner* mixture stress tensor	(2.16)
$\mathbf{g}$	Acceleration due to gravity	(2.7)
$\boldsymbol{\pi}$	Phase interaction force	(2.7)
$\mathbf{w}$	Diffusion velocity	(2.11)
$\mathbf{m}$	Angular momentum supply	(2.13)
$\mathbf{L}$	Velocity gradient	(2.18)
u	Internal energy	(2.18)
$\mathbf{q}$	Heat flux	(2.18)
r	Heat production rate	(2.18)
ε	Phase interaction energy supply	(2.18)
η	Entropy	(3.1)
θ	Absolute temperature	(3.1)
ψ	Helmholtz free energy	(3.4)
$\mathbf{K}$	Chemical potential tensor	(3.5)
ζ	Lagrangian multiplier	(4.4)
$\mathbf{X}$	Reference coordinates	(8.2)
$\mathbf{x}$	Spatial coordinates	(8.9)
μ, λ	Lamé constants	(8.22)

which enables (2.1) to be expressed by

$$(2.3) \qquad \frac{D^i}{Dt}\left(\phi_i \rho_i \det \mathbf{F}_i\right) = \Gamma_i \det \mathbf{F}_i,$$

where $\mathbf{F}_i$ is the deformation gradient of the ith phase with respect to the reference configuration. The volume fractions, ϕ_i, are subject to the constraint

$$(2.4) \qquad \sum_{i=1}^{n} \phi_i = 1,$$

which implies that the mixture is *saturated*.

The balance of mass for the mixture is expressed by

$$(2.5) \qquad \frac{D\rho_m}{Dt} + \rho_m \boldsymbol{\nabla} \cdot \mathbf{v}_m = 0,$$

where ρ_m and $\mathbf{v}_m$ are the density and velocity, respectively, of the mixture as a whole. A comparison of (2.5) with the summation of (2.2) over all n phases allows the mixture density, ρ_m, to be defined by

$$\rho_m = \sum_{i=1}^{n} \phi_i \rho_i,$$

and the mixture velocity, $\mathbf{v}_m$, to be defined by

$$\mathbf{v}_m = \frac{1}{\rho_m} \sum_{i=1}^{n} (\phi_i \rho_i \mathbf{v}_i),$$

while yielding the following expression for the conservation of mass:

$$(2.6) \qquad \sum_{i=1}^{n} \Gamma_i = 0.$$

2.2. Balance of linear momentum. The balance of linear momentum for the ith phase of an n-phase mixture is given by

$$(2.7) \qquad \phi_i \rho_i \frac{D^i \mathbf{v}_i}{Dt} = \boldsymbol{\nabla} \cdot \boldsymbol{\sigma}_i + \phi_i \rho_i \mathbf{g} + \boldsymbol{\pi}_i,$$

or, equivalently,

$$(2.8) \qquad \frac{\partial}{\partial t}(\phi_i \rho_i \mathbf{v}_i) + \boldsymbol{\nabla} . (\phi_i \rho_i \mathbf{v}_i \otimes \mathbf{v}_i) = \boldsymbol{\nabla} \cdot \boldsymbol{\sigma}_i + \phi_i \rho_i \mathbf{g} + \boldsymbol{\pi}_i + \Gamma_i \mathbf{v}_i,$$

where $\boldsymbol{\sigma}_i$ is the partial Cauchy stress tensor for the ith phase, $\mathbf{g}$ is the acceleration due to gravity, and $\boldsymbol{\pi}_i$ is the locally produced force per unit volume on the ith phase due to its interactions with the other phases. The symbol $\otimes$ denotes the dyadic vector product.

The balance of linear momentum for the mixture is expressed by

$$(2.9) \qquad \rho_m \frac{D\mathbf{v}_m}{Dt} = \boldsymbol{\nabla} \cdot \boldsymbol{\sigma}_m + \rho_m \mathbf{g},$$

where $\boldsymbol{\sigma}_m$ is the Cauchy stress tensor of the mixture as a whole. A comparison of (2.9) with the summation of (2.8) enables the mixture stress tensor to be defined by

$$(2.10) \qquad \boldsymbol{\sigma}_m = \sum_{i}(\boldsymbol{\sigma}_i - \phi_i \rho_i \mathbf{w}_i \otimes \mathbf{w}_i),$$

where $\mathbf{w}_i$ denotes the diffusion velocity defined by

$$(2.11) \qquad \mathbf{w}_i = \mathbf{v}_i - \mathbf{v}_m$$

and gives rise to the following expression for the conservation of linear momentum:

$$(2.12) \qquad \sum_{i=1}^{n}(\boldsymbol{\pi}_i + \Gamma_i \mathbf{v}_i) = 0.$$

2.3. Balance of angular momentum. The balance of angular momentum for the ith phase of an n-phase mixture is given by

(2.13)
$$\frac{\partial}{\partial t}\left(\phi_i \rho_i \mathbf{x} \times \mathbf{v}_i\right) + \boldsymbol{\nabla} \cdot \left(\phi_i \rho_i (\mathbf{x} \times \mathbf{v}_i) \otimes \mathbf{v}_i\right) = \boldsymbol{\nabla} \cdot (\mathbf{x} \times \boldsymbol{\sigma}_i) + \mathbf{x} \times (\phi_i \rho_i \mathbf{g} + \boldsymbol{\pi}_i + \Gamma_i \mathbf{v}_i) + \mathbf{m}_i,$$

where $\mathbf{m}_i$ is a vector representing the supply of angular momentum to the ith phase. The symbol $\times$ denotes a cross product, in which the quantity

$$(\mathbf{x} \times \boldsymbol{\sigma}_i)\mathbf{e} = \mathbf{x} \times (\boldsymbol{\sigma}_i \mathbf{e})$$

for all vectors $\mathbf{e}$ (see Bowen [12]). Appealing to the balance of linear momentum produces

$$(2.14) \qquad \mathbf{M}_i = \boldsymbol{\sigma}_i - \boldsymbol{\sigma}_i^T$$

from (2.13), where $\mathbf{M}_i$ is a skew-symmetric tensor arising from the angular momentum supply vector, $\mathbf{m}_i$. Since the sum of the momentum supplies over all phases must vanish, then

$$(2.15) \qquad \sum_{i=1}^{n} \mathbf{M}_i = \mathbf{0}.$$

Thus, the summation of (2.14) over all phases implies that the *inner* part of the mixture stress tensor, which is defined by Truesdell and Toupin [42] as

$$(2.16) \qquad \boldsymbol{\sigma}_I = \sum_{i=1}^{n} \boldsymbol{\sigma}_i,$$

is symmetric. Noting that the quantity

$$\sum_{i=1}^{n} \phi_i \rho_i \mathbf{w}_i \otimes \mathbf{w}_i$$

must also be symmetric implies that the mixture stress tensor is symmetric. Note, however, that the partial Cauchy stress tensors are symmetric if and only if $\mathbf{m}_i = \mathbf{0}$ (and hence $\mathbf{M}_i = \mathbf{0}$), that is, for nonpolar materials. In this particular study, it is assumed that the components of the growing tissue do behave as nonpolar materials, so that $\mathbf{m}_i = \mathbf{0}$ and that

$$(2.17) \qquad \boldsymbol{\sigma}_i = \boldsymbol{\sigma}_i^T.$$

A more general theory would have to be developed to consider tissues comprising micropolar fluids.

2.4. Balance of energy. The energy balance for the ith phase of an n-phase mixture is given by

$$(2.18) \qquad \phi_i \rho_i \frac{D^i u_i}{Dt} = tr(\mathbf{L}_i \boldsymbol{\sigma}_i) - \boldsymbol{\nabla} \cdot \mathbf{q}_i + \phi_i \rho_i r_i + \varepsilon_i,$$

or, equivalently,

$$(2.19) \qquad \frac{\partial}{\partial t}(\phi_i \rho_i u_i) + \boldsymbol{\nabla} \cdot (\phi_i \rho_i u_i \mathbf{v}_i) = tr(\mathbf{L}_i \boldsymbol{\sigma}_i) - \boldsymbol{\nabla} \cdot \mathbf{q}_i + \phi_i \rho_i r_i + \varepsilon_i + \Gamma_i u_i,$$

where $\mathbf{q}_i$ is a measure of the rate of heat flow across a unit area from the ith constituent, r_i is the rate of heat production per unit mass within the ith constituent, ε_i is the energy supply per unit mass per unit time to the ith constituent due to energy exchange between the constituents, u_i is the internal energy per unit mass of the ith constituent, and $\mathbf{L}_i$ is the velocity gradient of the ith constituent with respect to spatial coordinates.

Truesdell and Toupin [42] argue that for the overall conservation of energy in the mixture, "the energy supplied by an excess internal energy rate, plus the energy supplied by the work of the excess inertial forces against diffusion, plus the energy supplied by the creation of mass, must add up to zero for the mixture." This implies the following expression for the conservation of energy:

$$\sum_{i=1}^{n} \left[\varepsilon_i + \Gamma_i \left(u_i + \frac{1}{2} \mathbf{w}_i \cdot \mathbf{w}_i \right) + \mathbf{w}_i \cdot \pi_i \right] = 0,$$

or, equivalently, by appealing to (2.12),

$$(2.20) \qquad \sum_{i=1}^{n} \left[\varepsilon_i + \Gamma_i \left(u_i + \frac{1}{2} \mathbf{v}_i \cdot \mathbf{v}_i \right) + \mathbf{v}_i \cdot \pi_i \right] = 0.$$

3. The second law of thermodynamics. The second law of thermodynamics, which may be expressed in the form of the Clausius–Duhem inequality, places limitations on the admissible paths of thermodynamic processes, thereby placing restrictions on constitutive equations. The Clausius–Duhem inequality states that the rate of entropy increase is greater than or equal to the entropy input rate.

Following Rajagopal and Tao [37], it is assumed that the second law of thermodynamics holds for the mixture as a whole. In addition, a single, spatially uniform temperature is assumed for all phases since growth involves exchanges of mass among the phases and because the growth process itself is slow in comparison with the time it would take for any possible temperature gradients to equilibrate. Indeed, it is unlikely that stresses arising from a gradient of thermal expansion would be significant in biological tissues. Therefore if η_i denotes the entropy per unit mass of the ith constituent and θ denotes the absolute temperature of the mixture, then the inequality may be expressed by

$$(3.1) \qquad \sum_i \left[\frac{D^i}{Dt} (\phi_i \rho_i \eta_i) + \phi_i \rho_i \eta_i \boldsymbol{\nabla} . \mathbf{v}_i + \boldsymbol{\nabla} . \left(\frac{\mathbf{q}_i}{\theta} \right) - \frac{\phi_i \rho_i r_i}{\theta} \right] \geq 0.$$

The entropy inequality for the mixture is given by

$$(3.2) \qquad \rho_m \frac{D\eta_m}{Dt} + \sum_i \boldsymbol{\nabla} . \left(\frac{\mathbf{h}_i}{\theta} \right) - \sum_i \left(\frac{\phi_i \rho_i r_i}{\theta} \right) \geq 0,$$

where $\mathbf{h}_i$ is an influx vector for the ith constituent—as yet unrelated to $\mathbf{q}_i$—and η_m is the entropy density for the mixture defined by

$$\eta_m = \frac{1}{\rho_m} \sum_i \phi_i \rho_i \eta_i.$$

Hence, reconciling (3.1) and (3.2) requires the constitutive postulate,

$$(3.3) \qquad \mathbf{h}_i = \mathbf{q}_i + \phi_i \rho_i \theta \eta_i \mathbf{w}_i.$$

The second axiom of thermodynamics, as expressed by (3.1), may now be manipulated further to obtain a form from which constitutive equations may be deduced readily. To this end, the internal energies, u_i, will be eliminated in favor of the Helmholtz free energy densities, ψ_i, where

$$(3.4) \qquad \psi_i = u_i - \theta \eta_i.$$

Employing the Helmholtz free energy is particularly expedient when deducing constitutive equations since it is the portion of the internal energy available for doing mechanical work at constant temperature [30]. Further, the process of deducing constitutive equations is facilitated by the introduction of the chemical potential for each phase, which, for *general* mixtures, is given by the linear transformation

$$\mathbf{K}_i = \psi_i \mathbf{I} - \frac{\boldsymbol{\sigma}_i}{\phi_i \rho_i}.$$

The change of variables brought about by this transformation is common in the established literature relating to thermodynamic theories of constitutive equations. (See Bowen [11, 12] and Bowen and Wiese [14] for further details on the use of the chemical potential tensor in the study of general mixtures.)

Now, incorporating the balance of mass (2.1) and the energy equation (2.18) and introducing the variables ψ_i and $\mathbf{K}_i$ enable the second law of thermodynamics to be expressed by the dissipation inequality

$$(3.5) \qquad -tr \sum_{i=1}^{n} \phi_i \rho_i \mathbf{K}_i . \mathbf{L}_i - \rho_m \eta_m \frac{D\theta}{Dt} - \sum_{i=1}^{n} \frac{D^i \Psi_i}{Dt} - \sum_{i=1}^{n} \mathbf{v}_i . \left(\boldsymbol{\pi}_i + \frac{\Gamma_i}{2} \mathbf{v}_i \right) \geq 0,$$

where

$$(3.6) \qquad \Psi_i = \phi_i \rho_i \psi_i$$

represents the Helmholtz free energy of the ith constituent per unit mixture volume. A full derivation of this inequality is given in the appendix.

4. The assumption of incompressibility. In the present paper it will be assumed that each of the n phases is intrinsically incompressible, thereby placing an added constraint on their motion and giving rise to an indeterminacy in the second law of thermodynamics. The assumption of incompressibility is a common one in mathematical models of biological tissues on account of the high water content of the cells and interstitial fluid and the very low compressibility of other extracellular constituents, such as the large macromolecules comprising the extracellular matrix [1].

The balance of mass for the ith phase may now be expressed by

$$\frac{\partial \phi_i}{\partial t} + \boldsymbol{\nabla} . (\phi_i \mathbf{v}_i) = \frac{\Gamma_i}{\rho_i},$$

the summation of which over the n phases gives

$$(4.1) \qquad \sum_{i=1}^{n} (\boldsymbol{\nabla} \phi_i . \mathbf{v}_i + \phi_i \boldsymbol{\nabla} . \mathbf{v}_i) = \sum_{i=1}^{n} \frac{\Gamma_i}{\rho_i} \triangleq \hat{\gamma},$$

employing the saturation constraint (2.4). At this point, the principle of material frame-indifference (or *objectivity*) is considered, which requires that the response of the material and its individual constituents (and hence its constitutive equations, to be developed later from the present analysis) be independent of the observer [6]. Since relative velocities are objective, while individual velocities are not, (4.1) may be expressed in terms of relative velocities by noting that

$$\sum_{i=1}^{n} \mathbf{v}_i . \boldsymbol{\nabla} \phi_i = \sum_{i=1}^{n} (\mathbf{v}_i - \mathbf{v}_1) . \boldsymbol{\nabla} \phi_i,$$

where one phase is nominated as the reference phase with the subscript 1. Assuming that the densities of all phases are equal (so that $\rho_i = \rho_m = \rho$ and $\hat{\gamma} = 0$) enables (4.1) to reduce to

$$(4.2) \qquad \sum_{i=1}^{n} \left[(\mathbf{v}_i - \mathbf{v}_1) . \boldsymbol{\nabla} \phi_i + \phi_i tr \mathbf{L}_i \right] = 0.$$

From a mathematical standpoint, this assumption of equal phase densities allows the model to isolate the growth-induced stresses arising from spatially nonuniform (incompatible) growth, without the potentially confounding effects of additional stresses associated with density changes. In addition, the assumption of equal densities simplifies the ensuing analysis considerably. Further, the argument may be justified from a phenomenological point of view by noting that in a growing tissue, the growth process itself arises from exchanges of mass among individual tissue constituents. In particular, cells grow and proliferate by taking in interstitial fluid—water and proteins (and other molecules contained in the interstitial fluid)—and relinquish these substances on cell death. Thus, while different phases may exhibit fundamentally different mechanical behavior, they are composed of similar substances.

Now, recognizing that

$$\mathbf{L}_i = \grave{\mathbf{F}}_i \mathbf{F}_i^{-1}$$

by the chain rule, where

$$\grave{\mathbf{F}}_i = \frac{D^i \mathbf{F}_i}{Dt},$$

and that

$$(4.3) \qquad \sum_{i=1}^{n} \mathbf{v}_i . \left(\boldsymbol{\pi}_i + \frac{\Gamma_i}{2} \mathbf{v}_i \right) = \sum_{i=1}^{n} \left[\boldsymbol{\pi}_i + \frac{1}{2} \Gamma_i (\mathbf{v}_i - \mathbf{v}_1) \right] . (\mathbf{v}_i - \mathbf{v}_1)$$

now enables the second axiom of thermodynamics to be expressed in the form

$$-tr \sum_{i=1}^{n} \mathbf{F}_i^{-1} (\phi_i \rho \mathbf{K}_i - \phi_i \zeta \mathbf{I}) \grave{\mathbf{F}}_i - \rho \eta_m \frac{D\theta}{Dt} - \sum_{i=1}^{n} \frac{D^i \Psi_i}{Dt}$$

$$(4.4) \qquad - \sum_{i=1}^{n} \left[\boldsymbol{\pi}_i + \frac{1}{2} \Gamma_i (\mathbf{v}_i - \mathbf{v}_1) - \zeta \boldsymbol{\nabla} \phi_i \right] . (\mathbf{v}_i - \mathbf{v}_1) \geq 0,$$

where ζ is a Lagrangian multiplier.

5. Constitutive assumptions for a general n-phase mixture. As expressed by Coleman and Noll in [17], "a material is defined by a constitutive assumption, which is a restriction on the processes that are admissible in a body consisting of the material."

In discussing the various principles governing constitutive equations, Passman and Nunziato [33] describe the principle of equipresence as "too general," claiming that it is "difficult to accept as a universal axiom appropriate to all mixture theories." (According to this principle, "all dependent variables depend on all independent variables, unless the entropy inequality requires otherwise" [25, 41].) They proceed to explain that "in multiphase mixtures (where) the individual constituents are clearly separated physically, ... it is plausible to think of the mixture as being ideal, or phase separated. For such mixtures the Principle of Equipresence can reasonably be replaced by the Principle of Phase Separation." By this principle, the material-specific dependent variables of a given phase (such as the stress and the Helmholtz free energy density) depend only on the independent variables of that phase. The interaction variables (such as the momentum transfer term, $\boldsymbol{\pi}_i$) depend on all the independent variables. (See Passman and Nunziato [33] for a more detailed discussion of these principles.)

Much of the classical work in this field has relied on the former, more general principle. Thus, in predicating the current study on these classical, well-established approaches, this paper appeals to this general principle in deducing thermodynamically appropriate constitutive equations in spite of the fact that the individual phases of biological tissues are clearly separated and distinct. Nevertheless, the simpler principle of phase separation is used to advantage in subsequent analysis, allowing the constitutive equations to be manipulated into useable forms.

Furthermore, Ehlers [19] emphasises the fact that "the general constitutive framework must be based on the assumption of second-grade materials . . . , thus making use of the most natural framework in constitutive modelling for multiphase media, additionally avoiding so-called 'simple' results." Thus, following Bowen [12], Bowen and Weise [14], and Ehlers [19], and noting from (4.2) that the constitutive assumptions for $\mathbf{K}_i$ and $\boldsymbol{\pi}_i$ must reflect an indeterminacy consistent with the entropy inequality, the following general constitutive postulate is proposed:

$$\left(\Psi_i, \eta_i, \left(\boldsymbol{\pi}_i + \frac{1}{2}\Gamma_i(\mathbf{v}_i - \mathbf{v}_1) - \zeta\boldsymbol{\nabla}\phi_i\right), (\phi_i\rho\mathbf{K}_i - \phi_i\zeta\mathbf{I}), \mathbf{q}\right)$$

(5.1)
$$= f(\theta, \mathbf{F}_j, \dot{\mathbf{F}}_j, \mathbf{G}_j, \phi_j, \mathbf{n}_j, (\mathbf{v}_j - \mathbf{v}_1)),$$

where f is a smooth function, with the following quantities being defined for clarity:

$$\mathbf{G}_j = \mathbf{Grad}\mathbf{F}_j$$

and

$$\mathbf{n}_j = \boldsymbol{\nabla}\phi_j.$$

As discussed by Bowen in [10] and [12], (5.1) describes a mixture which allows for the combined effects of elasticity, heat conduction, diffusion, viscosity, buoyancy, immiscibility, and variable volume fractions. As noted by Bowen in [13], "an *immiscible* mixture is one where locally one can distinguish between mixture volumes and constituent volumes (and therefore) a model of an immiscible mixture would necessarily allow the volume fractions to effect the mixture response." Having established a general framework, then, it remains for a *particular* constitutive postulate to be chosen to carry the analysis through to completion, to arrive at a full set of modeling equations.

6. A biphasic mechanical model of tissue growth. In this section, the general constitutive assumption (5.1) is applied to a two-phase model comprising an elastic solid (indicated by the subscript s) and an inviscid fluid (indicated by the subscript f), being the simplest case of a solid-multiphase model. In this case, the constitutive equations reduce to

(6.1)
$$\left(\Psi_i, \eta_i, \left(\boldsymbol{\pi}_f + \frac{1}{2}\Gamma_f(\mathbf{v}_f - \mathbf{v}_s) - \zeta\boldsymbol{\nabla}\phi_f\right), (\phi_i\rho\mathbf{K}_i - \phi_i\zeta\mathbf{I}), \mathbf{q}\right) = f(\theta, \mathbf{F}_s, \mathbf{G}_s, (\mathbf{v}_f - \mathbf{v}_s))$$

with $i = f, s$. Since the effect of viscosity is not being considered in this simplified model, the derivatives of the deformation gradients do not appear among the independent variables in (6.1). The volume fractions and their gradients are also omitted from the set of independent variables since the *specific* Helmholtz free energy, ψ_i, is to

be considered independent of volume fraction, with the volume-averaged Helmholtz free energy, Ψ_i, being related to volume fraction via (3.6). Note that in a two-phase model, only one of the mass exchange terms, Γ_i, or volume fraction terms, ϕ_i, need be considered since the constraints (2.4) and (2.6) give the corresponding terms for the other phase. Further, since one of the phases is a solid and the other a fluid, the volume fractions ϕ_s and $\phi_f = 1 - \phi_s$ will henceforth be referred to as the *solidity* and the *porosity*, respectively.

Using (6.1) the total derivative of the Helmholtz free energy for the solid is given by

$$
\frac{D^s \Psi_s}{Dt} = \left(\frac{\partial \Psi_s}{\partial \theta}\right)\left(\frac{D\theta}{Dt}\right) + tr\left(\frac{\partial \Psi_s}{\partial \mathbf{F}_s}\right)^T \dot{\mathbf{F}}_s + C\left(\frac{\partial \Psi_s}{\partial \mathbf{G}_s}\right) \otimes \dot{\mathbf{G}}_s
$$
$$
+ \left(\frac{\partial \Psi_s}{\partial(\mathbf{v}_f - \mathbf{v}_s)}\right) \cdot \left[\frac{D^f(\mathbf{v}_f - \mathbf{v}_s)}{Dt} + \dot{\mathbf{F}}_f \mathbf{F}_f^{-1}(\mathbf{v}_s - \mathbf{v}_f) - \dot{\mathbf{F}}_s \mathbf{F}_s^{-1}(\mathbf{v}_s - \mathbf{v}_f)\right],
$$

while the total derivative of the Helmholtz free energy for the fluid is given by

$$
\frac{D^f \Psi_f}{Dt} = \left(\frac{\partial \Psi_f}{\partial \theta}\right)\left(\frac{D\theta}{Dt}\right) + tr\left(\frac{\partial \Psi_f}{\partial \mathbf{F}_s}\right)^T \left[\dot{\mathbf{F}}_s + \mathbf{G}_s \mathbf{F}_s^{-1}(\mathbf{v}_f - \mathbf{v}_s)\right]
$$
$$
+ C\left(\frac{\partial \Psi_f}{\partial \mathbf{G}_s}\right) \otimes \left[\dot{\mathbf{G}}_s + (\mathbf{Grad}\mathbf{G}_s)\mathbf{F}_s^{-1}(\mathbf{v}_f - \mathbf{v}_s)\right]
$$
$$
+ \left(\frac{\partial \Psi_f}{\partial(\mathbf{v}_f - \mathbf{v}_s)}\right) \cdot \left[\frac{D^f(\mathbf{v}_f - \mathbf{v}_s)}{Dt}\right].
$$

Therefore the entropy inequality becomes

$$
-tr\sum_{i=f,s} \mathbf{F}_i^{-1}\left(\phi_i\rho\mathbf{K}_i - \phi_i\zeta\mathbf{I}\right)\dot{\mathbf{F}}_i - \rho\eta_m\frac{d\theta}{dt}
$$
$$
-\left(\boldsymbol{\pi}_f + \frac{1}{2}\Gamma_f(\mathbf{v}_f - \mathbf{v}_s) - \zeta\boldsymbol{\nabla}\phi_f\right).(\mathbf{v}_f - \mathbf{v}_s) - \left(\frac{\partial \Psi_I}{\partial \theta}\right)\frac{D\theta}{Dt}
$$
$$
-tr\mathbf{F}_s^{-1}\left(\mathbf{F}_s\left(\frac{\partial \Psi_I}{\partial \mathbf{F}_s}\right)^T - (\mathbf{v}_s - \mathbf{v}_f) \otimes \left(\frac{\partial \Psi_s}{\partial(\mathbf{v}_f - \mathbf{v}_s)}\right)\right)\dot{\mathbf{F}}_s
$$
$$
-(\mathbf{v}_f - \mathbf{v}_s).\left(\mathbf{F}_s^{-1T}\left(\frac{\partial \Psi_f}{\partial \mathbf{F}_s}[\mathbf{G}_s]\right)\right)
$$
$$
-C\left(\frac{\partial \Psi_I}{\partial \mathbf{G}_s}\right) \otimes \dot{\mathbf{G}}_s - (\mathbf{v}_f - \mathbf{v}_s).\left(\mathbf{F}_s^{-1T}\left(\frac{\partial \Psi_f}{\partial \mathbf{G}_s}[\mathbf{Grad}\mathbf{G}_s]\right)\right)
$$
$$
-\left(\frac{\partial \Psi_I}{\partial(\mathbf{v}_f - \mathbf{v}_s)}\right) \cdot \left[\frac{D^f(\mathbf{v}_f - \mathbf{v}_s)}{Dt}\right]
$$
$$
-tr\mathbf{F}_f^{-1}\left((\mathbf{v}_s - \mathbf{v}_f) \otimes \left(\frac{\partial \Psi_s}{\partial(\mathbf{v}_f - \mathbf{v}_s)}\right)\right)\dot{\mathbf{F}}_f \geq 0,
$$

where

$$
\Psi_I = \sum_{i=f,s} \Psi_i = \sum_{i=f,s} \phi_i\rho_i\psi_i
$$

denotes the inner part of the mixture Helmholtz free energy. Here, the notation $\mathbf{X}[\mathbf{Y}]$, where $\mathbf{X}$ is a tensor of rank p and $\mathbf{Y}$ is a tensor of rank $p+1$, denotes a vector defined

in component form by

$$\mathbf{X}[\mathbf{Y}] = X_{k_1 k_2 \ldots k_p} Y^{k_1 k_2 \ldots k_p q} \mathbf{e}_q.$$

where $\mathbf{e}_q$ are basis vectors. (See, for example, (1.10) in Bowen and Weise [14] or (1.1.58) in Bowen [12].) Now rearranging the inequality produces

$$-tr\mathbf{F}_s^{-1} \left(\phi \rho_s \mathbf{K}_s - \phi_s \zeta \mathbf{I} + \mathbf{F}_s \left(\frac{\partial \Psi_I}{\partial \mathbf{F}_s} \right)^T - (\mathbf{v}_s - \mathbf{v}_f) \otimes \left(\frac{\partial \Psi_s}{\partial (\mathbf{v}_f - \mathbf{v}_s)} \right) \right) \dot{\mathbf{F}}_s$$

$$- tr\mathbf{F}_f^{-1} \left(\phi_f \rho \mathbf{K}_f - \phi_f \zeta \mathbf{I} + (\mathbf{v}_s - \mathbf{v}_f) \otimes \left(\frac{\partial \Psi_s}{\partial (\mathbf{v}_f - \mathbf{v}_s)} \right) \right) \dot{\mathbf{F}}_f$$

$$- \left(\rho \eta_m + \frac{\partial \Psi_I}{\partial \theta} \right) \frac{D\theta}{Dt} - \left(\frac{\partial \Psi_I}{\partial \mathbf{g}} \right) \cdot \frac{D\mathbf{g}}{Dt} - C \left(\frac{\partial \Psi_I}{\partial \mathbf{G}_s} \right) \otimes \dot{\mathbf{G}}_s$$

$$- (\mathbf{v}_f - \mathbf{v}_s) \cdot \left(\mathbf{F}_s^{-1T} \left(\frac{\partial \Psi_f}{\partial \mathbf{G}_s} [\mathbf{Grad} \mathbf{G}_s] \right) \right) - \left(\frac{\partial \Psi_I}{\partial (\mathbf{v}_f - \mathbf{v}_s)} \right) \cdot \left[\frac{D^f (\mathbf{v}_f - \mathbf{v}_s)}{Dt} \right]$$

$$- \left[\boldsymbol{\pi}_f + \frac{1}{2} \Gamma_f (\mathbf{v}_f - \mathbf{v}_s) - \zeta \boldsymbol{\nabla} \phi_f + \mathbf{F}_s^{-1T} \left(\frac{\partial \Psi_f}{\partial \mathbf{F}_s} [\mathbf{G}_s] \right) \right] \cdot (\mathbf{v}_f - \mathbf{v}_s) \geq 0.$$

Following Coleman and Noll's argument [17],

$$\theta, \ \mathbf{F}_s, \ \mathbf{G}_s \ \text{and} \ (\mathbf{v}_f - \mathbf{v}_s)$$

are held *fixed* while *varying* the quantities

$$\frac{D\theta}{Dt}, \ \dot{\mathbf{F}}_s, \ \dot{\mathbf{G}}_s, \ \mathbf{Grad} \mathbf{G}_s \ \text{and} \ \frac{D^f (\mathbf{v}_f - \mathbf{v}_s)}{Dt}.$$

This yields the following necessary and sufficient conditions:

$$(6.2) \qquad \phi_s \rho \mathbf{K}_s - \phi_s \zeta \mathbf{I} + \mathbf{F}_s \left(\frac{\partial \Psi_I}{\partial \mathbf{F}_s} \right)^T - (\mathbf{v}_s - \mathbf{v}_f) \otimes \left(\frac{\partial \Psi_s}{\partial (\mathbf{v}_f - \mathbf{v}_s)} \right) = \mathbf{0},$$

$$(6.3) \qquad \phi_f \rho \mathbf{K}_f - \phi_f \zeta \mathbf{I} + (\mathbf{v}_s - \mathbf{v}_f) \otimes \left(\frac{\partial \Psi_s}{\partial (\mathbf{v}_f - \mathbf{v}_s)} \right) = \mathbf{0},$$

$$\rho \eta_m = - \frac{\partial \Psi_I}{\partial \theta},$$

$$\frac{\partial \Psi_I}{\partial \mathbf{G}_s} = \mathbf{0},$$

$$\sum_{i=f,s} (\mathbf{v}_i - \mathbf{v}_s) \cdot \left(\mathbf{F}_s^{-1T} \left(\frac{\partial \Psi_f}{\partial \mathbf{G}_s} [\mathbf{Grad} \mathbf{G}_s] \right) \right) = \mathbf{0},$$

$$\frac{\partial \Psi_I}{\partial (\mathbf{v}_f - \mathbf{v}_s)} = \mathbf{0},$$

and

$$(6.4) \qquad -\mathbf{f} \cdot (\mathbf{v}_f - \mathbf{v}_s) \geq 0,$$

where

$$\mathbf{f} = \boldsymbol{\pi}_f + \frac{1}{2} \Gamma_f (\mathbf{v}_f - \mathbf{v}_s) - \zeta \boldsymbol{\nabla} \phi_f + \mathbf{F}_s^{-1T} \left(\frac{\partial \Psi_f}{\partial \mathbf{F}_s} [\mathbf{G}_s] \right).$$

7. Development of linearized constitutive equations. In this section, the constitutive equations (6.2), (6.3), and (6.4) deduced in the previous section will be linearized about the thermodynamic equilibrium using the method discussed by Bowen [12], in order to express the equations in useable forms.

Let $\hat{\xi}$ denote the complete set of independent variables

$$\hat{\xi} = (\mathbf{F}_s, \mathbf{G}_s, (\mathbf{v}_f - \mathbf{v}_s)),$$

noting that there is no longer any dependence on temperature or temperature gradients. Let $\hat{\xi}^{0E}$ denote the subset of these variables,

$$\hat{\xi}^{0E} = (\mathbf{F}_s, \mathbf{G}_s, \mathbf{0}).$$

Let $\hat{\xi}^{0R}$ denote the reference state about which the constitutive equations for $\mathbf{f}$ and $\boldsymbol{\sigma}_s$ will be linearized,

$$\hat{\xi}^{0R} = (\mathbf{I}, \mathbf{0}, \mathbf{0}).$$

At the state $\hat{\xi}^{0E}$, where $\mathbf{v}_s = \mathbf{v}_f$, the quantity

$$-\mathbf{f}.(\mathbf{v}_f - \mathbf{v}_s) \geq 0$$

is a minimum, such that $\hat{\xi}^{0E}$ defines the thermodynamic equilibrium. Now in the vicinity of the thermodynamic equilibrium,

$$\phi_s \rho \mathbf{K}_s = \phi_s \zeta \mathbf{I} - \mathbf{F}_s \left(\frac{\partial \Psi_I}{\partial \mathbf{F}_s} \right)^T,$$

$$\phi_f \rho \mathbf{K}_f = \phi_f \zeta \mathbf{I},$$

and

$$\mathbf{f} = -\kappa(\mathbf{v}_s - \mathbf{v}_f),$$

where κ is a constant, sometimes referred to as the diffusive drag coefficient. Therefore,

(7.1)
$$\boldsymbol{\sigma}_s = \phi_s \rho \psi_s \mathbf{I} - \phi_s \zeta \mathbf{I} + \mathbf{F}_s \left(\frac{\partial \Psi_I}{\partial \mathbf{F}_s} \right)^T,$$

(7.2)
$$\boldsymbol{\sigma}_f = \phi_f \rho \psi_f \mathbf{I} - \phi_f \zeta \mathbf{I},$$

and

(7.3)
$$\boldsymbol{\pi}_f = -\kappa(\mathbf{v}_s - \mathbf{v}_f) - \frac{1}{2}\Gamma_f(\mathbf{v}_s - \mathbf{v}_f) + \zeta \boldsymbol{\nabla}\phi_f - \mathbf{F}_s^{-1T} \left(\frac{\partial \Psi_f}{\partial \mathbf{F}_s}[\mathbf{G}_s] \right).$$

Now, appealing to the principle of phase separation,

$$\boldsymbol{\sigma}_s = (\phi_s \rho \psi_s - \phi_s \zeta)\mathbf{I} + \rho \mathbf{F}_s \left(\frac{\partial(\phi_s \psi_s + \phi_f \psi_f)}{\partial \mathbf{F}_s} \right)^T$$

$$= -\phi_s(\zeta - \rho\psi_s)\mathbf{I} + \rho \mathbf{F}_s \left(\frac{\partial \phi_s}{\partial \mathbf{F}_s}\psi_s + \phi_s \frac{\partial \psi_s}{\partial \mathbf{F}_s} - \frac{\partial \phi_s}{\partial \mathbf{F}_s}\psi_f \right)^T.$$

Hence,

$$(7.4) \qquad \boldsymbol{\sigma}_s = -\phi_s(\zeta - \rho\psi_s)\mathbf{I} + \phi_s\rho\mathbf{F}_s\left(\frac{\partial\psi_s}{\partial\mathbf{F}_s}\right)^T + \rho(\psi_s - \psi_f)\mathbf{F}_s\left(\frac{\partial\phi_s}{\partial\mathbf{F}_s}\right)^T.$$

Similarly, for the momentum transfer terms, the principle of phase separation gives

$$(7.5) \qquad \boldsymbol{\pi}_f = -\kappa(\mathbf{v}_f - \mathbf{v}_s) - \frac{1}{2}\Gamma_f(\mathbf{v}_f - \mathbf{v}_s) + \zeta\boldsymbol{\nabla}\phi_f + \mathbf{F}_s^{-1T}\left(\rho\psi_f\left(\frac{\partial\phi_s}{\partial\mathbf{F}_s}\right)[\mathbf{G}_s]\right).$$

8. Modeling biological growth: Mass exchanges, solid deformation, and fluid flow. To reduce (7.4) to a usable form, an expression for $\frac{\partial\phi_s}{\partial\mathbf{F}_s}$ must be deduced from the balance of mass for the solid phase, which is given by

$$(8.1) \qquad \frac{D^s}{Dt}(\rho\phi_s\det\mathbf{F}_s) = \Gamma_s\det\mathbf{F}_s.$$

Thus, in general

$$(8.2) \qquad \rho\phi_s\det\mathbf{F}_s = \int_0^t \Gamma_s(\mathbf{X}_s, \tau)\det\mathbf{F}_s(\mathbf{X}_s, \tau)d\tau \triangleq \hat{\Theta}_s,$$

where

$$\hat{\Theta}_s = \hat{\Theta}_s(\mathbf{X}_s, t),$$

and $\mathbf{X}_s$ denotes the reference coordinates. Hence, using Jacobi's identity [42],

$$\frac{\partial(\det\mathbf{F}_s)}{\partial\mathbf{F}_s} = (\det\mathbf{F}_s)\mathbf{F}_s^{-1T},$$

the derivative of the solidity with respect to the solid deformation gradient is given by

$$(8.3) \qquad \frac{\partial\phi_s}{\partial\mathbf{F}_s} = -\phi_s\mathbf{F}_s^{-1T} + \frac{1}{\rho\det\mathbf{F}_s}\frac{\partial\hat{\Theta}_s}{\partial\mathbf{F}_s}.$$

Therefore, (7.4) becomes

(8.4)

$$\boldsymbol{\sigma}_s = -\phi_s(\zeta - \rho\psi_s)\mathbf{I} + \phi_s\rho\mathbf{F}_s\left(\frac{\partial\psi_s}{\partial\mathbf{F}_s}\right)^T - \phi_s\rho(\psi_s - \psi_f) + \frac{(\psi_s - \psi_f)}{\det\mathbf{F}_s}\mathbf{F}_s\left(\frac{\partial\hat{\Theta}_s}{\partial\mathbf{F}_s}\right)^T.$$

Thus the constitutive equations are

$$(8.5) \qquad \boldsymbol{\sigma}_s = -\phi_s P\mathbf{I} + \phi_s\rho\mathbf{F}_s\left(\frac{\partial\psi_s}{\partial\mathbf{F}_s}\right)^T + \frac{(\psi_s - \psi_f)}{\det\mathbf{F}_s}\mathbf{F}_s\left(\frac{\partial\hat{\Theta}_s}{\partial\mathbf{F}_s}\right)^T$$

and

$$(8.6) \qquad \boldsymbol{\sigma}_f = -\phi_f P\mathbf{I},$$

where

$$(8.7) \qquad P = \zeta - \rho\psi_f.$$

In addition,

$$(8.8) \qquad \frac{\partial\phi_s}{\partial\mathbf{X}_s} = \frac{\partial\phi_s}{\partial\mathbf{F}_s}\left[\frac{\partial\mathbf{F}_s}{\partial\mathbf{X}_s}\right] = \left(-\phi_s\mathbf{F}_s^{-1T} + \frac{1}{\rho\det\mathbf{F}_s}\frac{\partial\hat{\Theta}_s}{\partial\mathbf{F}_s}\right)[\mathbf{G}_s].$$

Now

(8.9)
$$\boldsymbol{\nabla}\phi_s = \frac{\partial \phi_s}{\partial \mathbf{x}_s} = \mathbf{F}_s^{-1T} \frac{\partial \phi_s}{\partial \mathbf{X}_s},$$

where $\mathbf{x}_s$ denotes spatial coordinates. Hence

$$\boldsymbol{\nabla}\phi_s = \mathbf{F}_s^{-1T} \left(\frac{\partial \phi_s}{\partial \mathbf{F}_s}\right)[\mathbf{G}_s] = \mathbf{F}_s^{-1T}\left(-\phi_s \mathbf{F}_s^{-1T} + \frac{1}{\rho \det \mathbf{F}_s}\frac{\partial \hat{\Theta}_s}{\partial \mathbf{F}_s}\right)[\mathbf{G}_s].$$

Thus, (7.5) for the momentum transfer term for the fluid phase, $\boldsymbol{\pi}_f$, now becomes

$$\boldsymbol{\pi}_f = -\kappa(\mathbf{v}_f - \mathbf{v}_s) - \frac{1}{2}\Gamma_f(\mathbf{v}_f - \mathbf{v}_s) + \zeta\boldsymbol{\nabla}\phi_f + \rho\psi_f\boldsymbol{\nabla}\phi_s$$

(8.10)
$$= P\boldsymbol{\nabla}\phi_f - \kappa(\mathbf{v}_f - \mathbf{v}_s) - \frac{1}{2}\Gamma_f(\mathbf{v}_f - \mathbf{v}_s).$$

Noting the conservation of linear momentum,

$$\boldsymbol{\pi}_f + \Gamma_f\mathbf{v}_f + \boldsymbol{\pi}_s + \Gamma_s\mathbf{v}_s = \mathbf{0}$$

then gives the momentum transfer term for the solid phase, $\boldsymbol{\pi}_s$, being

(8.11)
$$\boldsymbol{\pi}_s = P\boldsymbol{\nabla}\phi_s + \kappa(\mathbf{v}_f - \mathbf{v}_s) - \frac{1}{2}\Gamma_f(\mathbf{v}_f - \mathbf{v}_s).$$

In a detailed analysis of Darcy's law for growing porous media, Preziosi and Farina [36] have shown that the process of interphase mass exchange plays a negligible role in momentum transfer. Thus, the final term in each of (8.10) and (8.11) may be neglected in practice.

Returning to the constitutive equation for the stress in the solid (8.5), note that the quantity $\hat{\Theta}_s$ depends on both the mass exchange term, Γ_s, and the solid phase deformation, $\mathbf{F}_s$. Clearly, then, manipulation of this equation into a useable form requires a phenomenological assumption about the functional form of the mass exchange term. Furthermore, the distinguishing feature of a mass-exchange model which describes biological growth, as opposed to, say, models which describe solidification/melting or some other phase change, is the fact that the mass-exchange term, Γ_s, and the expansion/contraction of the solid matrix, $\det \mathbf{F}_s$, *are not independent*. Indeed, such is the very essence of the unique closure problem peculiar to the study of biological growth, and it is a novel feature of the present work that such phenomenological aspects of growing tissues may be incorporated into the modeling framework.

Consider that the balance of mass for the solid phase may also be expressed in the form

(8.12)
$$\rho\frac{D^s\phi_s}{Dt} + \phi_s\rho\frac{1}{\det\mathbf{F}_s}\frac{D^s(\det\mathbf{F}_s)}{Dt} = \Gamma_s.$$

Note that

$$\rho\frac{D^s\phi_s}{Dt} = \frac{D^s}{Dt}\left(\frac{m_s}{V_m}\right),$$

where m_s is the mass of the solid phase in V_m, the volume of the mixture. Now

$$\frac{D^s}{Dt}\left(\frac{m_s}{V_m}\right) = \frac{D^sm_s}{Dt}\left(\frac{1}{V_m}\right) - \frac{\phi_s\rho}{V_m}\frac{D^sV_m}{Dt}.$$

Since

$$\frac{D^s m_s}{Dt}\left(\frac{1}{V_m}\right) = \Gamma_s,$$

the quantity

$$-\frac{\phi_s \rho}{V_m}\frac{D^s V_m}{Dt}$$

reflects the time rate of change of the solidity which results from the flow of fluid into, or out of, the deformed solid matrix. Now since

$$\Gamma_s = \underbrace{\frac{D^s}{Dt}\left(\frac{m_s}{V_m}\right)}_{total} - \underbrace{\left(-\frac{\phi_s \rho}{V_m}\frac{D^s V_m}{Dt}\right)}_{flow/deformation},$$

then

$$\underbrace{\frac{D^s(\phi_s\rho)}{Dt}}_{total} + \underbrace{\phi_s\rho\frac{1}{\det \mathbf{F}_s}\frac{D^s(\det \mathbf{F}_s)}{Dt}}_{flow/deformation} = \underbrace{\frac{D^s}{Dt}\left(\frac{m_s}{V_m}\right)}_{total} + \underbrace{\left(\frac{\phi_s\rho}{V_m}\frac{D^s V_m}{Dt}\right)}_{flow/deformation}$$

$$= \Gamma_s$$

describes the mass balance for the solid phase.

Therefore, since the solidity is regulated by two separate processes—mass exchange and solid matrix deformation/fluid flow—a further constitutive postulate is required to relate any two of the three quantities ϕ_s, Γ_s, and $\det\mathbf{F}_s$ to decompose the balance of mass into two independent equations.

Suppose, for example, that the mass exchange and solid matrix deformation are related in such a way as to keep the volume fractions constant, reflecting a tissue which tends to exhibit a "natural" ratio of cells to extracellular fluid. (Note that this particular choice of constitutive postulate would be insufficient to model a growing tumor tissue which contains regions of coagulative necrosis, since these regions consist predominantly of fluid and cellular debris and are therefore characterized by significantly higher proportions of fluid than the rest of the tissue.) In this case, the balance of mass would be represented by

(8.13) $$\rho\frac{D^s \phi_s}{Dt} = 0$$

and

(8.14) $$\rho\phi_s\frac{1}{\det\mathbf{F}_s}\frac{D^s(\det\mathbf{F}_s)}{Dt} = \rho\phi_s\boldsymbol{\nabla}\cdot\mathbf{v}_s = \Gamma_s.$$

Now that the constitutive postulate (8.14) has been proposed, the phenomenological assumption for Γ_s is no longer required to be a function of $\det\mathbf{F}_s$.

Assuming, for example, that Γ_s is proportional to the effective cell density, $\rho\phi_s$, and to some regulating factor such as nutrient concentration, c, implies that

(8.15) $$\Gamma_s = \alpha\rho\phi_s c,$$

where α is a constant of proportionality and where the functional form for c will also be determined by a phenomenological assumption (appealing to a diffusion model, say).

Now (8.1) becomes

$$\frac{1}{\rho\phi_s \det \mathbf{F}_s} \frac{D^s}{Dt}(\rho\phi_s \det \mathbf{F}_s) = \alpha c,$$

so that

$$\rho\phi_s \det \mathbf{F}_s = e^{\int_0^t \alpha c(\mathbf{X}_s, \tau) d\tau},$$

which gives

$$(8.16) \qquad \frac{\partial \phi_s}{\partial \mathbf{F}_s} = -\phi_s \mathbf{F}_s^{-1T}.$$

Now the constitutive equations reduce to

$$(8.17) \qquad \boldsymbol{\sigma}_s = -\phi_s P\mathbf{I} + \phi_s \rho \mathbf{F}_s \left(\frac{\partial \psi_s}{\partial \mathbf{F}_s}\right)^T$$

and

$$(8.18) \qquad \boldsymbol{\sigma}_f = -\phi_f P\mathbf{I},$$

with P being given by (8.7). Substitution of the new definition for $\frac{\partial \phi_s}{\partial \mathbf{F}_s}$ into (8.8) and (8.9) then produces (8.10) and (8.11), illustrating that the momentum equations are unaffected by the simplified definition for $\frac{\partial \phi_s}{\partial \mathbf{F}_s}$.

8.1. Linear elasticity. If the solid phase is assumed to be elastically isotropic, the Helmholtz free energy density is a function of the solid deformation gradient, $\mathbf{F}_s$, through the left Cauchy–Green strain tensor defined by $\mathbf{B}_s = \mathbf{F}_s \mathbf{F}_s^T$, so that

$$(8.19) \qquad \mathbf{F}_s \left(\frac{\partial \psi_s}{\partial \mathbf{F}_s}\right)^T = 2\mathbf{B}_s \frac{\partial \psi_s}{\partial \mathbf{B}_s}.$$

To formulate a linearized constitutive equation, an approximate expression is required for the right-hand side of (8.19) which is valid in the vicinity of the reference state $\hat{\xi}^{0R}$. Departures from $\hat{\xi}^{0R}$ may be measured by the quantity ϵ defined by

$$\epsilon^2 = tr\mathbf{H}_s\mathbf{H}_s^T + C\left(\mathbf{GradH_s} \otimes \mathbf{GradH_s}\right) + (\mathbf{v}_f - \mathbf{v}_s)\cdot(\mathbf{v}_f - \mathbf{v}_s),$$

where $\mathbf{H}_s = \mathbf{F}_s - \mathbf{I}$ is the displacement gradient of the solid phase. Thus, departure from the reference state, $\hat{\xi}^{0R}$, is *small* when $\epsilon < 1$.

Moreover,

$$\begin{aligned}\mathbf{B}_s &= \mathbf{I} + 2\mathbf{E}_s + \mathbf{H}_s\mathbf{H}_s^T \\ &= \mathbf{I} + 2\mathbf{E}_s + O(\epsilon^2),\end{aligned}$$

where $\mathbf{E}_s$ is the classical infinitesimal strain tensor defined by

$$(8.20) \qquad \mathbf{E}_s = \frac{1}{2}\left(\mathbf{H}_s + \mathbf{H}_s^T\right).$$

Thus,

$$(8.21) \qquad \mathbf{F}_s\left(\frac{\partial \psi_s}{\partial \mathbf{F}_s}\right)^T = \frac{\partial \psi_s}{\partial \mathbf{E}_s} + 2\mathbf{E}_s\left(\frac{\partial \psi_s}{\partial \mathbf{E}_s}(\hat{\xi}^{0R})\right)$$

in the linear theory. The Helmholtz free energy density for the solid phase, ψ_s, is now to be expanded into a polynomial about $\hat{\xi}^{0R}$, including terms up to second order since ψ_s must be differentiated to obtain the stress. Furthermore, since the Helmholtz free energy is, by definition, the energy available to do mechanical work, it is a function only of the component of the strain tensor associated with a stress response. Indeed, the strain tensor $\mathbf{E}_s$ may be decomposed into the contribution due to growth $\mathbf{E}_s^G$ and the contribution due to stress $\mathbf{E}_s^S$, i.e.,

$$\mathbf{E}_s = \mathbf{E}_s^G + \mathbf{E}_s^S.$$

Now,

$$(8.22) \qquad \psi_s\left(\mathbf{B}_s\right) = \psi_s\left(\mathbf{I}\right) + \sigma_0\left(tr\mathbf{E}_s^S\right) + \frac{1}{2}\lambda_0\left(tr\mathbf{E}_s^S\right)^2 + \mu_0 tr\left(\mathbf{E}_s^S\mathbf{E}_s^S\right) + O(\epsilon^3).$$

Thus, substituting (8.22) into (8.21) yields

$$\boldsymbol{\sigma}_s = -\phi_s P\mathbf{I} + \lambda\left(tr\mathbf{E}_s^S\right)\mathbf{I} + 2\mu\mathbf{E}_s^S,$$

where

$$\lambda = \lambda(\rho_s, \phi_s) = \lambda_0$$

and

$$\mu = \mu(\rho_s, \phi_s) = \mu_0 + \sigma_0,$$

where σ_0, the so-called prestress, will be assumed zero. Now, the portion of the strain tensor due to growth may be expressed by

$$\mathbf{E}_s^G = g\boldsymbol{\Omega},$$

where g is the increase in volume per unit volume of the solid matrix due to growth (as yet unrelated to Γ_s), and

$$(8.23) \qquad \boldsymbol{\Omega} \triangleq \begin{bmatrix} \gamma_1 & 0 & 0 \\ 0 & \gamma_2 & 0 \\ 0 & 0 & \gamma_3 \end{bmatrix}$$

defines the anisotropy tensor, where γ_1, γ_2, and γ_3 are the anisotropic growth multipliers defined by Araujo and McElwain [4, 3] with $\gamma_1 + \gamma_2 + \gamma_3 = 1$. Hence, isotropic growth corresponds to $\gamma_1 = \gamma_2 = \gamma_3 = \frac{1}{3}$. By allowing the tissue to grow anisotropically in response to the prevailing stress field, so that the expansion occurs preferentially in directions of least stress, the constitutive law is able to exhibit stress-relaxation in the absence of viscous dissipation. The mathematical theory of anisotropic growth has been developed by Araujo and McElwain [4, 3], while the phenomenon has been demonstrated experimentally by Helmlinger et al. [24]. Thus, in regularizing the elasticity by incorporating stress-relaxation into the growth component of the constitutive equation rather than in the stress-response component, anisotropic growth may be said to impart a *pseudo-viscoelasticity* to growing tissues. Appropriate functional forms for the anisotropic growth multipliers will be considered in the next paper in this series.

Now the constitutive equation for the solid phase becomes

$$\boldsymbol{\sigma}_s = -\phi_s P \mathbf{I} + \lambda \left(tr\mathbf{E}_s - g \right) \mathbf{I} + 2\mu \left(\mathbf{E}_s - g\boldsymbol{\Omega} \right)$$

(8.24)
$$= -\phi_s P \mathbf{I} + \lambda tr\mathbf{E}_s \mathbf{I} + 2\mu \mathbf{E}_s - g \left(3\lambda + 2\mu \right) \boldsymbol{\Omega}.$$

Note that (8.24) was derived based on the two key assumptions of the intrinsic incompressibility of the phases and constant volume fractions, which together imply that $\lambda \to \infty$. While this may generally be introduced to the model by initially permitting compressibility and then allowing λ to tend to infinity in the *solution* of the boundary value problem, a more convenient approach in this case is to make the strain tensor the subject of the equation by noting that the trace of (8.24) is

$$tr\mathbf{E}_s = \frac{tr\boldsymbol{\sigma}_s + 3\phi_s P}{3\lambda + 2\mu} + g,$$

which gives

(8.25)
$$\mathbf{E}_s = \frac{1}{2\mu}\boldsymbol{\sigma}_s - \frac{\lambda}{2\mu(3\lambda + 2\mu)}(tr\boldsymbol{\sigma}_s + 3\phi_s P)\mathbf{I} + g\boldsymbol{\Omega}.$$

Now, in the limit as $\lambda \to \infty$, (8.25) becomes

(8.26)
$$\mathbf{E}_s = \frac{1}{2\mu}\boldsymbol{\sigma}_s - \left(\frac{tr\boldsymbol{\sigma}_s + 3\phi_s P}{6\mu} \right) \mathbf{I} + g\boldsymbol{\Omega}.$$

Note that while (8.26) represents a correct statement of the relationship between stress and strain when growth occurs, it must be able to reflect the fact that growth is a continuous process which creates movement. Thus, to accommodate the continuous expansion of the solid matrix due to the growth process, (8.25) must be differentiated with respect to time using an objective convected tensorial derivative such as the corotational (Jaumann) derivative (see, for example, [8] or [27]). Thus, (8.26) becomes

$$\frac{\mathcal{D}\mathbf{E}_s}{\mathcal{D}t} = \frac{1}{2\mu}\frac{\mathcal{D}\boldsymbol{\sigma}_s}{\mathcal{D}t} - \frac{1}{6\mu}\frac{\mathcal{D}}{\mathcal{D}t}\left(tr\boldsymbol{\sigma}_s + 3\phi_s P \right) \mathbf{I} + \frac{\mathcal{D}g}{\mathcal{D}t}\boldsymbol{\Omega},$$

where the notation $\frac{\mathcal{D}}{\mathcal{D}t}$ denotes an appropriate convected derivative. Taking the trace of this new equation now gives[1]

$$\frac{\mathcal{D}g}{\mathcal{D}t} = \boldsymbol{\nabla} \cdot \mathbf{v}_s + \frac{3\phi_s}{2\mu}\frac{\mathcal{D}P}{\mathcal{D}t},$$

which identifies the relationship between g and Γ_s via (8.14), being

(8.27)
$$\Gamma_s = \phi_s \rho \frac{\mathcal{D}g}{\mathcal{D}t} - \frac{3\phi_s^2 \rho}{2\mu}\frac{\mathcal{D}P}{\mathcal{D}t}.$$

This enables the constitutive equation to be expressed in the form

$$\frac{\mathcal{D}\mathbf{E}_s}{\mathcal{D}t} = \frac{1}{2\mu}\frac{\mathcal{D}\boldsymbol{\sigma}_s}{\mathcal{D}t} - \frac{1}{6\mu}\frac{\mathcal{D}}{\mathcal{D}t}\left(tr\boldsymbol{\sigma}_s + 3\phi_s P \right) \mathbf{I} + \left(\boldsymbol{\nabla} \cdot \mathbf{v}_s + \frac{3\phi_s}{2\mu}\frac{\mathcal{D}P}{\mathcal{D}t} \right) \boldsymbol{\Omega}$$

---

[1]Strictly, the trace of the convected derivative of the infinitesimal strain tensor should be the divergence of the velocity vector with respect to the *reference* coordinates, i.e., $\mathbf{Div}(\mathbf{v_s})$ rather than $\boldsymbol{\nabla} \cdot \mathbf{v}_s$, based on the definition of the infinitesimal strain tensor given in (8.20). Nevertheless, if the strains required to ensure compatibility are small, as appropriate to the use of linearized constitutive equations, then $\mathbf{Div}(\mathbf{v_s})$ and $\boldsymbol{\nabla} \cdot \mathbf{v}_s$ may be used interchangeably here.

or

$$(8.28) \qquad \frac{\mathcal{D}\mathbf{E}_s}{\mathcal{D}t} = \boldsymbol{\nabla} \cdot \mathbf{v}_s \boldsymbol{\Omega} + \frac{1}{2\mu} \frac{\mathcal{D}}{\mathcal{D}t} \left(\boldsymbol{\sigma}_s + \frac{1}{3} tr \boldsymbol{\sigma}_s \right) + \frac{\phi_s}{2\mu} \frac{\mathcal{D}P}{\mathcal{D}t} \left(3\boldsymbol{\Omega} - \mathbf{I} \right),$$

which reduces to

$$(8.29) \qquad \frac{\mathcal{D}\mathbf{E}_s}{\mathcal{D}t} = \frac{1}{3} \boldsymbol{\nabla} \cdot \mathbf{v}_s \mathbf{I} + \frac{1}{2\mu} \frac{\mathcal{D}}{\mathcal{D}t} \left(\boldsymbol{\sigma}_s + \frac{1}{3} tr \boldsymbol{\sigma}_s \right)$$

in the special case of isotropic growth.

9. Summary of biphasic equations and comparison with single phase equations. Table 9.1 gives a summary of the suite of equations for the biphasic model of a growing tissue developed in this paper. Intriguingly, only the special case of isotropic growth gives rise to a solid phase constitutive equation identical to that used in single phase models, which consider growth as an analogy to thermal expansion. Nevertheless, it is essential to recognize that this combination of elasticity and isotropic growth does not incorporate the crucial aspect of stress-relaxation into the constitutive law. Indeed Lubkin and Jackson [29] explain that "the fatal mathematical combination of multiple phases, elasticity, and contractility renders the contractile-poroelastic model ill-posed.... The elasticity must then be regularized by a viscous term in order for solutions to exist." Araujo and McElwain [4] have shown that the elasticity may be regularized by considering *anisotropic* growth, thereby obviating the necessity to appeal to more complicated viscoelastic principles in many situations.

TABLE 9.1
Comparison of biphasic equations with single phase equivalents.

Equation type	Biphasic equations	Single phase equation
Balance of mass	$\phi_s \rho \boldsymbol{\nabla} \cdot \mathbf{v}_s = \Gamma_s$ $\rho \frac{D^s \phi_s}{Dt} = 0$ $\boldsymbol{\nabla} \cdot (\phi_s \mathbf{v}_s + \phi_f \mathbf{v}_f) = 0$	$\rho \boldsymbol{\nabla} \cdot \mathbf{v} = \Gamma$
Constitutive equations: Isotropic growth	$\frac{\mathcal{D}\mathbf{E}_s}{\mathcal{D}t} = \frac{1}{3} \boldsymbol{\nabla} \cdot \mathbf{v}_s \mathbf{I}$ $\quad + \frac{1}{2\mu} \frac{\mathcal{D}}{\mathcal{D}t} \left(\boldsymbol{\sigma}_s + \frac{1}{3} tr \boldsymbol{\sigma}_s \right)$ $\boldsymbol{\sigma}_f = -\phi_f P \mathbf{I}$	$\frac{\mathcal{D}\mathbf{E}_s}{\mathcal{D}t} = \frac{1}{3} \boldsymbol{\nabla} \cdot \mathbf{v}_s \mathbf{I}$ $\quad + \frac{1}{2\mu} \frac{\mathcal{D}}{\mathcal{D}t} \left(\boldsymbol{\sigma}_s + \frac{1}{3} tr \boldsymbol{\sigma}_s \right)$
Anisotropic growth	$\frac{\mathcal{D}\mathbf{E}_s}{\mathcal{D}t} = \boldsymbol{\nabla} \cdot \mathbf{v}_s \boldsymbol{\Omega}$ $\quad + \frac{1}{2\mu} \frac{\mathcal{D}}{\mathcal{D}t} \left(\boldsymbol{\sigma}_s + \frac{1}{3} tr \boldsymbol{\sigma}_s \right)$ $\quad + \frac{\phi_s}{2\mu} \frac{\mathcal{D}P}{\mathcal{D}t} \left(3\boldsymbol{\Omega} - \mathbf{I} \right)$ $\boldsymbol{\sigma}_f = -\phi_f P \mathbf{I}$	$\frac{\mathcal{D}\mathbf{E}_s}{\mathcal{D}t} = \boldsymbol{\nabla} \cdot \mathbf{v}_s \boldsymbol{\Omega}$ $\quad + \frac{1}{2\mu} \frac{\mathcal{D}}{\mathcal{D}t} \left(\boldsymbol{\sigma}_s + \frac{1}{3} tr \boldsymbol{\sigma}_s \right)$
Momentum equations[2]	$\boldsymbol{\nabla} \cdot \boldsymbol{\sigma}_s + \kappa(\mathbf{v}_f - \mathbf{v}_s) = 0$ $\phi_f \boldsymbol{\nabla} P = -\kappa(\mathbf{v}_f - \mathbf{v}_s)$	$\boldsymbol{\nabla} \cdot \boldsymbol{\sigma} = 0$

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[2]Note that, in keeping with other published models of growing tissues [26, 36], inertial and body forces, as well as mass-exchange effects, are neglected in the momentum equations presented here.

10. Concluding remarks. In this paper, a theoretical framework for a solid-multiphase model of a growing tissue has been presented which extends the concepts of poroelasticity to accommodate continuous volumetric growth. Moreover, in incorporating a solid phase, the model provides a basis for the study of residual stresses, which is of fundamental importance in a wide range of studies in biology, physiology, and tissue engineering.

The general equations developed in sections 2 through 6 have been applied to a two-phase model of an elastic solid and an inviscid fluid in sections 7 through 9. The analysis points to a crucial phenomenological aspect of tissue growth, illustrating that such a process must consist of a coordinated combination of the "swelling" of the solid (cellular) phase due to the influx of extracellular fluid—which is, in essence, the inverse of the consolidation concept of poroelasticity—and the exchange of mass whereby extracellular fluid is incorporated into the cellular phase. This combination of processes necessitates the inclusion of an additional constitutive postulate—in which the mass-exchange term is related to the solid phase expansion—among the modeling equations to close the model.

In the present paper, a particular constitutive postulate has been chosen which reflects a tissue whose ratio of cells to extracellular fluid is constant throughout its volume. The assumption of linear-elasticity and *mechanical* isotropy (cf. isotropic *growth*) for the solid phase then enables simple constitutive equations between stress and strain to be specified for both the solid and fluid phases. Solutions to these biphasic equations will be presented in the next paper in this series.

This work may be extended in a number of ways. More complicated relationships between interphase mass exchange and solid phase expansion may be proposed, enabling the model to consider the formation of necrotic regions. Additionally, the equations could be rederived by incorporating a dependence of the Helmholtz free energy of the solid phase, Ψ_s, on both the solid deformation gradient, $\mathbf{F}_s$, and its convected derivative, $\overset{\circ}{\mathbf{F}}_s$ (see sections 6 and 7 of the present paper) to produce a viscoelastic constitutive law (see, for example, Pioletti et al. [35]). This would enable the elasticity of the solid phase to be regularized in situations where anisotropic growth provides insufficient stress-relaxation [3].

Appendix. Development of the dissipation inequality. In this section, the second axiom of thermodynamics as expressed by (3.1) will be manipulated further to obtain a form from which constitutive equations may be deduced readily. Incorporating the balance of mass as expressed by (2.1) enables (3.1) to be expressed in the form

$$(A.1) \qquad \sum_{i=1}^{n} \frac{1}{\theta} \left[\Gamma_i \eta_i \theta + \phi_i \rho_i \theta \frac{d^i \eta_i}{dt} + \theta \boldsymbol{\nabla} \cdot \left(\frac{\mathbf{q}_i}{\theta} \right) - \phi_i \rho_i r_i \right] \geq 0.$$

Further, incorporating the energy equation (2.18) enables (A.1) to be expressed in a form which does not include the rate of heat production per unit mass within the ith constituent, r_i, explicitly, being

$$\sum_{i=1}^{n} \frac{1}{\theta} \left[\Gamma_i \eta_i \theta + \phi_i \rho_i \theta \frac{d^i \eta_i}{dt} + \theta \boldsymbol{\nabla} \cdot \left(\frac{\mathbf{q}_i}{\theta} \right) - \phi_i \rho_i \frac{d^i u_i}{dt} + tr(\mathbf{L}_i \boldsymbol{\sigma}_i) - \boldsymbol{\nabla} \cdot \mathbf{q}_i + \varepsilon_i \right] \geq 0.$$

Introducing the relation

$$\hat{\epsilon}_i \triangleq \varepsilon_i + \Gamma_i \left(u_i + \frac{1}{2} \mathbf{v}_i \cdot \mathbf{v}_i \right) + \mathbf{v}_i \cdot \pi_i$$

now enables the inequality to be expressed in the form

$$\sum_{i=1}^{n}\left[\phi_i\rho_i\left(\theta\frac{d^i\eta_i}{dt}-\frac{d^iu_i}{dt}\right)+tr(\mathbf{L}_i\boldsymbol{\sigma}_i)+\hat{\epsilon}_i-\Gamma_i\left(u_i+\frac{1}{2}\mathbf{v}_i.\mathbf{v}_i-\eta_i\theta\right)-\mathbf{v}_i.\pi_i\right]\geq 0.$$

The internal energies, u_i, will be eliminated at this point in favor of the Helmholtz free energy densities, ψ_i, where

(A.2) $$\psi_i = u_i - \theta\eta_i.$$

Hence, the inequality becomes

$$-\sum_{i=1}^{n}\phi_i\rho_i\frac{d^i\psi_i}{dt}-\rho_m\eta_m\frac{d\theta}{dt}+tr\sum_{i=1}^{n}(\mathbf{L}_i\boldsymbol{\sigma}_i)-\sum_{i=1}^{n}\Gamma_i\left(\psi_i+\frac{1}{2}\mathbf{v}_i.\mathbf{v}_i\right)-\sum_{i=1}^{n}\mathbf{v}_i.\pi_i\geq 0.$$

At this stage, the chemical potential is introduced, being the linear transformation defined by

$$\mathbf{K}_i = \psi_i\mathbf{I} - \frac{\boldsymbol{\sigma}_i}{\phi_i\rho_i};$$

see Bowen and Wiese [14], noting that in the present paper it is assumed that $\boldsymbol{\sigma}_i = \boldsymbol{\sigma}_i^T$ (see section 2.3). Therefore,

$$-\sum_{i=1}^{n}\phi_i\rho_i\frac{d^i\psi_i}{dt}-\rho_m\eta_m\frac{d\theta}{dt}-tr\sum_{i=1}^{n}\phi_i\rho_i\mathbf{K}_i.\mathbf{L}_i+tr\sum_{i=1}^{n}\phi_i\rho_i\psi_i\mathbf{L}_i$$
$$-\sum_{i=1}^{n}\Gamma_i\psi_i-\sum_{i=1}^{n}\mathbf{v}_i.\left(\pi_i+\frac{\Gamma_i}{2}\mathbf{v}_i\right)\geq 0,$$

which further reduces to

(A.3) $$-tr\sum_{i=1}^{n}\phi_i\rho_i\mathbf{K}_i.\mathbf{L}_i-\rho_m\eta_m\frac{d\theta}{dt}-\sum_{i=1}^{n}\frac{d^i}{dt}(\phi_i\rho_i\psi_i)-\sum_{i=1}^{n}\mathbf{v}_i.\left(\pi_i+\frac{\Gamma_i}{2}\mathbf{v}_i\right)\geq 0$$

by appealing to the balance of mass. Some authors (see, for example, Bowen [12]) define the quantity

$$\Psi_i = \phi_i\rho_i\psi_i$$

which represents the Helmholtz free energy of the ith constituent per unit mixture volume. Rewriting (A.3) in terms of Ψ_i gives

(A.4) $$-tr\sum_{i=1}^{n}\phi_i\rho_i\mathbf{K}_i.\mathbf{L}_i-\rho_m\eta_m\frac{d\theta}{dt}-\sum_{i=1}^{n}\frac{d^i\Psi_i}{dt}-\sum_{i=1}^{n}\mathbf{v}_i.\left(\boldsymbol{\pi}_i+\frac{\Gamma_i}{2}\mathbf{v}_i\right)\geq 0.$$

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