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Physical Laws for Mechanobiology

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Abstract

Higher-level physical laws applicable to biological tissues are presented that will permit the modeling of metabolic activity at the cellular level, including variations in the mass of a tissue. Here the tissue is represented as a fluid/solid mixture, wherein molecular solutes transport within the fluid, and cells can migrate throughout the porous solid. Variations in mass can arise via exchanges in mass between the constituent phases within a control volume such that mass is conserved in the tissue overall. The governing balance laws for mass, momentum, energy, and entropy are a special case of those describing a chemically reacting mixture with diffusion. Thermodynamic constraints on the constitutive structure are addressed.

1. Introduction

In the absence of gravity, or in reduced gravity environments like on the surfaces of the Moon or Mars, astronauts' bodies will undergo physical changes brought about by these varied states of gravity (Buckey 2006). The forces carried by their musculoskeletal frames will be altered, because their weights will be reduced. Many vital tissues will resorb and remodel due of these changes in gravity, altering their masses, densities, and architectures. This will bring about changes in the physical capabilities of these astronauts, with the potential of placing their health at increased risk (compared to their health risk here on Earth). If an injury were to occur, it could increase the health risk of the remaining crew, and even impact the ability of the crew to achieve its mission objectives. Higher-level physical laws pertinent to investigating such risk scenarios are presented in this paper.

To address many of the specific risk scenarios pertaining to astronaut health during long-duration voyages deep into space will require numeric simulations, as no data base from past experiences exists to draw inference from at this time. These simulations will likely be based upon biochemical, biomechanical, and mechanobiological models that span the length and physiologic scales of molecules, cells, tissues, organs, and organisms. We are of the opinion that studies intended to bridge such vast length and physiologic scales will require the cells, solute molecules, interstitial fluid, and extra cellular matrix of living tissue to be addressed individually in an unifying framework. The physical laws presented in this paper provide a theoretical foundation for studies such as these to be done.

Relevant fields of study include (G. A. Holzapfel 2006, personal communication):

- Biophysics: The science of biology and medicine, as revealed through applications of physical laws and theories.

- Biomechanics: The study of living systems through developments, extensions, and applications of mechanics targeting to better explain phenomena in biology, medicine, and bioengineering. Biomechanics focuses on whether or how function follows structure via physical laws.

- Mechanobiology: The study of biological reactions of cells in response to changes in their mechanical environment, as in growth, remodeling, adaptation, and repair. Mechanobiology focuses on whether or how structure follows function via biological laws.

This is a biophysics paper whose future applications will reside primarily in the discipline of mechanobiology and, to a lesser degree, in biomechanics.

In an assessment of the role of computational sciences in the development and application of higher-level physical laws, like mixture theory, the Nobel Prize Laureate for Physics in 1998, Robert Laughlin, recently stated the truism (Laughlin 2002): "It is not generally possible to start from the wrong equations and get the right result." Our intention is to pay particular attention in getting the physics correct, within the confines of a predefined set of assumptions that pertain to biology, so that numeric computations conforming with these assumptions will have the capability of making accurate predictions.

(a) Mixture Theories in Tissue Mechanics

Binary models of porous elastic solids (cells, collagen, elastin, bone, muscle, etc.) saturated with inviscid fluids (water, saline, plasma, lymphatic fluids, etc.) go by the names of 'biphasic theory' in the soft-tissue mechanics literature (cf. Mow et al. 1980) and 'poroelasticity' in the hard-tissue mechanics literature (cf. Cowin 2001). Both are mixture theories that can trace their origins back to Biot's (1941) original theory for soil consolidation, to which Truesdell (1957) gave rigor. They are equivalent theories under certain conditions, most notably, under an assumption of intrinsic incompressibility (Kenyon 1978).

A 'triphasic theory' was developed latter on to improve upon the predictions of biphasic theory in the osmotic swelling of cartilage. This was achieved through the actions of charged anions and cations introduced as solute phases into their mixture formulation (Lai et al. 1991). 'Bicomponent theory' is a simpler alternative to multi fluidic-phase theories in that it has treated filtration, osmotic swelling, and buoyancy effects as separate local forces of interaction between the liquid and solid components, without the need to introduce additional fluidic phases (Lanir 1987). A recent comparison between the triphasic and bicomponent theories has demonstrated that they possess like capabilities (Wilson et al. 2005).

Another modification to mixture theory was introduced by Mak (1986), who replaced the elastic matrix of biphasic theory with a viscoelastic matrix in order to account for the viscoelastic attributes of the intrinsic gels (proteoglycans, hyaluronic acids, etc.) and matrix constituents (collagen, muscle, etc.) that convect with the porous solid in an assumed affine manner.

(b) Growth Theories in Tissue Mechanics

Cells will change the mass, architecture, and/or volume of both themselves and their surrounding tissue, the extra cellular matrix, in their effort to maintain homeostasis (Wang & Thampatty 2006). Growth, in a general usage of the word, is said to occur whenever the volume fraction of the porous solid increases at the expense of the volume fraction of the interstitial fluid due to cell activity.

There has been a recent flurry of papers addressing the physical laws of mass, motion, and thermodynamics pertaining to open-system continua where mass is being created locally (e.g., Epstein & Maugin 2000; Klisch & Lotz 2000; Humphrey & Rajagopal 2002; Lubarda & Hoger 2002; Klisch & Hoger 2003; Kuhl & Steinmann 2003; Garikipati et al. 2004; Menzel 2005; and Guillou & Ogden 2006). These studies extend the earlier works of Hsu (1968), Cowin & Hegedus (1976), and Skalak et al. (1982). A common class of problems mentioned in all of these papers is tissue growth.

Cowin & Hegedus (1976) derived balance laws for a porous single-phase continuum. Klisch & Lotz (2000) applied balance laws for a fluid/solid mixture. Humphrey & Rajagopal (2002) applied balance laws for a fluid/multiple-solid mixture, where they constrained all solid constituents to deform with the same affine motion, and then applied the rule-of-mixtures from homogenization theory to quantify stress in the solid. Klisch & Hoger (2003) provide balance laws for tissues derived from many mixture scenarios. Garikipati et al. (2004) derived balance laws for a multiple-fluid/solid mixture. And the others applied balance laws that pertain to a dense single-phase continuum. Our approach is to consider a four-phase mixture that we show to be a special case of Truesdell's (1957) theory for chemically reacting mixtures with diffusion. Here, the fluid transports a population of solutes needed for metabolism, and the solid hosts a population of cells that utilize these metabolites.

All of the above mentioned tissue theories allow for volumetric growth, while the theories of Epstein & Maugin (2000), Kuhl & Steinmann (2003), Garikipati et al. (2004), and Guillou & Ogden (2006) allow for an additional growth through a flux of mass. In contrast, our theory introduces growth and other biological activities through various mass exchanges between the constituents present within a mass element.

Most of these theories introduce a multiplicative decomposition of the deformation gradient, e.g., $\mathbf{F} = \mathbf{F}_e\mathbf{F}_g$ (cf. Taber 1995), wherein the elastic $\mathbf{F}_e$ and growth $\mathbf{F}_g$ tensors are often interpreted with slight variations betwixt them, which usually include some form of further multiplicative refinement. In such theories, growth is a tensor field, viz. $\mathbf{F}_g$, whose evolution must be specified by some constitutive law. Such a decomposition of the deformation gradient is always permissible in single-phase continua. We do not introduce a multiplicative decomposition of the deformation gradient; we cannot, because $\mathbf{F}$ is not defined in our theory. However, one could define such a decomposition for the extra cellular matrix in our mixture theory, viz., $\mathbf{F}^m = \mathbf{F}_e^m\mathbf{F}_g^m$, if one so desired.

An alternative approach to the notion of a growth tensor is found in Humphrey & Rajagopal (2002), where they introduced the idea of a survival function as a means for assigning natural configurations to constituents belonging to mass points at the time of their creation. This function accounts for the rate of production and the life span of each solid constituent. It enters into the theory as a kernel function

in a Volterra integral equation of the second kind, like those used in the literature of viscoelastic liquids. Of such configurations, they state: "It is differences in natural configurations, not incompatible strains, that likely leave a tissue stressed in the absence of applied tractions." We find this to be a more appealing approach than that of decomposing the deformation gradient, as it better reflects the interface between physics and biology.

(c) Approach Taken

A volume element of tissue is considered to be comprised of four types of constituents: an interstitial miscible liquid (iml) suspending a population of solutes (pos), and an extra cellular matrix (ecm) hosting a population of cells (poc). Each constituent may itself be an assembly of many other sub-constituents, but that level of sophistication is not required at this time in order for us to be able to derive a set of higher-level physical laws that govern tissue and permit the modeling of biological activity. However, such distinctions will become necessary when constructing mechanobiologic constitutive models for specific tissues, which lies beyond the scope of the present paper.

The various documents mentioned above, where physical laws have been derived for tissue growth, are applicable to open-system continua; that is, mass can be created and/or destroyed within a material element in these theories. The theory presented here describes a closed-system continuum where mass is conserved within a material element. It is a fluid/solid mixture theory, where the fluid is comprised of an iml suspending a pos, while the solid is comprised of an ecm hosting a poc. Cells manage themselves and their surrounding environment by, in essence, converting mass from one form into another in order to suit some function, be it biological, chemical, or physical (Wang & Thampatty 2006). As an analog, cells are factories that, in a physical sense, regulate exchanges in mass between the various constituents of tissue. The nutrients that these cellular factories run on arrive as molecules suspended by the liquid that surrounds them; furthermore, their wastes depart as suspended particles in this same bathing liquid. So, in our approach to mechanobiology, mass is neither created nor destroyed at a continuum point, but rather, it is moved from one phase to another through biological processes.

Adopting the premise of Lai et al. (1991), the fluid phase of tissue is considered to be comprised of a miscible liquid (the solvent or iml) that suspends soluble molecules (the solutes or pos). In like manner, adopting the simplifying premise of Humphrey & Rajagopal (2002), the solid phase (the porous lattice or ecm) is considered to be comprised of various constituents that experience the same affine deformation, each with their own natural configuration. Managing this structure is the responsibility of a poc. If the stresses carried by the various solid constituents are assumed to sum according to the rule-of-mixtures, as dictated by homogenization theory, then tractions can be assigned at the boundaries in a straightforward manner. These assumptions are idealizations, and exceptions can be put forward for each of them. Nevertheless, many important problems can be solved where these assumptions hold, and it is the physical laws that govern this class of problems that we choose to address.

The scope of our theory is quite broad in that it will allow for the modeling of cellular activity (e.g., cell birth, death, metabolism, and migration), tissue behavior

(e.g., growth, swelling, remodeling, healing, and nutrient/waste transport), and mechanical response (e.g., stress, strain, and energy), all within the same framework. Applications of our theory to specific tissues undergoing specified biological and/or physical processes are left to future papers.

Supposition 1. Biological tissues are porous materials saturated with miscible fluids that suspend solute molecules. The solid material is comprised of an assembly of constituents that experience the same affine deformation, but that possess different natural configurations. This porous solid contains a distribution of cells that attach to the matrix and are capable of locomotion by migrating through its cavities. Cells are the caretakers of tissue, and in the execution of their various duties, they convert mass from one form belonging to some constituent into another form possibly belonging to a different constituent in a manner that conserves mass overall.

2. Terminology

(a) Acronyms

ecm	extra cellular matrix . . . . . $\alpha = m$	poc	population of cells . . . . . $\alpha = c$
iml	interstitial miscible liquid . . $\alpha = \ell$	pos	population of solutes . . . . . $\alpha = s$

(b) Nomenclature

a^α	free-energy supplies, $\alpha \in \{c, \ell, m, s\}$	r	radius
$\mathcal{B}$	volume in 3-space	r, r^α	heat productions
c^α	density of mass supplies	s^α	density of entropy supplies
d_t, d_t^α	material derivatives	t	time
$\mathrm{d}a$	differential element of area	$\boldsymbol{t}$, $\boldsymbol{t}^\alpha$	traction vectors
$\mathrm{d}m$, $\mathrm{d}m^\alpha$	differential elements of mass	$\mathbf{T}$	Cauchy stress tensor
$\mathrm{d}v$, $\mathrm{d}v^\alpha$	differential elements of volume	$\mathbf{T}^\alpha$	partial stress tensors
$\mathcal{D}^c$	diffusion coefficient of a cell type	$\boldsymbol{u}^\alpha$	diffusion velocity vectors
$\mathcal{D}^{cs}$	solute driven cell diffusion coefficient	$\boldsymbol{v}^\alpha$	velocity vectors
		$\mathbf{W}$, $\mathbf{W}^\alpha$	vorticity tensors
$\mathcal{D}^s$	diffusion coefficient of a solute type	$\boldsymbol{x}$	current position vector
		$\dot{\boldsymbol{x}}$	velocity vector
$\mathbf{D}$, $\mathbf{D}^\alpha$	strain-rate tensors	$\ddot{\boldsymbol{x}}$	acceleration vector
e^α	density of internal-energy supplies	$\boldsymbol{X}^m$	reference vector for the ecm
$\boldsymbol{e}_i$	basis vector, $i = 1, 2, 3$	β, β^α	arbitrary mass-averaged fields
$\mathbf{F}^\alpha$	deformation gradient tensors	γ, γ^α	density of entropy productions
$\boldsymbol{g}$	gravity vector	$\delta\mathcal{B}$	surface in 3-space
h	time-step size	ϵ, ϵ^α	internal energies
$\mathbf{I}$	identity tensor	η	viscosity
J^m	Jacobian of the ecm deformation	η, η^α	entropies
k	Boltzmann's constant	θ	absolute temperature
$\mathbf{L}$, $\mathbf{L}^\alpha$	velocity gradient tensors	μ^α	mass fractions
M_j	molecular weight of solute j	ρ, ρ^α	partial mass densities
n_j	molar concentration of solute j	$\dot{\rho}_\beta^\alpha$	mass transfer rate from β to α
$\boldsymbol{n}$	outward unit normal vector	ϱ^α	actual mass densities
N_c	number of cell species	ϕ^α	volume fractions
N_s	number of solute species	$\boldsymbol{\varphi}$	motion map for the ecm
$\boldsymbol{p}^\alpha$	momentum supplies	ψ, ψ^α	Helmholtz free energies
$\boldsymbol{q}$, $\boldsymbol{q}^\alpha$	heat flux vectors	$\boldsymbol{\psi}$	motion map for the iml

3. Mixtures

We adopt the approach of mixture theory (Truesdell 1957) to implement our superposition, and to establish the physical laws that govern it. The reader is referred to the review article by Bowen (1976), the text by Rajagopal & Tao (1995), and the references cited therein for more thorough treatments on mixture theory. The former gives an excellent presentation of the classical theory for mixtures, while the latter presents a nice collection of solved boundary-value problems.

The derivation of constitutive equations for specific tissue types, and the construction of variational principles required to solve boundary value problems that pertain to these constitutive formulæ are the topics of future research endeavors, and their publications.

(a) Masses and Volumes

At any given instant in time, let a differential element of volume be comprised of four distinct sub-volumes

$$\mathrm{d}v = \sum \mathrm{d}v^{\alpha} = \mathrm{d}v^{c} + \mathrm{d}v^{\ell} + \mathrm{d}v^{m} + \mathrm{d}v^{s}, \quad \alpha \in \{c, \ell, m, s\}, \tag{3.1}$$

where properties with an index of $^{\ell}$ or ^{s} designate an affiliation with the iml or pos phases of the fluid, and properties with an index of ^{m} or ^{c} designate an affiliation with the ecm or poc phases of the solid, respectively, while an index of $^{\alpha}$ can represent any one of these four constituents, and a summand without limits is considered to sum α over all four of its phases. Volume fractions are then defined as

$$\phi^{\alpha} = \mathrm{d}v^{\alpha}/\mathrm{d}v \quad \text{with} \quad 0 < \phi^{\alpha} < 1 \quad \therefore \quad \sum \phi^{\alpha} = 1, \tag{3.2}$$

which sum to 1 because tissues are considered to be simply connected. The volume fraction of each constituent will vary between tissue type. In the literature, the volume fraction of fluid, which in our theory is quantified by $\phi^{\ell} + \phi^{s}$, is called the porosity.

The total mass $\mathrm{d}m$ of a volume element $\mathrm{d}v$ is the sum of its constituent masses in that

$$\mathrm{d}m = \sum \mathrm{d}m^{\alpha}. \tag{3.3}$$

The density of this mass element is

$$\rho = \mathrm{d}m/\mathrm{d}v, \tag{3.4}$$

which has partial mass densities ρ^{α} that satisfy

$$\rho = \sum \rho^{\alpha} \quad \text{wherein} \quad \rho^{\alpha} = \mathrm{d}m^{\alpha}/\mathrm{d}v, \tag{3.5}$$

and actual mass densities ϱ^{α} that are given by

$$\varrho^{\alpha} = \mathrm{d}m^{\alpha}/\mathrm{d}v^{\alpha} \quad \text{with} \quad \rho^{\alpha} = \phi^{\alpha}\varrho^{\alpha} \quad \therefore \quad \rho = \sum \phi^{\alpha}\varrho^{\alpha}. \tag{3.6}$$

It is also useful to define mass fractions (or concentrations) as

$$\mu^{\alpha} = \mathrm{d}m^{\alpha}/\mathrm{d}m = \rho^{\alpha}/\rho \quad \therefore \quad \sum \mu^{\alpha} = 1, \tag{3.7}$$

which sum to 1 because tissues are saturated mixtures.

(b) Kinematics

We select a Cartesian coordinate system $(1, 2, 3)$ described by a set of orthonormal base vectors $\{\boldsymbol{e}_1, \boldsymbol{e}_2, \boldsymbol{e}_3\}$, where $\boldsymbol{e}_i \cdot \boldsymbol{e}_j = \delta_{ij}$ and $\boldsymbol{e}_i \times \boldsymbol{e}_j = \epsilon_{ijk}\, \boldsymbol{e}_k$, with the repeated index k being summed from 1 to 3 in the usual manner. Here $\cdot$ and $\times$ denote the inner and cross products, respectively, while δ_{ij} signifies the Kroneker delta, and ϵ_{ijk} is the permutation symbol.

At current time t, let all four constituent mass points $\mathrm{d}m^\alpha$ co-habitate with one another at some volume element $\mathrm{d}v$ resulting in a mass element $\mathrm{d}m$ located by the coordinates $\{x_1, x_2, x_3\}$, or equivalently, by the position vector $\boldsymbol{x} = x_i\, \boldsymbol{e}_i$.

(i) Primitive Variables

The velocity vector is typically selected as the primitive kinematic variable in fluid mechanics; whereas, in mixture theory, position vectors belonging to the various phases are usually assigned as its primitives. Here we break with this tradition and select velocity vectors as the primitive kinematic variables for the iml, poc & pos, and we employ a position vector as the primitive kinematic variable for the ecm. This mitigates the need to establish reference configurations for all constituents except for the ecm.

In accordance with supposition 1, we assign a set of coordinates $\{X_1^m, X_2^m, X_3^m\}$ to a mass point $\mathrm{d}m^m$ of an ecm to establish its reference location $\boldsymbol{X}^m = X_i^m\, \boldsymbol{e}_i$ at some initial time t_0. Let the motion of this mass point through space be described by

$$\boldsymbol{X}^m = \boldsymbol{\varphi}^{-1}(\boldsymbol{x}, t) \quad \text{and} \quad \boldsymbol{x} = \boldsymbol{\varphi}(\boldsymbol{X}^m, t), \tag{3.8}$$

where the vector mapping function $\boldsymbol{\varphi} = \varphi_i\, \boldsymbol{e}_i$ is considered to be continuous, sufficiently differentiable, and invertible; hence, $\boldsymbol{\varphi}^{-1}$ exists. The velocity of an ecm mass point is therefore given by

$$\boldsymbol{v}^m(\boldsymbol{x}, t) = \partial_t \varphi_i\, \boldsymbol{e}_i, \tag{3.9}$$

wherein $\partial_t(\bullet) = \partial(\bullet)/\partial t$ is the partial derivative taken with respect to time t, with $\bullet$ denoting an arbitrary field.

Also in accordance with supposition 1, let the motion of mass point $\mathrm{d}m^\ell$ for the iml be described by

$$\boldsymbol{v}^\ell = \boldsymbol{\psi}(\boldsymbol{x}, t), \tag{3.10}$$

where the vector mapping function $\boldsymbol{\psi} = \psi_i \boldsymbol{e}_i$ quantifies the velocity of the miscible liquid, and is considered to be continuous and sufficiently differentiable, but unlike $\boldsymbol{\varphi}$, $\boldsymbol{\psi}$ need not be invertible.

Collectively, the iml & ecm constitute a classic fluid/solid mixture to which we now add the attributes needed to incorporate biology.

In accordance with supposition 1, let the motion of mass point $\mathrm{d}m^s$ for the pos be described by the vector mapping

$$\boldsymbol{v}^s = \boldsymbol{\psi}(\boldsymbol{x}, t) - \sum_{i=1}^{N_s} \mathcal{D}_i^s \operatorname{grad} \ln \rho_i^s \quad \text{with} \quad \rho^s = \sum_{i=1}^{N_s} \rho_i^s, \tag{3.11}$$

where $\mathcal{D}_i^s$ is the solute diffusion coefficient, and ρ_i^s is the mass density, both belonging to species i in some pos that contains N_s species. The gradient operator

$\text{grad}(\bullet) = \partial(\bullet)/\partial x_i\, \boldsymbol{e}_i$ denotes a partial derivative taken with respect to the current position $\boldsymbol{x}$. The first term on the right-hand side of equation (3.11) describes the fluid velocity of the liquid that suspends these particles as it flows through the tissue; it is the velocity map of the iml given in equation (3.10). The second term accounts for a perturbation to this mean velocity field caused by Brownian motion of the solute particles, as described by Fick's first law for random diffusion. The minus sign ensures that solutes migrate from regions of high concentration (or density) to regions of low concentration.

Einstein's theory for Brownian motion, the topic of his 1905 Ph.D. thesis, provides a formula for quantifying the diffusion coefficient of a spherical body with radius r suspended in a fluid of viscosity η that is subject to the random bombardment of atoms from within the fluid; it being,

$$\mathcal{D} = k\theta/6\pi\eta r, \tag{3.12}$$

where k is Boltzmann's constant, and θ is the absolute temperature (i.e., $\theta > 0$). This formula can be applied to quantify, for example, the diffusion coefficients of globular proteins, to which the $\mathcal{D}_i^s$ refer. However, this formula must not be used for purposes of quantifying the diffusion coefficients associated with cell migration presented below. These coefficients need to be experimentally determined. The pos diffuse according to Einstein's physics for Brownian motion; whereas, the poc diffuse under their own locomotive processes. The diffusion coefficient $\mathcal{D}^s$ will diminish whenever the solute size approaches the pore size of the matrix material, which varies with tissue type, and will become zero whenever the solute size exceeds the pore size, with the tissue now acting as a filter.

Finally, in accordance with supposition 1, let the motion of mass point $\mathrm{d}m^c$ for the poc be described by the vector mapping

$$\boldsymbol{v}^c = \partial_t \boldsymbol{\varphi} - \sum_{i=1}^{N_c} \mathcal{D}_i^c \,\text{grad}\ln\rho_i^c + \sum_{i=1}^{N_c}\sum_{j=1}^{N_s} \mathcal{D}_{ij}^{cs} \,\text{grad}\ln\rho_j^s \quad \text{with} \quad \rho^c = \sum_{i=1}^{N_c} \rho_i^c, \tag{3.13}$$

where $\mathcal{D}_i^c$ is the cell diffusion coefficient associated with random cell locomotion, and ρ_i^c is the mass density, both of species i belonging to some poc that contains N_c species, while $\mathcal{D}_{ij}^{cs}$ is the cell diffusion coefficient of cell species i whose locomotion occurs as a response to the presence of solute species j. The first term on the right-hand side of equation (3.13) is a passive contribution that describes the velocity of the deforming matrix to which the cells adhere; it is the time derivative of the ecm motion map given in equation (3.8). The second term is an active contribution that accounts for the haptotaxis migration of cells along a cell concentration gradient, which is described by Fick's first law for random diffusion in accordance with, e.g., Nobel's (1987) experimental observation that cell locomotion is Markovian. The third term is another type of active contribution to cell diffusion. This term accounts for the chemotaxis migration of cells along a chemical concentration gradient. The positive sign affiliated with this term implies that the diffusion coefficient will be positive whenever cells are attracted to a chemical stimulus, and negative whenever they repel from it. Not all cell species are capable of locomotion, so some of the $\mathcal{D}_i^c$ will be zero valued, and as such, their $\mathcal{D}_{ij}^{cs}$ will be zero valued, too. Furthermore, most solute species j in a pos do not serve as an attraction potential for cells of

species i that are capable of locomotion and which belong to some poc; hence, most of the coefficients $\mathcal{D}_{ij}^{cs}$ will be zero valued for cell species i where $\mathcal{D}_i^c$ is non-zero.

The physical laws derived herein, as they apply to the pos and poc, pertain to their collective populations, not to the individual species of which they are comprised. Equations (3.11 & 3.13) quantify averaging schemes used to establish these kinematic responses.

(ii) Kinematic Variables

Mixture theory averages the velocities of its constituent phases, which we suppose obey equations (3.9–3.11 & 3.13), in order to obtain a representative velocity field for the mixture which, in our case, we conjecture to be descriptive of tissue. In particular, the mean (or barycentric) velocity is defined as

$$\dot{\boldsymbol{x}} = \sum \mu^\alpha \boldsymbol{v}^\alpha \quad \text{or equivalently} \quad \rho \dot{\boldsymbol{x}} = \sum \rho^\alpha \boldsymbol{v}^\alpha, \tag{3.14}$$

which is a mass-weighted average of the local velocity fields (Truesdell 1957). The diffusion velocity

$$\boldsymbol{u}^\alpha = \boldsymbol{v}^\alpha - \dot{\boldsymbol{x}} \quad \therefore \quad \sum \rho^\alpha \boldsymbol{u}^\alpha = \boldsymbol{0}, \tag{3.15}$$

proves to be a useful measure describing the velocities of the constituents relative to the overall velocity of the mixture.

By defining material derivatives for the phase constituents as

$$\mathrm{d}_t^\alpha(\bullet) = \partial_t(\bullet) + \operatorname{grad}(\bullet) \cdot \boldsymbol{v}^\alpha, \tag{3.16}$$

where $\mathrm{d}_t^\alpha(\bullet)$ denotes the total derivative taken with respect to time t of a field belonging to the α^{th} phase, one obtains a material derivative for the barycentric frame that is given by

$$\mathrm{d}_t(\bullet) = \partial_t(\bullet) + \operatorname{grad}(\bullet) \cdot \dot{\boldsymbol{x}} \quad \therefore \quad \rho\, \mathrm{d}_t(\bullet) = \sum \rho^\alpha \mathrm{d}_t^\alpha(\bullet), \tag{3.17}$$

where $\mathrm{d}_t(\bullet)$ denotes the total derivative taken with respect to time t of a field belonging to the continuum mixture, such that

$$\mathrm{d}_t^\alpha(\bullet) = \mathrm{d}_t(\bullet) + \operatorname{grad}(\bullet) \cdot \boldsymbol{u}^\alpha, \tag{3.18}$$

which is another identity of value. It is vital to distinguish between the material derivatives of the phases d_t^α from the material derivative of the mixture d_t during the construction of a mixture theory, and in its applications.

The ecm has a deformation gradient tensor associated with it that is defined by

$$\begin{aligned} \mathbf{F}^m &= \operatorname{GRAD} \boldsymbol{\varphi} = \frac{\partial \varphi_i}{\partial X_j^m}\, \boldsymbol{e}_i \otimes \boldsymbol{e}_j, \\ (\mathbf{F}^m)^{-1} &= \operatorname{grad} \boldsymbol{\varphi}^{-1} = \frac{\partial \varphi_i^{-1}}{\partial x_j}\, \boldsymbol{e}_i \otimes \boldsymbol{e}_j, \end{aligned} \tag{3.19}$$

so that $\mathbf{F}^m(\mathbf{F}^m)^{-1} = (\mathbf{F}^m)^{-1}\mathbf{F}^m = \mathbf{I}$, wherein $\mathbf{I} = \delta_{ij}\, \boldsymbol{e}_i \otimes \boldsymbol{e}_j$ is the identity tensor, with operator $\otimes$ denoting the dyadic product, which satisfies $(\boldsymbol{e}_i \otimes \boldsymbol{e}_j)\, \boldsymbol{v} = (\boldsymbol{v} \cdot \boldsymbol{e}_j)\, \boldsymbol{e}_i$

for all vectors $\boldsymbol{v}$. Because of the invertibility of mapping $\boldsymbol{\varphi}$, it follows that the Jacobian of this deformation is non-zero, viz.,

$$J^m = \det \mathbf{F}^m \neq 0, \tag{3.20}$$

where det designates a matrix determinant, in this case, of components $\mathrm{F}^m_{ij} = \partial\varphi_i/\partial X^m_j$ where $\mathbf{F}^m = \mathrm{F}^m_{ij}\, \boldsymbol{e}_i \otimes \boldsymbol{e}_j$. Because velocity is the primitive variable in the other three phases, these phases do not associate with a reference configuration a priori, and as such, they do not possess deformation gradient tensors that can be constructed in said manner. We will return to this point later.

Velocity gradient tensors for the four separate phases are defined by

$$\mathbf{L}^\alpha = \operatorname{grad} \boldsymbol{v}^\alpha = \frac{\partial v^\alpha_i}{\partial x_j}\, \boldsymbol{e}_i \otimes \boldsymbol{e}_j, \tag{3.21}$$

whose associated velocity vectors are given in equations (3.9–3.11 & 3.13), and whose components are $\mathrm{L}^\alpha_{ij} = \partial v^\alpha_i/\partial x_j$. The mean velocity gradient is similarly defined by

$$\mathbf{L} = \operatorname{grad} \dot{\boldsymbol{x}} = \frac{\partial \dot{x}_i}{\partial x_j}\, \boldsymbol{e}_i \otimes \boldsymbol{e}_j, \tag{3.22}$$

which, incidently, relates to the velocity gradients of the constituents through the formula

$$\rho\mathbf{L} = \sum_\alpha \big(\rho^\alpha \mathbf{L}^\alpha + \boldsymbol{u}^\alpha \otimes \operatorname{grad} \rho^\alpha\big). \tag{3.23}$$

Hence, equations (3.14 & 3.23) establish maps between kinematic fields of the subcontinua (i.e., the phases) and the continuum (i.e., the mixture).

The symmetric parts of the constituent and mean velocity gradients,

$$\mathbf{D}^\alpha = \tfrac{1}{2}\big(\mathbf{L}^\alpha + (\mathbf{L}^\alpha)^{\mathrm{T}}\big) \quad \text{and} \quad \mathbf{D} = \tfrac{1}{2}\big(\mathbf{L} + \mathbf{L}^{\mathrm{T}}\big), \tag{3.24}$$

define their strain rates, while their associated skew-symmetric parts,

$$\mathbf{W}^\alpha = \tfrac{1}{2}\big(\mathbf{L}^\alpha - (\mathbf{L}^\alpha)^{\mathrm{T}}\big) \quad \text{and} \quad \mathbf{W} = \tfrac{1}{2}\big(\mathbf{L} - \mathbf{L}^{\mathrm{T}}\big), \tag{3.25}$$

quantify their vorticities, and as such

$$\mathbf{L}^\alpha = \mathbf{D}^\alpha + \mathbf{W}^\alpha \quad \text{and} \quad \mathbf{L} = \mathbf{D} + \mathbf{W}, \tag{3.26}$$

wherein $^{\mathrm{T}}$ designates the transpose, e.g., given $\mathbf{L} = \mathrm{L}_{ij}\, \boldsymbol{e}_i \otimes \boldsymbol{e}_j$ then $\mathbf{L}^{\mathrm{T}} = \mathrm{L}_{ji}\, \boldsymbol{e}_i \otimes \boldsymbol{e}_j$.

(iii) Deformation Gradients from Velocity Gradients

The local kinematic fields relate to the global kinematic fields through the velocities (equation 3.14) and velocity gradients (equation 3.23). In stark contrast, local/global mappings do not exist for either an initial position vector $\boldsymbol{X}$ or a deformation gradient tensor $\mathbf{F}$, regardless of whether one chooses velocities or displacements as the kinematic primitives (cf. Bowen 1976).

Simple fluids with memory (Coleman & Noll 1964), for example, require a knowledge of the deformation history of the fluid; in particular, of the relative deformation gradient $\mathbf{F}_t(\tau) = \partial x_i(t)/\partial x_j(\tau)\, \boldsymbol{e}_i \otimes \boldsymbol{e}_j$ defined for any reference time τ, $\tau \leq t$. In

tissue mechanics, relative deformation gradients of a solid phase have been used by Humphrey & Rajagopal (2002) to handle the birth and death events of the constituents therein. To obtain such measures of deformation for the poc, iml & pos phases in our formulation, where the velocity vectors $\boldsymbol{v}^c$, $\boldsymbol{v}^\ell$ & $\boldsymbol{v}^s$ are the primitives, not the position vectors $\boldsymbol{x}^c$, $\boldsymbol{x}^\ell$ & $\boldsymbol{x}^s$, will require an integration of their gradients.

One can begin by discretizing the interval of integration $[0,t]$ into N sub-intervals such that $0 = t_0 < t_1 < \cdots < t_{N-1} < t_N = t$. Provided that the velocity gradient $\mathbf{L}^\alpha$ is known, and its associated deformation gradient $\mathbf{F}^\alpha$ is being sought, as in a finite element implementation of our theory, one can start by assigning an initial condition of

$$\mathbf{F}^\alpha_{t_k}(t_k) = \mathbf{I}, \tag{3.27}$$

so that $\mathbf{F}^\alpha_{t_n}(t_k)$ can be approximated for any $n > k$, given that $k = 0, 1, 2, \ldots, n-1$ and $n = 1, 2, \ldots, N$, by employing, e.g., a mid-point predictor

$$\widehat{\mathbf{F}}^\alpha_{t_n}(t_k) = \mathbf{F}^\alpha_{t_{n-2}}(t_k) + 2h\,\mathbf{L}^\alpha(t_{n-1})\,\mathbf{F}^\alpha_{t_{n-1}}(t_k), \quad n \geq k+2, \tag{3.28}$$

that can be started at $n = k+1$ with the forward-Euler predictor

$$\widehat{\mathbf{F}}^\alpha_{t_{k+1}}(t_k) = \mathbf{I} + h\,\mathbf{L}^\alpha(t_k), \tag{3.29}$$

which are then corrected with the trapezoidal rule

$$\mathbf{F}^\alpha_{t_n}(t_k) = \mathbf{F}^\alpha_{t_{n-1}}(t_k) + \tfrac{1}{2}h\Big(\mathbf{L}^\alpha(t_{n-1})\,\mathbf{F}^\alpha_{t_{n-1}}(t_k) + \mathbf{L}^\alpha(t_n)\,\widehat{\mathbf{F}}^\alpha_{t_n}(t_k)\Big), \tag{3.30}$$

when advancing the solution over an uniform time step of $h = t_n - t_{n-1}\ \forall\ n$. Here we are solving the governing differential equation $\dot{\mathbf{F}}^\alpha = \mathbf{L}^\alpha\mathbf{F}^\alpha$ using a predictor/corrector with accuracy $O\big(h^3\ddot{\mathbf{F}}^\alpha\big)$. Other integrators could be used, too.

4. Mass Balance in Tissues

Any good textbook in continuum mechanics can be consulted to acquire detailed derivations of the conservation laws that govern continua (e.g., Holzapfel 2000). Here we use axioms for stating the physical laws that govern continua, and postulates for stating extensions to these axioms that are assumed to apply to the sub-continua, viz., the phases of a mixture.

Consider a connected and bounded region $\mathcal{B}$ fixed in 3-space in an Eulerian frame at current time t that is enclosed by a surface $\delta\mathcal{B}$. Such a region establishes a control volume through which a physical law can be transcribed from axiom into formula.

(a) Balance of Mass

Axiom 1. The rate at which mass increases inside of $\mathcal{B}$ equals the flux of mass entering across $\delta\mathcal{B}$.

Axiom 1 is a statement for mass conservation in a continuum, which assumes the form of an integral equation; in particular,

$$\partial_t \int_{\mathcal{B}} \rho\,\mathrm{d}v = -\int_{\delta\mathcal{B}} \rho\dot{\boldsymbol{x}}\cdot\boldsymbol{n}\,\mathrm{d}a, \tag{4.1}$$

where $\mathrm{d}v$ is an element of volume, $\mathrm{d}a$ is an element of surface area, and $\boldsymbol{n}$ is its unit normal. The surface integral is negated due to the convention that $\boldsymbol{n}$ points outward. Provided that the integrands are continuous and sufficiently differentiable, then an application of the divergence theorem to the surface integral in equation (4.1) allows the resulting integral equation to be recast as the field equation

$$\mathrm{d}_t \rho + \rho \operatorname{div} \dot{\boldsymbol{x}} = 0, \tag{4.2}$$

with $\operatorname{div} \boldsymbol{v} = \partial v_i / \partial x_i$ signifying the divergence operator, and where use has been made of the identity

$$\operatorname{div}(\rho \boldsymbol{v}) = \operatorname{grad}(\rho) \cdot \boldsymbol{v} + \rho \operatorname{div} \boldsymbol{v}. \tag{4.3}$$

Our theory differs from the existing theories for tissue growth discussed in the Introduction of this paper in that here mass is conserved. Our theory describes a closed-system continuum; whereas, prior growth theories describe open-system continua, viz., their counterparts to our equation (4.2) have values other than zero on their right-hand sides.

Postulate 1. For a phase in a mixture, the rate at which mass increases inside of $\mathcal{B}$ equals the flux of mass entering across $\delta\mathcal{B}$, plus any masses that are being exchanged between it and the other phases within $\mathcal{B}$.

As a matter of notation, let $\dot{\rho}^{\text{destination}}_{\text{source}}$ represent the rate at which mass is being moved from a 'source' phase to a 'destination' phase within a control volume. With there being four separate phases, there exist twelve possible exchange rates. Only a few are expected to be active for any given tissue type; nevertheless, all twelve cases are considered in the construction of our general theory. What functional forms these terms may take on is tissue dependent. This is a constitutive modeling issue, and as such, is not addressed herein. It is through these functions, in part, that biological laws and physical laws can interact.

The mass balance governing the ecm within a tissue, as described in supposition 1 and constrained by postulate 1, obeys the integral equation

$$\partial_t \int_{\mathcal{B}} \rho^m \, \mathrm{d}v = - \int_{\delta\mathcal{B}} \rho^m \boldsymbol{v}^m \cdot \boldsymbol{n} \, \mathrm{d}a + \int_{\mathcal{B}} \left(\dot{\rho}^m_c - \dot{\rho}^c_m + \dot{\rho}^m_\ell - \dot{\rho}^\ell_m + \dot{\rho}^m_s - \dot{\rho}^s_m \right) \mathrm{d}v, \tag{4.4}$$

whose local form is the field equation

$$\mathrm{d}^m_t \rho^m + \rho^m \operatorname{div} \boldsymbol{v}^m = c^m \quad \text{with} \quad c^m = \dot{\rho}^m_c - \dot{\rho}^c_m + \dot{\rho}^m_\ell - \dot{\rho}^\ell_m + \dot{\rho}^m_s - \dot{\rho}^s_m, \tag{4.5}$$

where c^m is the density of mass supply to the extra cellular matrix, i.e., the rate per unit volume at which mass is being moved from the three other phases into the ecm, minus the rate at which it is being removed from the ecm and placed into the other three phases. This formula can be rewritten as

$$\mathrm{d}^m_t \left(\rho^m \det \mathbf{F}^m \right) = c^m \det \mathbf{F}^m, \tag{4.6}$$

because of the identity $\mathrm{d}^m_t \det \mathbf{F}^m = \det \mathbf{F}^m \operatorname{div} \boldsymbol{v}^m$ (cf. equation 1.2.12 in Bowen 1976), from which it immediately follows that

$$\det \mathbf{F}^m = 1, \tag{4.7}$$

whenever the matrix phase is incompressible, which is a good assumption for soft tissues, but not for hard tissues.

The mass balance governing the poc within a tissue, as described in supposition 1 and constrained by postulate 1, obeys the integral equation

$$\partial_t \int_{\mathcal{B}} \rho^c \, \mathrm{d}v = -\int_{\delta\mathcal{B}} \rho^c \boldsymbol{v}^c \cdot \boldsymbol{n} \, \mathrm{d}a + \int_{\mathcal{B}} \left(\dot{\rho}^c_\ell - \dot{\rho}^\ell_c + \dot{\rho}^c_m - \dot{\rho}^m_c + \dot{\rho}^c_s - \dot{\rho}^s_c \right) \mathrm{d}v, \tag{4.8}$$

whose local form is

$$\mathrm{d}^c_t \rho^c + \rho^c \operatorname{div} \boldsymbol{v}^c = \mathscr{c}^c \quad \text{with} \quad \mathscr{c}^c = \dot{\rho}^c_\ell - \dot{\rho}^\ell_c + \dot{\rho}^c_m - \dot{\rho}^m_c + \dot{\rho}^c_s - \dot{\rho}^s_c, \tag{4.9}$$

where $\mathscr{c}^c$ is the density of mass supply to the population of cells, i.e., the rate per unit volume at which mass is being moved from the three other phases into the poc, minus the rate at which it is being removed from the poc and placed into the other three phases. From this equation, it immediately follows that

$$\operatorname{tr} \mathbf{L}^c = \operatorname{div} \boldsymbol{v}^c = 0, \tag{4.10}$$

whenever the cells are incompressible, which is a good assumption, with $\operatorname{tr}\mathbf{L} = \mathrm{L}_{ii}$ signifying the trace operator.

The mass balance governing the iml within a tissue, as described in supposition 1 and constrained by postulate 1, obeys the integral equation

$$\partial_t \int_{\mathcal{B}} \rho^\ell \, \mathrm{d}v = -\int_{\delta\mathcal{B}} \rho^\ell \boldsymbol{v}^\ell \cdot \boldsymbol{n} \, \mathrm{d}a + \int_{\mathcal{B}} \left(\dot{\rho}^\ell_c - \dot{\rho}^c_\ell + \dot{\rho}^\ell_m - \dot{\rho}^m_\ell + \dot{\rho}^\ell_s - \dot{\rho}^s_\ell \right) \mathrm{d}v, \tag{4.11}$$

whose local form is the field equation

$$\mathrm{d}^\ell_t \rho^\ell + \rho^\ell \operatorname{div} \boldsymbol{v}^\ell = \mathscr{c}^\ell \quad \text{with} \quad \mathscr{c}^\ell = \dot{\rho}^\ell_c - \dot{\rho}^c_\ell + \dot{\rho}^\ell_m - \dot{\rho}^m_\ell + \dot{\rho}^\ell_s - \dot{\rho}^s_\ell, \tag{4.12}$$

where $\mathscr{c}^\ell$ is the density of mass supply to the interstitial miscible liquid, i.e., the rate per unit volume at which mass is being moved from the three other phases into the iml, minus the rate at which it is being removed from the iml and placed into the other three phases. From this equation, it immediately follows that

$$\operatorname{tr} \mathbf{L}^\ell = 0 \tag{4.13}$$

whenever the liquid phase is incompressible, which is a good assumption.

Finally, the mass balance governing the pos within a tissue, as described in supposition 1 and constrained by postulate 1, obeys the integral equation

$$\partial_t \int_{\mathcal{B}} \rho^s \, \mathrm{d}v = -\int_{\delta\mathcal{B}} \rho^s \boldsymbol{v}^s \cdot \boldsymbol{n} \, \mathrm{d}a + \int_{\mathcal{B}} \left(\dot{\rho}^s_c - \dot{\rho}^c_s + \dot{\rho}^s_\ell - \dot{\rho}^\ell_s + \dot{\rho}^s_m - \dot{\rho}^m_s \right) \mathrm{d}v, \tag{4.14}$$

whose local form is the field equation

$$\mathrm{d}^s_t \rho^s + \rho^s \operatorname{div} \boldsymbol{v}^s = \mathscr{c}^s \quad \text{with} \quad \mathscr{c}^s = \dot{\rho}^s_c - \dot{\rho}^c_s + \dot{\rho}^s_\ell - \dot{\rho}^\ell_s + \dot{\rho}^s_m - \dot{\rho}^m_s, \tag{4.15}$$

where $\mathscr{c}^s$ is the density of mass supply to the population of solutes, i.e., the rate per unit volume at which mass is being moved from the three other phases into the

pos, minus the rate at which it is being removed from the pos and placed into the other three phases. From this equation, it immediately follows that

$$\operatorname{tr} \mathbf{L}^s = 0 \tag{4.16}$$

whenever the solutes are incompressible, which is probably a reasonable assumption. A means by which the mass density for a pos can be quantified is via

$$\rho^s = \sum_{j=1}^{N_s} \rho_j^s = \sum_{j=1}^{N_s} n_j M_j, \tag{4.17}$$

where n_j is the molar concentration (number of moles per cubic centimeter) and M_j is the molecular weight (grams per mole) of solute molecule j.

The four mass supplies, which are mass rates per unit volume, satisfy the identity

$$\sum c^\alpha = 0, \tag{4.18}$$

in accordance with their definitions given in equations (4.5, 4.9, 4.12 & 4.15). Hence, our physical laws for tissue are a special case of Truesdell's (1957) physical laws for chemically reacting mixtures with diffusion.

From the identity in equation (4.3), along with equations (3.5, 3.7 & 3.14), the sum of the constituent mass-balance laws listed in equations (4.5, 4.9, 4.12 & 4.15) equates with the conservation of mass stated in equation (4.2). In this regard, our theory differs from the existing theories for tissue growth discussed in the Introduction. Our theory, like Truesdell's (1957) and Bowen's (1969, 1976) theories, describes a closed-system continuum wherein mass is conserved both at a mass point and throughout the body. Prior tissue growth theories describe open-system continua wherein mass can be either created or destroyed at a mass point, with a tacit implication that mass is somehow being conserved at some higher level of organization such as the organism.

It is convenient to express the balance equation that governs mass in each of the constituent phases as a single integral equation

$$\partial_t \int_{\mathcal{B}} \rho^\alpha \, \mathrm{d}v = -\int_{\delta\mathcal{B}} \rho^\alpha \boldsymbol{v}^\alpha \cdot \boldsymbol{n} \, \mathrm{d}a + \int_{\mathcal{B}} c^\alpha \, \mathrm{d}v, \tag{4.19}$$

whose local form is

$$\mathrm{d}_t^\alpha \rho^\alpha + \rho^\alpha \operatorname{div} \boldsymbol{v}^\alpha = c^\alpha, \tag{4.20}$$

wherein $\alpha \in \{c, \ell, m, s\}$. In a general sense, the density of mass supply c^α represents a sum of rates at which masses are leaving the three other phases to be absorbed by the α^{th} phase, minus a sum of rates at which masses are departing from the α^{th} phase to be absorbed by the other three phases.

The equation for mass balance in the α^{th} constituent, equation (4.20), and the associated formula governing mass balance in the overall mixture, equation (4.18), comprise what is theorem 1 in Truesdell's (1957) monumental paper.

A balance formula of the form

$$\mathrm{d}_t^m \rho^c + \rho^c \operatorname{div} \boldsymbol{v}^m = \operatorname{div}\big(\mathcal{D} \operatorname{grad} \rho^c\big) + c^c, \tag{4.21}$$

has been used by Tranquillo & Murray (1993) in their modeling of wound closure, and by Gómez-Benito et al. (2006) in their modeling of bone healing, with the mass supply c^c introducing terms akin to those of the logistics equation in order to model cell mitosis (birth) and apoptosis (death). Equation (4.21) is an alternative way to write equation (4.9) for mass balance in the poc, given the definition for $\boldsymbol{v}^c$ provided in equation (3.13).

(i) Rates for Mass-Averaged Fields

Consider an arbitrary field β defined as the mass-weighted average of its constituents

$$\beta = \sum \mu^\alpha \beta^\alpha \quad \text{or equivalently} \quad \rho\beta = \sum \rho^\alpha \beta^\alpha. \tag{4.22}$$

From equation (3.18), it follows that

$$\mathrm{d}_t \beta^\alpha = \mathrm{d}_t^\alpha \beta^\alpha - \operatorname{grad} \beta^\alpha \cdot \boldsymbol{u}^\alpha, \tag{4.23}$$

whilst from equations (3.15, 3.18 & 4.3), and an application of the chain rule to equation (3.7), viz., $\rho\, \mathrm{d}_t \mu^\alpha = \mathrm{d}_t \rho^\alpha - \mu^\alpha \mathrm{d}_t \rho$, which is further simplified via equation (4.2) for mass conservation, it follows that the balance law governing mass in each constituent phase, equation (4.20), can be recast as

$$\rho\, \mathrm{d}_t \mu^\alpha = -\operatorname{div}\big(\rho^\alpha \boldsymbol{u}^\alpha\big) + c^\alpha, \tag{4.24}$$

such that equations (4.22–4.24), in the company of equation (4.3), collectively yield (cf. equation 1.2.17 in Bowen 1976)

$$\begin{aligned} \rho\, \mathrm{d}_t\big(\mu^\alpha \beta^\alpha\big) &= \rho^\alpha\, \mathrm{d}_t \beta^\alpha + \beta^\alpha\, \rho\, \mathrm{d}_t \mu^\alpha \\ &= \rho^\alpha\, \mathrm{d}_t^\alpha \beta^\alpha - \operatorname{div}\big(\rho^\alpha \beta^\alpha \boldsymbol{u}^\alpha\big) + c^\alpha \beta^\alpha, \end{aligned} \tag{4.25}$$

and therefore

$$\rho\, \mathrm{d}_t \beta = \sum \Big(\rho^\alpha \mathrm{d}_t^\alpha \beta^\alpha - \operatorname{div}\big(\rho^\alpha \beta^\alpha \boldsymbol{u}^\alpha\big) + c^\alpha \beta^\alpha\Big), \tag{4.26}$$

which is a formula of extreme importance in mixture theory. This formula establishes how local fields map into their associated global fields. It is the predominant averaging formula of mixture theory.

As a matter of illustration,

$$\rho \ddot{\boldsymbol{x}} = \sum \Big(\rho^\alpha \mathrm{d}_t^\alpha \boldsymbol{v}^\alpha - \operatorname{div}\big(\rho^\alpha \boldsymbol{v}^\alpha \otimes \boldsymbol{u}^f\big) + c^\alpha \boldsymbol{v}^\alpha\Big) \tag{4.27}$$

quantifies the barycentric acceleration of a mixture.

5. Balance Laws for Tissues

In the prior section, we have shown that tissues can be treated as a special case of chemically reacting mixtures with diffusible constituents. Consequently, one can immediately write down the physical laws that govern them. The balance laws for mass, momentum, and energy are from theorems 1–3 of Truesdell (1957). The field equations governing entropy are derived in the appendix.

Tissues do not require the full generality of the theory for chemically reacting mixtures with diffusion. Certain simplifying assumptions can be imposed; in particular:

Assumption 1. The temperatures of the separate phases are equal.

Assumption 2. Second- and higher-order terms in diffusion velocity can be neglected.

Assumption 3. All moments of momenta can be neglected.

In accordance with these assumptions, the physical laws that govern the mass, momentum, energy, and entropy of each constituent in such a mixture are respectively

$$\begin{aligned} \mathrm{d}_t^\alpha \rho^\alpha &= -\rho^\alpha \operatorname{div} \boldsymbol{v}^\alpha + c^\alpha, \\ \rho^\alpha \mathrm{d}_t^\alpha \boldsymbol{v}^\alpha &= \operatorname{div} \mathbf{T}^\alpha + \rho^\alpha \boldsymbol{g} + \boldsymbol{p}^\alpha, \qquad \mathbf{T}^\alpha = (\mathbf{T}^\alpha)^{\mathrm{T}}, \\ \rho^\alpha \, \mathrm{d}_t^\alpha \epsilon^\alpha &= \operatorname{tr}\big(\mathbf{T}^\alpha \mathbf{D}^\alpha\big) - \operatorname{div} \boldsymbol{q}^\alpha + \rho^\alpha r^\alpha + e^\alpha, \\ \rho^\alpha \, \mathrm{d}_t^\alpha \eta^\alpha &= -\operatorname{div}\big(\boldsymbol{q}^\alpha/\theta\big) + \rho^\alpha r^\alpha/\theta + \mathfrak{s}^\alpha + \gamma^\alpha, \end{aligned} \tag{5.1}$$

where $\alpha \in \{c, \ell, m, s\}$ in our case. The laws that govern momentum and entropy utilized assumptions 1 & 3 in their derivations. Here ρ^α, ϵ^α, r^α, and η^α are the mass, internal energy, heat production, and entropy densities of the α^{th} constituent, while γ^α is its entropy production, θ is temperature, $\boldsymbol{g}$ is the gravity vector (the sole body force considered here), $\boldsymbol{v}^\alpha$ and $\boldsymbol{q}^\alpha$ is the velocity and heat flux vectors of the α^{th} constituent, and $\mathbf{T}^\alpha$ is its partial stress. Quantities $\boldsymbol{p}^\alpha$, e^α, and $\mathfrak{s}^\alpha$ are the rates at which momentum, internal energy, and entropy are being supplied to the α^{th} phase from the other three phases through processes linked to some mass supply c^α and/or some diffusion velocity $\boldsymbol{u}^\alpha$.

Their counterparts, the physical laws that govern the overall mixture, are satisfied implicitly by the following set of constraint equations

$$\begin{aligned} \sum c^\alpha &= 0, \\ \sum \big(\boldsymbol{p}^\alpha + c^\alpha \boldsymbol{u}^\alpha\big) &= \mathbf{0}, \\ \sum \Big(e^\alpha + \operatorname{tr}\big(\mathbf{T}^\alpha \operatorname{grad} \boldsymbol{u}^\alpha\big) + c^\alpha \epsilon^\alpha\Big) &= 0, \\ \sum \Big(\mathfrak{s}^\alpha + \operatorname{div}\big(\rho^\alpha \psi^\alpha \boldsymbol{u}^\alpha/\theta\big) + c^\alpha \eta^\alpha\Big) &= 0, \\ \sum \gamma^\alpha &\geq 0, \end{aligned} \tag{5.2}$$

where assumptions 1 & 2 have been imposed, and where $\psi^\alpha = \epsilon^\alpha - \eta^\alpha \theta$ denotes the Helmholtz free energy of the α^{th} phase. The first formula in equation (5.2) is just equation (4.18). The second formula, like the first, is as it appears in Truesdell (1957). However, the third formula is different, because of how work is considered to map (see equation 5.5). In our formulation, the additional work lost or gained through diffusion $\operatorname{tr}\big(\mathbf{T}^\alpha \operatorname{grad} \boldsymbol{u}^\alpha\big)$ is accounted for. In Truesdell's (1957) and Bowen's (1976) formulation, this effect is quantified by $\boldsymbol{p}^\alpha \cdot \boldsymbol{u}^\alpha$, which is associated with a different heat flux map than is given in equation (5.5). The remaining two formulæ in equation (5.2) are new to the best of my knowledge, and are derived in the appendix.

The formulæ in equation (5.2) are equivalent to the well-known field equations

$$\begin{aligned} \mathrm{d}_t \rho &= -\rho \operatorname{div} \dot{\boldsymbol{x}}, \\ \rho \, \mathrm{d}_t \dot{\boldsymbol{x}} &= \operatorname{div} \mathbf{T} + \rho \boldsymbol{g}, & \mathbf{T} &= \mathbf{T}^{\mathrm{T}}, \\ \rho \, \mathrm{d}_t \epsilon &= \operatorname{tr} (\mathbf{T}\mathbf{D}) - \operatorname{div} \boldsymbol{q} + \rho r, \\ \rho \, \mathrm{d}_t \eta &= -\operatorname{div}(\boldsymbol{q}/\theta) + \rho r/\theta + \gamma, & \gamma &\geq 0, \end{aligned} \tag{5.3}$$

which are classic in their construction. In accordance with assumption 2, as it pertains to the internal energy, the mappings

$$\rho = \sum \rho^\alpha, \quad \dot{\boldsymbol{x}} = \sum \mu^\alpha \boldsymbol{v}^\alpha, \quad \epsilon = \sum \mu^\alpha \epsilon^\alpha, \quad \eta = \sum \mu^\alpha \eta^\alpha, \tag{5.4}$$

establish how the various local fields that reside on the left-hand sides of the formulæ in equation (5.1), as arguments of their material derivatives, relate to their continuum counterparts in the formulæ of equation (5.3). Also in accordance with assumption 2, which has been imposed on all of the formulæ to follow except for that of the heat production, one obtains the mappings

$$\begin{aligned} \mathbf{T} &= \sum \mathbf{T}^\alpha, \\ \operatorname{tr} (\mathbf{T}\mathbf{D}) &= \sum \Big(\operatorname{tr} \left(\mathbf{T}^\alpha \mathbf{D}^\alpha \right) - \operatorname{tr} \left(\mathbf{T}^\alpha \operatorname{grad} \boldsymbol{u}^\alpha \right) \Big), \\ \boldsymbol{q} &= \sum \left(\boldsymbol{q}^\alpha + \rho^\alpha \epsilon^\alpha \boldsymbol{u}^\alpha \right), \\ r &= \sum \mu^\alpha r^\alpha, \end{aligned} \tag{5.5}$$

which establish how the various local fields relate to their global counterparts that reside on the right-hand sides of these formulæ.

See, for example, Bowen (1976) for the derivations and representations that hold whenever asumptions 1–3 do not apply. We point out that Bowen (1976) further decomposes $\operatorname{tr} \left(\mathbf{T}^\alpha \operatorname{grad} \boldsymbol{u}^\alpha \right)$ into $\operatorname{div} \left(\mathbf{T}^\alpha \boldsymbol{u}^\alpha \right) - \boldsymbol{u}^\alpha \cdot \operatorname{div} \mathbf{T}^\alpha$, which is mathematically correct, and in doing so he is lead to different mapping formulæ for $\boldsymbol{q}$ and ϵ^α than those that are given in equations (5.2 & 5.5). Both of our formulations are mathematically correct. We find our formulation to be more intuitive. Bowen (1976) refers to our $\boldsymbol{q}$ as $\boldsymbol{k}$.

6. Constitutive Structure

The customary means by which constitutive equations are derived is to introduce a Lagendre transformation that swaps entropy for temperature as an independent thermodynamic variable, with temperature having the advantage of being capable of measurement. This particular transformation exchanges the internal energy with the Helmholtz free energy as the thermodynamic state function, which arose naturally in our derivation of entropy production, equation (A.8), and allows one to combine the formulæ for the first- and second-laws of thermodynamics into a single formula, with the outcome being a Gibbs-like equation.

Let the velocity fields for the four constituents of tissue be described by

$$\begin{aligned}
\boldsymbol{v}^{\ell} &= \boldsymbol{\psi}(\boldsymbol{x}, t), \\
\boldsymbol{v}^{m} &= \partial_t \boldsymbol{\varphi}(\boldsymbol{X}^m, t), \\
\boldsymbol{v}^{s} &= \boldsymbol{v}^{\ell} - \sum_{i=1}^{N_s} \mathcal{D}_i^s \operatorname{grad} \ln \rho_i^s, \\
\boldsymbol{v}^{c} &= \boldsymbol{v}^{m} - \sum_{i=1}^{N_c} \left(\mathcal{D}_i^c \operatorname{grad} \ln \rho_i^c - \sum_{j=1}^{N_s} \mathcal{D}_{ij}^{cs} \operatorname{grad} \ln \rho_j^s \right),
\end{aligned} \tag{6.1}$$

in accordance with supposition 1.

A common form adopted for the constitutive structure of momentum supply is (cf. equation 2.1.12 in Bowen 1976)

$$\boldsymbol{p}^{\alpha} = -\sum_{\beta} \sigma^{\alpha\beta} \operatorname{grad} \rho^{\beta} - \sum_{\beta} \xi^{\alpha\beta} \boldsymbol{v}^{\beta} - \zeta^{\alpha} \operatorname{grad} T, \tag{6.2}$$

where the first term on the right-hand side introduces a buoyancy effect, the second term introduces a Stokes drag effect, and the last term introduces a Soret thermal-diffusion effect, with $\sigma^{\alpha\beta}$, $\xi^{\alpha\beta}$, and ζ^{α} denoting material constants. For example, the biphasic theory of Klisch & Lotz (2000) utilizes Stokean drag as their constitutive equation for momentum supply in their modeling of the annulus fibrosus.

Appendix. Balance of Entropy With Its Production

Unlike axiom 1, which is a law of conservation (i.e., an equality), the second law of thermodynamics in its classic presentation establishes an inequality. Following the approach promulgated by Truesdell & Noll (1965, pg. 295), one can postulate the existence of an entropy production term that 'balances' this classic entropy inequality, thereby putting the axiom for the second law into a format that can be readily applied down to the level of the sub-continua of a mixture.

Axiom 2. The rate at which entropy increases inside of $\mathcal{B}$ equals the flux of entropy entering across $\delta\mathcal{B}$, plus the entropy expended by the heat fluxing across its surface $\delta\mathcal{B}$ and by the heat generating within its volume $\mathcal{B}$, plus a non-negative rate of entropy generation created internally by other irreversible processes.

Axiom 2 is a statement of the second law of rational thermodynamics, whose mathematical interpretation is

$$\partial_t \int_{\mathcal{B}} \rho\eta \, \mathrm{d}v = -\int_{\delta\mathcal{B}} \rho\eta \, \dot{\boldsymbol{x}} \cdot \boldsymbol{n} \, \mathrm{d}a - \int_{\delta\mathcal{B}} (\boldsymbol{q}/\theta) \cdot \boldsymbol{n} \, \mathrm{d}a + \int_{\mathcal{B}} \left(\rho r/\theta + \gamma \right) \mathrm{d}v, \tag{A.1}$$

which satisfies a Clausius-Duhem constraint via the integral inequality

$$\int_{\mathcal{B}} \gamma \, \mathrm{d}v \geq 0, \tag{A.2}$$

wherein η and r are the entropy and rate of heat production per unit mass, θ is the absolute temperature, $\boldsymbol{q}$ is the heat flux, and γ is the rate of entropy production per unit volume brought about by internal irreversible processes. Following conventional arguments, and simplifying with equation (4.2) for mass conservation, these integral equations are equivalent to the field equations

$$\rho \, \mathrm{d}_t \eta = -\mathrm{div}(\boldsymbol{q}/\theta) + \rho r/\theta + \gamma, \tag{A.3}$$

and

$$\gamma \geq 0, \tag{A.4}$$

where the latter formula handles the inequality from the second law of thermodynamics, as it applies to a continuum. These results are well known.

Postulate 2. For a phase in a mixture, the rate at which entropy increases inside of $\mathcal{B}$ equals the flux of entropy entering across $\delta\mathcal{B}$, plus the entropy expended by the heat fluxing across its surface $\delta\mathcal{B}$ and by the heat generating within its volume $\mathcal{B}$, plus a ~~non-negative~~ rate of entropy generation created internally by other irreversible processes, plus any entropies that are being exchanged between it and the other phases within $\mathcal{B}$.

Given that equation (4.20) establishes the law governing mass balance within the phases of a mixture then, in accordance with postulate 2 and assumption 1, a balance of the entropy with its production in the α^{th} constituent requires that

$$\partial_t \int_{\mathcal{B}} \rho^\alpha \eta^\alpha \, \mathrm{d}v = -\int_{\delta\mathcal{B}} \rho^\alpha \eta^\alpha \, \boldsymbol{v}^\alpha \cdot \boldsymbol{n} \, \mathrm{d}a - \int_{\delta\mathcal{B}} \left(\boldsymbol{q}^\alpha/\theta\right) \cdot \boldsymbol{n} \, \mathrm{d}a + \int_{\mathcal{B}} \left(\rho^\alpha r^\alpha/\theta + \gamma^\alpha + \mathfrak{s}^\alpha + c^\alpha \eta^\alpha\right) \mathrm{d}v, \tag{A.5}$$

where η^α is the entropy per unit mass and γ^α is the rate of entropy production per unit volume, both within the α^{th} phase, while $\mathfrak{s}^\alpha$ is the density of entropy supply originating from an exchange of entropies between it and the other constituent phases. When written as a field equation, simplifying with equation (4.20) for mass balance, one gets

$$\rho^\alpha \, \mathrm{d}_t^\alpha \eta^\alpha = -\mathrm{div}\left(\boldsymbol{q}^\alpha/\theta\right) + \rho^\alpha r^\alpha/\theta + \gamma^\alpha + \mathfrak{s}^\alpha, \tag{A.6}$$

which is a balance law that governs entropy and its production at the constituent level. By introducing the notions of entropy production and entropy supply, we are able to construct an entropy law for the individual phases of a mixture in a manner that is consistent with the construction of their mass, momentum, and energy laws. In this regard, our approach differs from the classic approach outlined in Bowen (1976) wherein γ, γ^α, and $\mathfrak{s}^\alpha$ have not been introduced.

It is important to point out that postulate 2 does not carry over a 'non-negative' constraint on γ^α that is otherwise imposed on γ in axiom 2; in other words, it is admissible for a γ^α to be negative as-long-as γ is always non-negative.

By assigning the mappings

$$\gamma = \sum \gamma^{\alpha} \quad \text{and} \quad \rho\eta = \sum \rho^{\alpha}\eta^{\alpha}, \tag{A.7}$$

one is able to express $\rho\, \mathrm{d}_t \eta$ in terms of local fields via equation (4.26) leading to

$$\sum \Big(\mathscr{s}^{\alpha} + \operatorname{div}\big(\rho^{\alpha}\psi^{\alpha}\boldsymbol{u}^{\alpha}/\theta\big) + \mathscr{c}^{\alpha}\eta^{\alpha} \Big) = 0, \tag{A.8}$$

where the mappings for heat flux $\boldsymbol{q}$ and heat production r obtained from the energy balance formulæ have been applied, as listed in equation (5.5) wherein the expression for $\boldsymbol{q}$ requires an application of assumption 2. Here $\psi^{\alpha} = \epsilon^{\alpha} - \eta^{\alpha}\theta$ defines the Helmholtz free energy for the α^{th} constituent. Equation (A.8) forces the entropy supply to be in balance with the entropy lost or gained through diffusion and through mass supply.

(a) Helmholtz Free Energy Formulation

The conservation of energy listed in equation (5.3) and the balance of entropy with its production derived in equation (A.3) combine to produce

$$\rho\, \mathrm{d}_t \psi = -\rho\eta\, \mathrm{d}_t \theta + \operatorname{tr}(\mathbf{T}\mathbf{D}) - \boldsymbol{q} \cdot \operatorname{grad}(\ln\theta) - \gamma\theta, \tag{A.9}$$

where $\psi = \epsilon - \eta\theta$ is the Helmholtz free energy function.

Likewise, the balance law for energy listed in equation (5.1) and the formula balancing entropy with its production derived in equation (A.6), both of which pertain to the constituents of a mixture, and combine to produce

$$\rho^{\alpha}\, \mathrm{d}_t^{\alpha} \psi^{\alpha} = -\rho^{\alpha}\eta^{\alpha}\, \mathrm{d}_t^{\alpha}\theta + \operatorname{tr}\big(\mathbf{T}^{\alpha}\mathbf{D}^{\alpha}\big) - \boldsymbol{q}^{\alpha} \cdot \operatorname{grad}(\ln\theta) - \gamma^{\alpha}\theta + \mathscr{a}^{\alpha}, \tag{A.10}$$

where $\mathscr{a}^{\alpha} = e^{\alpha} - \mathscr{s}^{\alpha}\theta$ is the density of free-energy supply associated with the α^{th} phase. Its constraint equation is obtained by multiplying temperature with the fourth formula in equation (5.2) and subtracting that from the third formula in equation (5.2).

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14. ABSTRACT
Higher-level physical laws applicable to biological tissues are presented that will permit the modeling of metabolic activity at the cellular level, including variations in the mass of a tissue. Here the tissue is represented as a fluid/solid mixture, wherein molecular solutes transport within the fluid, and cells can migrate throughout the porous solid. Variations in mass can arise via exchanges in mass between the constituent phases within a control volume such that mass is conserved in the tissue overall. The governing balance laws for mass, momentum, energy, and entropy are a special case of those describing a chemically reacting mixture with diffusion. Thermodynamic constraints on the constitutive structure are addressed.

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