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A Phase-Field Theory for Multi-constituent Diffusion and Deformation: Application to Avascular Tumor Growth

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Danial Faghihi, J. Tinsley Oden, Xinzeng Feng, Ernesto A.B.F. Lima, David A. Hormuth II, and Thomas E. Yankeelov

The Institute for Computational Engineering and Sciences
The University of Texas at Austin
Austin, Texas 78712

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A Phase-Field Theory for Multi-constituent Diffusion and Deformation: Application to Avascular Tumor Growth

Danial Faghihi[1], J. Tinsley Oden[1], Xinzeng Feng[1], Ernesto A.B.F. Lima[1], David A. Hormuth II[1], Thomas E. Yankeelov[2]

[1]The Institute for Computational Engineering and Sciences
[2]Departments of Biomedical Engineering, Diagnostic Medicine, and Oncology, Institute for Computational and Engineering Sciences, Livestrong Cancer Institutes

The University of Texas at Austin

Abstract

The paper develops a general class of thermodynamically consistent, continuum models based on mixture theory with phase effects that describe the behavior of a mass of N interacting constituents. Of these, M can be solid species undergoing large deformations, and $N - M$ can be compressible, non-Newtonian, viscous fluids. The fundamental building blocks on which to frame the mixture theories consist of the balance laws for mass and momentum, as well as energy balance and the entropy production inequality derived from the first and second laws of thermodynamics. A general phase-field framework is developed by closing the system through postulating constitutive equations to depict the physical phenomena of interest. For deducing the constitutive laws, the free energy and rate of dissipation potential are considered as primary potentials and thermodynamical forces are derived by considering the processes leading to energy storage and dissipation. The theory is then specified to simulate major features of the growth of tumors in a microenvironment through specific forms of free energy and dissipation. Additionally, biological growth and its interaction with the tumor deformation are included in this model through a physically and mathematically consistent framework.

Keywords: Mixture theory, Phase-field, Hyperelastic solid, Tumor growth

Contents

1 Introduction

There is a large and growing literature on mathematical and computational models of the physical and biological processes involved in the growth of cancer. A comprehensive history is provided by Araujo and McElwain [11], and several review papers have also appeared in recent years; see, e.g., [2, 57, 103, 111, 117, 124]. Most tumor models fall into the two main categories of discrete cell-based models and continuum models. The continuum approach considers the average of the global cell population behavior [33, 88, 102, 137, 140], while discrete approaches track and update individual cell dynamics using a certain sets of biophysical rules [16, 77, 115, 130]. Due to the rapid increase in computational cost of discrete methods with the number of cells modeled, continuum methods are often favored as a basis for providing predictions in systems on events at realistic macro spatial and temporal scales.

Many current continuum theories are based on single-phase tumors. Recently, multiphase mixture models have been developed to account for heterogeneities in cell-phenotypes and in the mechanical response of tumor phases; see, e.g., [7, 23, 26, 44, 45]. While such approaches can yield self-consistent frameworks, they are incapable of accounting for important physical and biological phenomena encountered in tumor progression. Modeling such complex biological processes can benefit from the use of a framework based on continuum theories of mixtures [22, 36, 102, 112] to incorporate various solid and fluid constituents involved in the underlying biophysical phenomena. Mixture theory has been a focus of much research in mechanics for many years [21] as a basis for treating the behavior of porous media involving two or more bodies interacting with one another. In mixture models, the governing equations consist of mass and momentum balance equations for each species, interphase mass and momentum exchange, along with appropriate constitutive equations.

One general approach to modeling multiphase materials is provided by so-called phase-field models [20], in which the interface between phases is handled automatically as a feature of the solution, and represents boundary layers between phases. In general, such models are obtained by incorporating gradients of the order parameters such as the concentrations of various constituents in the free energy functionals for a multiphase material so as to approximate surface energies at interfaces. The most notable model of this type is the Cahn-Hilliard model of binary phase separation [27] in which the free energy contains gradients in concentrations multiplied by parameters which characterize the thickness of smoothed interfaces between the phases. Phase field models have provided important frameworks for characterizing microstructure evolution at the mesoscale [54, 99, 131, 135], solidification [20], grain growth [96], dislocation dynamics [142], self-assembly of block copolymers [30] and many other multiphase phenomena in materials science, metallurgy, chemistry, and chemical engineering. Recently, phase-field models have been applied to simulate tumor growth [33, 88, 102, 140]. A multi-species framework allows for characterizing the interaction between (for example) the necrotic, apoptotic, quiescent, and proliferative cells present in solid, avascular tu-

mors. Furthermore, phase-field models based on mixture theory allow modeling other processes, such as angiogenesis and deformation to capture realistic features of tumor progression.

In addition to biochemical factors, mechanical stresses of the solid phase of a tumor play a vital role in the expansion, invasion, and metastasis of tumors [25, 74, 75, 85, 123, 133]. Mechanical stresses mainly arise due to heterogeneous tumor growth and the effect of surrounding tissue confinement; that is, heterogeneous growth leads to residual stresses generation, that occurs in normal tissues such as arteries [120, 125]. The external stresses on tumors produced by the surrounding tissues can be more pronounced than those incurred by the heterogeneous growth. The mechanical stresses moderate the development of solid tumors by compressing both the tumor cells and intra-tumoral blood vessels. This results in lowering the proliferation rate and inducing apoptosis of the tumor cells, but it can also enhance the potential invasiveness and metastatic of a tumor [68, 75, 97]. In this regard, tumor models needs to account for the mechanical aspects of the biological growth. Within the continuum mechanics framework, biological growth is treated as a change in both mass and form. Rendering gain and loss of mass into nonuniform changes in form is one of the central challenges in continuum mechanics and a subject of controversy among investigators; see, e.g., [3].

This paper develops a general class of thermodynamically consistent continuum models based on mixture theory with diffuse interface effects that describes the biomechanical behavior of a mass of N interacting constituents. M of these N constituents can be solid species undergoing large deformations and growth, and $N - M$ can be compressible, non-Newtonian, viscous fluids. A general phase-field framework is developed by considering the free energy and rate of dissipation potential as primary potentials and thermodynamical forces are derived considering the processes leading to energy storage and dissipation. The constitutive relations are then proposed to simulate major features of tumor growth in a microenvironment. The constitutive models are deduced from specific forms of the Helmholtz free energy and rate of dissipation. Special attention is given to model the effects of mechanical deformation in tumor progression. In this regard, growth effects and their interaction with the deformation are included in the model through physically and mathematically consistent construction.

2 Theoretical Framework: Coupled Diffusion-Deformation of Multi-species Mixtures

Our theoretical framework of our tumor growth model is founded in the continuum theory of mixtures, advanced by Truesdell [126], Truesdell and Toupin [129], Bowen [21, 22], and Eringen and Ingram [40, 73] and others. Parallel developments of theories of porous media share many aspects of mixture theory for two- or three-phase materials, as can be seen in works such as those by de Boer [35, 36] among many others. The development of diffuse-interface models based on mixture theory involves an additional level of complexity due to the dynamical effects associated with changes in the volume

fractions of the constituents. We follow the basic hypotheses of Truesdell and Noll [128] in developing a physically meaningful continuum theory. In this regard, the general theory governing a continuum mixture of N constituents is developed based on principles such as the balance laws for mass and momentum as well as energy and the inequality for entropy production. These laws are viewed as fundamental building blocks on which to frame theories of material behavior. Then a general phase-field version is developed by closing the system with constitutive equations. In this regard, the free energy and rate of dissipation potential are considered as primary potentials and thermodynamical forces are derived considering the processes leading to energy storage and dissipation.

2.1 A Continuum Theory of Mixture

In continuum mechanics, a body $\mathcal{B}$ is viewed as a set of material points that occupy subsets of Euclidean space as the motion of the body carries its through various configurations. It is convention to choose one such region as reference and refer to it as the reference configuration of $\mathcal{B}$. The material points of the body are identified with their positions $\mathbf{X} \in \mathcal{B}$. The underlying assumption of mixture theory [21, 22, 36, 102, 112] is that a material body $\mathcal{B}$ consists of N constituent species that occupy a common part of physical space at the same time. The body undergoes a motion which maps the reference configuration $\mathcal{B}$ onto a current configuration $\mathcal{B}_t$, with the spatial position of material points at time t, given by $\mathbf{x} = \mathcal{X}(\mathbf{X}, t)$. In an N-species mixture the motion is defined by

$$\mathbf{x} = \mathcal{X}_\alpha(\mathbf{X}_\alpha, t), \tag{1}$$

where $\alpha = 1, 2, \cdots, N$ and $\mathbf{X}_\alpha$ is the position of the material points of the α-th constituent in its reference configuration. The deformation gradient is defined by

$$\mathbf{F}_\alpha := \frac{\partial \mathcal{X}_\alpha}{\partial \mathbf{X}_\alpha}. \tag{2}$$

Each spatial position $\mathbf{x}$ is occupied by N different constituents, and each constituent has a mass density, $\hat{\rho}_\alpha(\mathbf{x}, t)$, representing the mass of the α-th constituent per unit volume of the mixture at time t. The mass density of the mixture at a point $(\mathbf{x}, t)$ is defined as[1],

$$\rho(\mathbf{x}, t) = \sum_\alpha \hat{\rho}_\alpha(\mathbf{x}, t), \tag{3}$$

and the mass concentration of the α-th constituent is defined by,

$$c_\alpha(\mathbf{x}, t) = \frac{\hat{\rho}_\alpha(\mathbf{x}, t)}{\rho(\mathbf{x}, t)}. \tag{4}$$

[1]Throughout the formulation the subscript α is an index taking on values, $1 \leq \alpha \leq N$, unless otherwise specified, and we shall use the abbreviated notation $\sum_\alpha = \sum_{\alpha=1}^{N}$.

The volume fraction of the α-th constituent is,

$$\phi_\alpha(\mathbf{x},t) = \frac{dv_\alpha}{dv}, \tag{5}$$

where dv is a differential volume containing the point $\mathbf{x}$, and dv_α is the proportion of volume occupied by constituent α. The (partial) density, ρ_α, is also defined as,

$$\hat{\rho}_\alpha(\mathbf{x},t) = \rho_\alpha(\mathbf{x},t)\phi_\alpha(\mathbf{x},t), \tag{6}$$

representing the mass of α-th constituent per unit volume of the constituent.

From (4) and (5) clearly,

$$\sum_\alpha c_\alpha = 1 \qquad , \qquad \sum_\alpha \phi_\alpha = 1. \tag{7}$$

In addition, the velocity of each constituent is defined as,

$$\mathbf{v}_\alpha(\mathbf{x},t) = \frac{\partial \mathcal{X}_\alpha(\mathbf{X}_\alpha,t)}{\partial t}, \tag{8}$$

and the mixture velocity is,

$$\mathbf{v} = \frac{1}{\rho}\sum_\alpha \rho_\alpha\phi_\alpha\mathbf{v}_\alpha. \tag{9}$$

The diffusion velocity for the α-th constituent is also defined by

$$\mathbf{u}_\alpha = \mathbf{v}_\alpha - \mathbf{v}. \tag{10}$$

with

$$\sum_\alpha \rho_\alpha\phi_\alpha\mathbf{u}_\alpha = 0. \tag{11}$$

The velocity gradient of each constituent, $\mathbf{L}_\alpha = \nabla\cdot\mathbf{v}_\alpha$, can be split into symmetric, $\mathbf{D}_\alpha$, and skew-symmetric, $\mathbf{W}_\alpha$, parts in which,

$$\mathbf{D}_\alpha = \frac{1}{2}(\nabla\mathbf{v}_\alpha + \nabla\mathbf{v}_\alpha^T) \qquad , \qquad \mathbf{W}_\alpha = \frac{1}{2}(\nabla\mathbf{v}_\alpha - \nabla\mathbf{v}_\alpha^T). \tag{12}$$

Finally, the link between Lagrangian and Eulerian descriptions in time derivatives can be made according to

$$\frac{d^\alpha\varphi}{dt} = \frac{\partial\varphi}{\partial t} + \mathbf{v}_\alpha\cdot\nabla\varphi, \tag{13}$$

where $d^\alpha\varphi/dt$ is the material time-derivative related to the motion of each constituent and φ is any differentiable function of $\mathbf{x}$ and t.

Each of the N species must satisfy its own balance laws consistent with the presence of interaction among constituents. The balance laws govern the behavior of a general mixture that must hold for all α, $1 \le \alpha \le N$, are presented in the next sections.

2.2 Macroscopic and Microscopic Force Balances

Let $\mathcal{R}_t$ denote an arbitrary spatial region convecting within the body $\mathcal{B}$ at time t. The basic balance laws for linear and angular momentum assert that the net force and momentum on $\mathcal{R}_t$ are balanced by temporal changes in the linear and angular momentum of $\mathcal{R}_t$. In this regard, the balance of linear momentum for α-constituent in the mixture requires,

$$\frac{d^\alpha}{dt}\int_{\mathcal{R}_t}\rho_\alpha\phi_\alpha\mathbf{v}_\alpha \mathrm{d}V = \int_{\partial\mathcal{R}_t}\mathbf{T}_\alpha.\mathbf{n}\ \mathrm{d}A + \int_{\mathcal{R}_t}(\rho_\alpha\phi_\alpha\mathbf{b}_\alpha)\mathrm{d}V, \tag{14}$$

where $\mathbf{T}_\alpha$ is the partial Cauchy stress tensor, $\mathbf{b}_\alpha$ is the body force per unit mass, $\mathbf{n}(\mathbf{x},t)$ denotes the outward unit normal field on the boundary $\partial\mathcal{R}_t$, and dA and dV are differential surface and volume elements of $\partial\mathcal{R}_t$. One can also consider an additional momentum supply term in (14) accounting for interaction of the α constituent with other components [102]. We ignore this term in the present work. Using the divergence theorem,

$$\int_{\partial\mathcal{R}_t}\mathbf{T}_\alpha.\mathbf{n}\ \mathrm{d}A = \int_{\mathcal{R}_t}\nabla\cdot\mathbf{T}_\alpha\ \mathrm{d}V,$$

and taking into account that (14) must hold for all spatial regions, leads to the *macro-force balance*,

$$\frac{d^\alpha\rho_\alpha\phi_\alpha\mathbf{v}_\alpha}{dt} = \nabla\cdot\mathbf{T}_\alpha + \rho_\alpha\phi_\alpha\mathbf{b}_\alpha, \tag{15}$$

which is equivalent to

$$\frac{\partial\rho_\alpha\phi_\alpha\mathbf{v}_\alpha}{\partial t} + \nabla\cdot(\rho_\alpha\phi_\alpha\mathbf{v}_\alpha\otimes\mathbf{v}_\alpha) = \nabla\cdot\mathbf{T}_\alpha + \rho_\alpha\phi_\alpha\mathbf{b}_\alpha. \tag{16}$$

In case of nonpolar materials (neglecting e.g., electromagnetic effects and micromoments), the balance of angular momentum results in the relation,

$$\mathbf{T}_\alpha = \mathbf{T}_\alpha^T \tag{17}$$

so the partial Cauchy stress is symmetric.

To describe the phase dynamics in the mixture, (following the arguments of Gurtin [58]), in addition to local force balances, we postulate the existence of a set of microscopic forces that accompany the evolution of each order parameter (i.e. volume fraction in present formulation). These thermodynamical forces are termed microscopic because they are involved with phenomena that occur at a scale (e.g., cell level) smaller than macroscopic interactions (e.g., tissue level). The notion of microscopic forces has been successfully applied to recover the classical formulation or to develop generalized frameworks such as strain gradient-plasticity theories [60, 61, 134], generalized heat transfer [41], micromorphic approaches [14, 42], and mixture theories of porous media [55, 108].

In the current formulation, the (micro-)kinematic of phase, ϕ_α, such as the phase separation and mixing of different components, is associated with three microforces $\boldsymbol{\xi}_\alpha$, π_α, and τ_α per unit volume. These nonlocal forces are balanced through the following relation,

$$\int_{\partial\mathcal{R}_t} \boldsymbol{\xi}_\alpha.\mathbf{n}\, \mathrm{d}A + \int_{\mathcal{R}_t} \pi_\alpha \mathrm{d}V + \int_{\mathcal{R}_t} \tau_\alpha \mathrm{d}V = 0, \tag{18}$$

where π_α is the internal microforce and τ_α is the external microforce associated with volume fraction[2] and $\boldsymbol{\xi}_\alpha$ is the thermodynamic stress conjugate to the gradient of species volume fractions and representing a flux through the boundary $\partial\mathcal{R}_t$. Making use of the divergence theorem and the fact that $\mathcal{R}_t$ is arbitrary leads to the following *species microforce balance*,

$$\nabla \cdot \boldsymbol{\xi}_\alpha + \pi_\alpha + \tau_\alpha = 0. \tag{19}$$

The additional balance law (19) arises due to considering the volume fraction of each constituent as an independent kinematical quantity in the mixture theory. In this regard, this force balance is essential in the theory of phase-field mixtures to account for the dynamical effects associated with changes in the volume fractions of the constituents, although it does not ordinarily arise in mixture theories. The general formulation described in this section leads to a basis of biological interpretations of microforces in tumor growth phenomena described in section 2.6[3].

2.3 Diffusing Species Mass Balance

The net mass of the diffusing species in the spatial region $\mathcal{R}_t$ is represented by $\int_{\mathcal{R}_t} \rho_\alpha \phi_\alpha \mathrm{d}V$. The species transport to $\mathcal{R}_t$ can be characterized by the rate at which the species is transported to $\mathcal{R}_t$ by diffusion across $\partial\mathcal{R}_t$ as well as the rate of transport to $\mathcal{R}_t$ by constituents external to the body. In this regard, species mass balance requires that,

$$\frac{d^\alpha}{dt} \int_{\mathcal{R}_t} \rho_\alpha \phi_\alpha \mathrm{d}V = -\int_{\partial\mathcal{R}_t} \mathbf{J}_\alpha.\mathbf{n}\, \mathrm{d}A + \int_{\mathcal{R}_t} S_\alpha \mathrm{d}V, \tag{20}$$

where $\mathbf{J}_\alpha$ is the mass flux and S_α is external species mass supplied (a source term). In other words, (20) suggests that the mass-rate-of-change of the α-th component must

[2]To simplify the notation, π_α and τ_α are defined as forces per unit volume. If these quantities are defined as forces per unit mass, they need to appear in (18) as $\rho_\alpha\phi_\alpha\pi_\alpha$ and $\rho_\alpha\phi_\alpha\tau_\alpha$ similar to the body force in (14).

[3]In theories of granular materials (e.g., Goodman and Cowin [55] and Passman, Nunziato, Walsh [101, 108]), the relation (19) is noted as the balance of equilibrated force. In the case of granular materials, the generalized microforces are physically interpreted as π_α being related to the pressure in the matrix acting on the voids and the material properties of the matrix, τ_α being related to an externally controlled pore pressure, and $\boldsymbol{\xi}$ as being a stress-type quantity and associated with the inter-granular contact forces which influence the packing or fabric of the mixture [76, 81, 101, 108]. Additionally, in [101] the internal force π_α is decomposed into a force supply associated with the species α and a force interaction associated with the interaction of α-th species with all other constituents. For simplicity of notation, we avoid such decompositions.

balance with the net rate of generation of the α-th component in $\mathcal{R}_t$. Using Reynolds' transport relation,

$$\frac{d^\alpha}{dt}\int_{\mathcal{R}_t}\phi_\alpha \mathrm{d}V = \int_{\mathcal{R}_t}(\frac{\partial \phi_\alpha}{\partial t} + \phi_\alpha \nabla\cdot\mathbf{v}_\alpha)\mathrm{d}V,$$

along with divergence theorem,

$$\int_{\partial\mathcal{R}_t}\mathbf{J}_\alpha.\mathbf{n}\ \mathrm{d}A = \int_{\mathcal{R}_t}\nabla\cdot\mathbf{J}_\alpha\ \mathrm{d}V,$$

one can derive the local *species mass balance* as

$$\frac{\partial \rho_\alpha\phi_\alpha}{\partial t} + \nabla\cdot(\rho_\alpha\phi_\alpha\mathbf{v}_\alpha) = S_\alpha - \nabla\cdot\mathbf{J}_\alpha. \tag{21}$$

According to Bowen [21], the right hand side of (21) is called the mass growth rate of the α component.

2.4 Force and Mass Balance for the Mixture

The balance equations for the mixture, governing the motion of a single body, should follow the individual species balance equation summing over all constituents. Thus the continuum balance laws of the full mixture can be written as,

$$\rho\frac{d\mathbf{v}}{dt} = \nabla\cdot\mathbf{T} + \mathbf{b}, \tag{22}$$

$$\nabla\cdot\boldsymbol{\xi} + \pi + \tau = 0, \tag{23}$$

$$\frac{\partial\rho}{\partial t} + \nabla\cdot(\rho\mathbf{v}) = 0, \tag{24}$$

subject to the following constraints,

$$\begin{aligned}
\mathbf{b} &= \frac{1}{\rho}\sum_\alpha \rho_\alpha\phi_\alpha\mathbf{b}_\alpha,\\
\sum_\alpha S_\alpha &= \sum_\alpha \nabla\cdot\mathbf{J}_\alpha,\\
\boldsymbol{\xi} &= \sum_\alpha \boldsymbol{\xi}_\alpha,\\
\pi &= \sum_\alpha \pi_\alpha,\\
\tau &= \sum_\alpha \tau_\alpha,\\
\mathbf{T} &= \sum_\alpha \mathbf{T}_\alpha - \rho_\alpha\phi_\alpha\mathbf{u}_\alpha\otimes\mathbf{u}_\alpha.
\end{aligned} \tag{25}$$

In the above relations, ρ, $\mathbf{T}$, $\mathbf{b}$, and $\mathbf{v}$ are the mass density, the Cauchy stress, the body force per unit mass, and velocity of the mixture, respectively.

2.5 Thermodynamics Derivation

2.5.1 The First Law: Balance of Energy

The first law of thermodynamics represents a balance between the internal energy of $\mathcal{R}_t$, the rate at which power is expended on $\mathcal{R}_t$, and the energy carried into $\mathcal{R}_t$ by species transport. In the present formulation, we consider isothermal processes (i.e., the heating $d\mathcal{Q}/dt \approx 0$) and assume that the kinetic energy is negligible. Defining the net internal energy of mixture as $\mathcal{E} = \int_{\mathcal{R}_t} \rho\varepsilon \mathrm{d}V$, with ε being the specific internal energy, the first law of thermodynamics is written as

$$\frac{d}{dt}\mathcal{E} = \mathcal{P}_{\text{ext}} + \mathcal{M}, \tag{26}$$

where $\mathcal{P}_{\text{ext}}$ is the external power. In addition to the classical terms of macroscopic forces, we consider non-classical terms contributing to the energy balance. This includes power expenditures of the microforces in $\mathcal{P}_{\text{ext}}$ along with energy flux due to the species diffusion (i.e., fluxes and sources). In (26), $\mathcal{M}$ is the (free-)energy carried into $\mathcal{R}_t$ by mass (species) transport (see, e.g., [58, 62, 89]). As $\mathbf{J}_\alpha$ and S_α carry with them a flux and supply of energy characterized by the chemical potential μ_α, we write

$$\mathcal{M} = \sum_\alpha \left(- \int_{\partial\mathcal{R}_t} \mu_\alpha \mathbf{J}_\alpha \cdot \mathbf{n} \, \mathrm{d}A + \int_{\mathcal{R}_t} \mu_\alpha S_\alpha \, \mathrm{d}V \right). \tag{27}$$

The chemical potential μ_α of species α is a quantity defined as the rate of change of free energy with respect to the change in the particle number of the species that are added or removed from the thermodynamic system. The magnitude of the chemical potential is independent of the size of the system, but it includes phenomena affecting diffusion; e.g., strain energy gradient, electric field, and temperature gradient[4].

From the mass balance relation (20), along with the divergence theorem,

$$\begin{aligned} \int_{\partial\mathcal{R}_t} \mu_\alpha \mathbf{J}_\alpha.\mathbf{n} \, \mathrm{d}A &= \int_{\mathcal{R}_t} \left(\mu_\alpha \nabla \cdot \mathbf{J}_\alpha + \mathbf{J}_\alpha \cdot \nabla\mu_\alpha\right) \, \mathrm{d}V \\ &= -\left(\mu_\alpha \frac{d^\alpha \rho_\alpha \phi_\alpha}{dt} - \mathbf{J}_\alpha \cdot \nabla\mu_\alpha - \mu_\alpha S_\alpha \right) \, \mathrm{d}V, \end{aligned}$$

[4]If the composition in a thermodynamic system of uniform temperature and pressure can change (e.g., due to a chemical reaction or phase transition), the fundamental thermodynamic relation, can be written as,

$$d\mathcal{E} = TdS - PdV + \sum_\alpha \mu_\alpha dn_\alpha,$$

where P is pressure and dn_α is the infinitesimal change of particle number of species α as particles are added or subtracted. This relation holds for both reversible and irreversible processes and is expressed as a microscopic change in internal energy $\mathcal{E}$ in terms of microscopic changes in entropy S and volume V. From the above relation the chemical potential, for the case of constant volume and entropy, is given by

$$\mu_\alpha = \left(\partial\mathcal{E}/\partial n_\alpha\right)_{S,V}.$$

Thus, in (27), μ_α characterizes the flux and supply of energy to the system and needs to be considered in the energy balance relation.

one can write,

$$\mathcal{M} = \sum_{\alpha} \int_{\mathcal{R}_t} \left(\mu_\alpha \frac{d^\alpha \rho_\alpha \phi_\alpha}{dt} - \mathbf{J}_\alpha \cdot \nabla \mu_\alpha \right) \, \mathrm{d}V.$$

Consequently, (26) can be written as,

$$\begin{aligned} \frac{d}{dt} \int_{\mathcal{R}_t} \rho \varepsilon \mathrm{d}V \;\; := \;\; & \sum_{\alpha} \int_{\mathcal{R}_t} \left(\mathbf{T}_\alpha : \mathbf{L}_\alpha + \tau_\alpha \frac{d^\alpha \phi_\alpha}{dt} \right) \, \mathrm{d}V + \sum_{\alpha} \int_{\partial \mathcal{R}_t} (\boldsymbol{\xi}_\alpha \cdot \mathbf{n}) \frac{d^\alpha \phi_\alpha}{dt} \, \mathrm{d}A \\ & + \sum_{\alpha} \int_{\mathcal{R}_t} \left(\mu_\alpha \frac{d^\alpha \rho_\alpha \phi_\alpha}{dt} - \mathbf{J}_\alpha \cdot \nabla \mu_\alpha \right) \, \mathrm{d}V. \end{aligned} \tag{28}$$

From the symmetry of the Cauchy stress in (17), the term $\mathbf{T}_\alpha : \mathbf{L}_\alpha$ can be replaced by $\mathbf{T}_\alpha : \mathbf{D}_\alpha$. Moreover, using the divergence theorem,

$$\int_{\partial \mathcal{R}_t} (\boldsymbol{\xi}_\alpha \cdot \mathbf{n}) \frac{d^\alpha \phi_\alpha}{dt} dA \;\; = \;\; \int_{\mathcal{R}_t} \boldsymbol{\xi}_\alpha \nabla \left(\frac{d^\alpha \phi_\alpha}{dt} \right) dV + \int_{\mathcal{R}_t} (\nabla \cdot \boldsymbol{\xi}_\alpha) \frac{d^\alpha \phi_\alpha}{dt} dV,$$

along with

$$\nabla \cdot \boldsymbol{\xi}_\alpha \frac{d^\alpha \phi_\alpha}{dt} + \tau_\alpha \frac{d^\alpha \phi_\alpha}{dt} = -\pi_\alpha \frac{d^\alpha \phi_\alpha}{dt}$$

derived from (19), the relation for the *local energy balance* is obtained as,

$$\begin{aligned} \rho \frac{d\varepsilon}{dt} \;\; = \;\; & \sum_{\alpha} \left(\mathbf{T}_\alpha : \mathbf{D}_\alpha - \pi_\alpha \frac{d^\alpha \phi_\alpha}{dt} + \boldsymbol{\xi}_\alpha \cdot \nabla \left(\frac{d^\alpha \phi_\alpha}{dt} \right) \right) \\ & + \sum_{\alpha} \left(\mu_\alpha \frac{d^\alpha \rho_\alpha \phi_\alpha}{dt} - \mathbf{J}_\alpha \cdot \nabla \mu_\alpha \right). \end{aligned} \tag{29}$$

It is worth mentioning that both $\mathbf{b}_\alpha$ and π_α act internal to the material in $\mathcal{R}_t$ at the macroscopic and microscopic length scales. While they exist in the force balances (15) and (19), they are not present in the working terms of the energy equation (28). Moreover, the balance equation (26) for the mixture is transferred into individual constituents, in which the local and global balances are related according to

$$\rho \frac{d\varepsilon}{dt} = \sum_{\alpha} \rho_\alpha \phi_\alpha \frac{d^\alpha \varepsilon_\alpha}{dt}. \tag{30}$$

2.5.2 The Second Law: Entropy Production Inequality

The second law of thermodynamics (entropy principle) is used here for imposing restrictions on constitutive equations. In mixture theory, while the implementation of such constraints for every individual species is possible and restrictive, its satisfaction for all constituents is a necessary and sufficient condition for the presence of dissipative

processes within the mixture [35, 36]. It should also be noted that the entropy inequality has to be manipulated to include fundamental and special physical properties of the system under study. Depending on the behavior of the body, the supplementary constraints might be taken into consideration at the local (constituent) level and/or applied globally to the full mixture[5]. Moreover, this inequality is a necessary constraint on constitutive equations. There is not a unique way to fulfill this inequality, and many choices that satisfy the inequality still might lead to inaccurate simulations of the physical phenomena.

The entropy production inequality requires that the free energy increases at a rate not greater than the rate at which work is performed. The net entropy production per unit time, is given by

$$\mathcal{N} = \frac{d}{dt}\int_{\mathcal{R}_t} \eta dV \geq 0, \tag{32}$$

where η is the specific entropy of the mixture and (32) is often referred to as the Clausius-Duhem inequality [65, 66]. The entropy density of the mixture can be written as sum of the specific entropy of individual constituents as

$$\rho\eta = \sum_{\alpha} \rho_\alpha \phi_\alpha \eta_\alpha. \tag{33}$$

We continue with the derivation of the Clausius-Duhem inequality by defining the Helmholtz (specific) free-energy of the mixture as,

$$\psi(\mathbf{x}, t) = \varepsilon(\mathbf{x}, t) - \theta(\mathbf{x}, t)\ \eta(\mathbf{x}, t). \tag{34}$$

The free-energy per unit volume is,

$$\Psi(\mathbf{x}, t) = \rho\psi(\mathbf{x}, t), \tag{35}$$

and considering the free energy for every individual species (e.g., [102]),

$$\Psi_\alpha = \rho_\alpha \phi_\alpha \psi_\alpha.$$

[5] In the continuum theory of mixtures, one might need to impose additional conditions (e.g., incompressibility or rigidity of any of the species or saturation condition), to treat the mixture as smeared continua. These conditions can be provided by Lagrange multipliers in postulating the entropy production inequality. For example, consider the saturation condition by taking the time derivative of $\phi = \sum_\alpha \phi_\alpha = 1$, and making use of (13), we find the following constraint must be imposed

$$\frac{\partial \phi}{\partial t} = \sum_{\alpha} \left(\frac{d^\alpha \phi_\alpha}{dt} - \mathbf{v}_\alpha \cdot \nabla \phi_\alpha \right) = 0. \tag{31}$$

One way to impose this constraint is to add the above relation to the entropy inequality using a Lagrange multiplier Q. Since the saturation condition constrains the motion, Q is an unknown reaction force called the interface pressure and it is physically interpreted as the pressure acting at the interface between phases required to maintain contact. This approach imposes the constraints according to the thermodynamic theory of constraint developed by Gurtin and Guidugli [63]. Alternatively, this condition can be considered as an additional energy term in the equation for energy balance and corresponding force balance; see, e.g., the multiphase mixture theories of Passman et al. [108] and Bedford and Drumheller [17].

Taking the time derivative of free-energy and substituting (29) into (34) along with (35), yields the local free-energy imbalance for fixed temperature $\theta = \theta_0$[6],

$$\begin{aligned} -\frac{d\Psi}{dt} &+ \sum_{\alpha} \left(\mathbf{T}_\alpha : \mathbf{D}_\alpha - \pi_\alpha \frac{d^\alpha \phi_\alpha}{dt} + \boldsymbol{\xi}_\alpha \cdot \nabla \left(\frac{d^\alpha \phi_\alpha}{dt} \right) \right) \\ &+ \sum_{\alpha} \left(\mu_\alpha \frac{d^\alpha \rho_\alpha \phi_\alpha}{dt} - \mathbf{J}_\alpha \cdot \nabla \mu_\alpha \right) \geq 0. \end{aligned} \tag{36}$$

The invariance properties discussed in the Appendix lead to all quantities in (36) being invariant under a change in frame.

The force balance equations (15) and (19), mass blance (21), along with first and second laws of thermodynamics (29) and (36) describe balance laws for a constituent α in a mixture of N constituents. The requirements that these balance laws must be consistent with those for the mixture as a whole, imposes constraints depicted in (25). This system is closed by adding suitable constitutive equations, describing the physical and biological processes that might take place in the mixture.

2.6 Deriving Force Balances From The Principles of Virtual Power

An alternative approach to determine the associated balance of macroscopic and microscopic forces is to use the principle of virtual power; see, e.g., [53, 59]. The main feature of this classical principle is a physical structure involving thermodynamic conjugate forces through the manner in which they expend power. This allows one to use the virtual-power principle to determine local and nonlocal force balances when the forms of the balances are not known *a priori* and provide a foundation to build more general theories; see, e.g., [41, 60, 61, 134].

The form of the power expenditure is determined by the terms contributing to the energy sources, and postulated in the first and second laws of thermodynamics. In this regard, the internal virtual power is expressed in terms of the energy contribution in $\mathcal{R}_t$ such as

$$\mathcal{P}_{\text{int}} = \sum_{\alpha} \int_{\mathcal{R}_t} \left(\mathbf{T}_\alpha : \mathbf{D}_\alpha - \pi_\alpha \frac{d^\alpha \phi_\alpha}{dt} + \boldsymbol{\xi}_\alpha \cdot \nabla \left(\frac{d^\alpha \phi_\alpha}{dt} \right) \right) dV. \tag{37}$$

The internal power is balanced by the power expended by traction $\mathbf{t}_\alpha$ on the surface $\partial\mathcal{R}_t$ and body force $\mathbf{b}_\alpha$ acting within the body to account for the inertia,

$$\mathcal{P}_{\text{ext}} = \sum_{\alpha} \left\{ \int_{\partial\mathcal{R}_t} \mathbf{t}_\alpha \cdot \mathbf{v}_\alpha dA + \int_{\mathcal{R}_t} (\rho_\alpha \phi_\alpha \mathbf{b}_\alpha \cdot \mathbf{v}_\alpha - \tau_\alpha \frac{d^\alpha \phi_\alpha}{dt}) dV + \int_{\partial\mathcal{R}_t} m_\alpha \frac{d^\alpha \phi_\alpha}{dt} dA \right\}. \tag{38}$$

[6]It should be noted that throughout this formulation we work with the free energy per unit volume of the mixture Ψ. Alternative derivations can be conducted using Helmholtz free-energy per unit mass ψ or or considering the free energy for every individual species, e.g. [102].

To account for the microscopic boundary conditions that arise from the volume fraction gradients, it is further assumed here that the external power is affected by the microtraction m_α that is a force conjugate to the time change of volume fractions on constituent interfaces [64, 102]. If we define virtual velocity to be $\mathcal{V} = (\tilde{\mathbf{v}}_\alpha, d^\alpha\tilde{\phi}_\alpha/dt)$ and write (37) and (38) for the corresponding internal and external expenditures of virtual power, then the principle of virtual power is the requirement that the virtual power balance $\mathcal{P}_{\text{int}} = \mathcal{P}_{\text{ext}}$ be satisfied for any subregion $\mathcal{R}_t$ of the deformed body and any virtual velocity $\mathcal{V}$. Using the divergence theorem,

$$\begin{aligned}\int_{\mathcal{R}_t} \mathbf{T}_\alpha : \tilde{\mathbf{L}}_\alpha dV &= \int_{\partial\mathcal{R}_t} (\mathbf{T}_\alpha \cdot \mathbf{n})\tilde{\mathbf{v}}_\alpha dA - \int_{\mathcal{R}_t} (\nabla \cdot \mathbf{T}_\alpha)\tilde{\mathbf{v}}_\alpha dV,\\ \int_{\mathcal{R}_t} \boldsymbol{\xi}_\alpha \cdot \nabla\left(\frac{d^\alpha\tilde{\phi}_\alpha}{dt}\right) dV &= \int_{\partial\mathcal{R}_t} (\boldsymbol{\xi}_\alpha \cdot \mathbf{n})\frac{d^\alpha\tilde{\phi}_\alpha}{dt} dA - \int_{\mathcal{R}_t} (\nabla \cdot \boldsymbol{\xi}_\alpha)\frac{d^\alpha\tilde{\phi}_\alpha}{dt} dV,\end{aligned}$$

and substituting into (37), along with equating the external power to the internal power ($\mathcal{P}_{\text{int}} = \mathcal{P}_{\text{ext}}$), results in,

$$\begin{aligned}\sum_\alpha \Bigg\{ \int_{\partial\mathcal{R}_t} (\mathbf{T}_\alpha \cdot \mathbf{n} - \mathbf{t}_\alpha)\tilde{\mathbf{v}}_\alpha dA &+ \int_{\mathcal{R}_t} (-\nabla \cdot \mathbf{T}_\alpha - \rho_\alpha\phi_\alpha\mathbf{b}_\alpha)\tilde{\mathbf{v}}_\alpha dV +\\ \int_{\mathcal{R}_t} (-\pi_\alpha - \tau_\alpha - \nabla \cdot \boldsymbol{\xi}_\alpha)\frac{d^\alpha\tilde{\phi}_\alpha}{dt} dV &+ \int_{\partial\mathcal{R}_t} (\boldsymbol{\xi}_\alpha \cdot \mathbf{n} - m_\alpha)\frac{d^\alpha\tilde{\phi}_\alpha}{dt} \Bigg\} dA = 0. \qquad (39)\end{aligned}$$

Since $\mathcal{R}_t$ and virtual velocities are arbitrary, the microscopic and macroscopic force balances and traction conditions follow form (39),

$$\begin{aligned}\text{macroforce balance :} \quad & \nabla \cdot \mathbf{T}_\alpha + \rho_\alpha\phi_\alpha\mathbf{b}_\alpha = 0, && (40)\\ \text{microforce balance :} \quad & \pi_\alpha + \tau_\alpha + \nabla \cdot \boldsymbol{\xi}_\alpha = 0, && (41)\\ \text{macrotraction condition :} \quad & \mathbf{t}_\alpha = \mathbf{T}_\alpha \cdot \mathbf{n}, && (42)\\ \text{microtraction condition :} \quad & m_\alpha = \boldsymbol{\xi}_\alpha \cdot \mathbf{n}. && (43)\end{aligned}$$

As indicated previously, the microforces π_α, τ_α, and $\boldsymbol{\xi}_\alpha$ are generalized forces that arise due to nonlocality encountered in the evolution of phase boundaries [64, 78][7]. In the context of biological events responsible for the growth of a tumor, these terms represent the power expended by the interaction and adhesion between cell concentrations due to rates of change of each volume fraction on the surface of the full mixture [33, 140].

The relations (40) - (43) demonstrate the consequence of the principle of virtual power. This shows that after postulating the proper form of energy balance law, the

[7] Using the principle of frame-indifference and the requirement that the internal power be invariant to changes in frame, it can be shown (see Appendix A.1) that the $\boldsymbol{\xi}_\alpha$ are frame-indifferent and the Cauchy stress $\mathbf{T}_\alpha$ is both frame-indifferent and symmetric. Symmetry of the Cauchy stress is also concluded from balance of the angular momenta in (17).

virtual power balance encapsulates the local force balance (15) as well as additional balance laws representing the events in smaller scales (19). In particular, without assuming *a priori* that the force and momentum balance laws are satisfied, they are derivable from another hypotheses; i.e., the principle of virtual power. Requiring the internal power $\mathcal{P}_{\text{int}}$ to be frame-indifferent, eliminates the need to impose balance of angular moments.

2.7 Coleman-Noll Procedure

The basic physical laws, consisting of the balance laws for mass and momentum as well as the first and second laws of thermodynamics, are presumed to hold for all bodies. It is necessary to propose constitutive equations for a particular material and the processes that bodies comprised of a given material may undergo. Within rational continuum mechanics, the Coleman-Noll procedure [32] can be used to derive requirements to constitutive equations once a specific form of the energy is introduced. According to Ziegler [145], continuum mechanics allows one to establish constitutive relations, deduced from free energy and dissipation functions characterizing reversible and irreversible processes, respectively. This leads to the decomposition of the thermodynamic conjugate forces into *energetic* and *dissipative* counterparts. The energetic forces are entirely determined by the specific free energy while the dissipative forces are determined from the dissipative function [143, 144]. Guided by the inequality (36), it is assumed that the Cauchy stress tensor for each species admits the decomposition into energetic and dissipative components,

$$\mathbf{T}_\alpha = \mathbf{T}_\alpha^{en} + \mathbf{T}_\alpha^{dis}, \tag{44}$$

while other thermodynamical conjugate forces are identified as completely energetic or dissipative in nature. This choice is made based upon our current knowledge about the physical and biological events that contribute to tumor growth process. In general, other conjugate forces can be decomposed as in (44) where additional phenomena are identified that contribute to energy storage and dissipation[8].

To derive the relation between thermodynamical forces and the Helmholtz free energy, Ψ, and dissipative potentials, $\mathcal{D}$, we initially consider a general form of free energy considering the contribution of μ and $\nabla\mu$, and assuming a system far from equilibrium (μ is not given).[9],

$$\begin{aligned}\Psi = \Psi\,(&\mathbf{F}_1, \cdots, \mathbf{F}_N, \rho_1, \cdots, \rho_N, \phi_1, \cdots, \phi_N,\\ &\nabla\phi_1, \cdots, \nabla\phi_N, \mu_1, \cdots, \mu_N, \nabla\mu_1, \cdots, \nabla\mu_N)\,.\end{aligned} \tag{45}$$

[8] An example can be found in the generalized Cahn-Hilliard equation derived by Gurtin [58] in which both the microstress $\boldsymbol{\xi}$ and microforce π are decomposed into energetic and dissipative counterparts.

[9] For a multiphase system, a condition for equilibrium is that the chemical potential of each component must be the same in all phases. This follows from the total change in free energy being zero at equilibrium; see, e.g., [121].

The time derivation of Ψ using the chain rule, results in

$$\begin{aligned}\frac{d\Psi}{dt} &= \sum_\alpha \left(\frac{\partial \Psi}{\partial \mathbf{F}_\alpha}\mathbf{D}_\alpha + \frac{\partial \Psi}{\partial \rho_\alpha}\frac{d^\alpha \rho_\alpha}{dt} + \frac{\partial \Psi}{\partial \phi_\alpha}\frac{d^\alpha \phi_\alpha}{dt} + \frac{\partial \Psi}{\partial (\nabla \phi_\alpha)}\frac{d^\alpha (\nabla \phi_\alpha)}{dt} \right. \\ &+ \left. \frac{\partial \Psi}{\partial \mu_\alpha}\frac{d^\alpha \mu_\alpha}{dt} + \frac{\partial \Psi}{\partial (\nabla \mu_\alpha)}\frac{d^\alpha (\nabla \mu_\alpha)}{dt} \right). \end{aligned} \tag{46}$$

Making use of the gradient of material time derivatives,

$$\nabla \left(\frac{d^\alpha \phi_\alpha}{dt} \right) = \frac{d^\alpha}{dt}(\nabla \phi_\alpha) + \nabla \cdot \mathbf{v}_\alpha \cdot \nabla \phi_\alpha,$$

along with substituting (46) into the free energy imbalance (36) and grouping terms together, we find the following inequality

$$\begin{aligned}&\sum_\alpha \left\{ \left(\mathbf{T}^{en}_\alpha - \frac{\partial \Psi}{\partial \mathbf{F}_\alpha} + \boldsymbol{\xi}_\alpha \otimes \nabla \phi_\alpha \right) \mathbf{D}_\alpha + \left(-\pi_\alpha + \rho_\alpha \mu_\alpha - \frac{\partial \Psi}{\partial \phi_\alpha} \right) \frac{d^\alpha \phi_\alpha}{dt} \right. \\ &+ \left(\boldsymbol{\xi}_\alpha - \frac{\partial \Psi}{\partial (\nabla \phi_\alpha)} \right) \frac{d^\alpha (\nabla \phi_\alpha)}{dt} - \frac{\partial \Psi}{\partial \mu_\alpha}\frac{d^\alpha \mu_\alpha}{dt} - \frac{\partial \Psi}{\partial (\nabla \mu_\alpha)}\frac{d^\alpha (\nabla \mu_\alpha)}{dt} + \mu_\alpha \rho_\alpha \frac{\partial \Psi}{\partial \rho_\alpha}\frac{d^\alpha \rho_\alpha}{dt} \\ &\left. + \mathbf{T}^{dis}_\alpha : \mathbf{D}_\alpha - \nabla \mu_\alpha \cdot \mathbf{J}_\alpha \right\} \geq 0. \end{aligned} \tag{47}$$

The classical Coleman-Noll argument asserts that, in order that the inequality (47) hold, the coefficient of quantities such as $\mathbf{D}_\alpha$, $d^\alpha \phi_\alpha / dt$, etc. must vanish as these terms can assume arbitrary large negative values. Thus, the fact that the time derivatives of the variables are arbitrary, results in the following choices being sufficient to ensure the free energy inequality,

$$\boldsymbol{\xi}_\alpha = \frac{\partial \Psi}{\partial (\nabla \phi_\alpha)}, \tag{48}$$

$$\mathbf{T}^{en}_\alpha = \frac{\partial \Psi}{\partial \mathbf{F}_\alpha} - \boldsymbol{\xi}_\alpha \otimes \nabla \phi_\alpha, \tag{49}$$

$$\pi_\alpha = \rho_\alpha \mu_\alpha - \frac{\partial \Psi}{\partial \phi_\alpha}. \tag{50}$$

The above relations defines the energetic part of the thermodynamic forces. Using the microforce balance (19), one can derive a relation for the chemical potential such as

$$\rho_\alpha \mu_\alpha = \frac{\partial \Psi}{\partial \phi_\alpha} - \nabla \cdot \boldsymbol{\xi}_\alpha - \tau_\alpha \tag{51}$$

which can be simplified further by replacing $\boldsymbol{\xi}_\alpha$ from (48).

By a similar Coleman-Noll argument we have,

$$\frac{\partial \Psi}{\partial \rho_\alpha} = 0, \quad \frac{\partial \Psi}{\partial \mu_\alpha} = 0, \quad \frac{\partial \Psi}{\partial (\nabla \mu_\alpha)} = \mathbf{0}, \tag{52}$$

suggesting that the thermodynamical process is admissible if and only if the Helmholtz free energy density is independent of ρ_α, μ_α and $\nabla\mu_\alpha$. Thus, it takes a simpler form,

$$\Psi = \Psi\left(\mathbf{F}_1, \cdots, \mathbf{F}_N, \phi_1, \cdots, \phi_N, \nabla\phi_1, \cdots, \nabla\phi_N\right). \tag{53}$$

One can initially assume more general forms of free energy considering contributions of other quantities; e.g., time derivative of the volume fraction [89–91]. The Coleman-Noll procedure then results in a corresponding reduction in the forms of the Helmholtz free energy.

Not all power expended on a spatial region can be transformed into changes in the free energy, and part of the power goes into dissipation. Thus, the remaining terms in the inequality (47), after considering (48)-(50), are the rate of dissipation potential,

$$\mathcal{D} = \sum_\alpha \left\{ \mathbf{T}_\alpha^{dis} : \mathbf{D}_\alpha - \nabla\mu_\alpha \cdot \mathbf{J}_\alpha \right\} \geq 0$$

The definition of the dissipative thermodynamic forces can then be obtained from the complementary part of dissipation potential as,

$$\mathbf{T}_\alpha^{dis} = \frac{\partial \mathcal{D}}{\partial \mathbf{D}_\alpha}, \tag{54}$$

$$\mathbf{J}_\alpha = \frac{\partial \mathcal{D}}{\partial \nabla\mu_\alpha}, \tag{55}$$

where

$$\mathcal{D} = \mathcal{D}\left(\mathbf{D}_1, \cdots, \mathbf{D}_N, \phi_1, \cdots, \phi_N, \nabla\phi_1, \cdots, \nabla\phi_N, \nabla\mu_1, \cdots, \nabla\mu_N\right). \tag{56}$$

2.8 Constitutive Relations for the Admissible Potentials

The continuum theory presented here attempts to provide a general framework for addressing many of the complex biological phenomena that take place in cancer. This consists of multiple interactions among various constituents. In this regard, it is considered that the N-species mixture consists of M solid constituents undergoing both hyper-elastic deformation and biological growth and $N - M$ viscous compressible fluid constituents. The Constitutive relations are defined through proposing two primary potentials, Helmholtz free energy and rate of dissipation.

2.8.1 Helmholtz Free Energy

In this work, we postulate the following general definition of the free energy of the mixture,

$$\Psi = \Psi^{\text{els}} + \Psi^{\text{chm}} + \Psi^{\text{int}} + \Psi^{\text{taxis}}, \tag{57}$$

where Ψ^{els} denotes elastic energy for solid species and Ψ^{chm} and Ψ^{int} represents (bio-)chemical energy and interface counterparts, respectively, normally employed in phase-field models. Here the free energy functional also includes the energy due to taxis-inducing chemical and molecular species, Ψ^{taxis}; see, e.g., [1, 33, 88].

Hereafter, we assume the fluid constituents of the mixture are compressible, thus

$$\frac{\partial \Psi^{\text{els}}}{\partial \mathbf{F}_\alpha} = -p_\alpha \mathbf{I}, \qquad M < \alpha \leq N,$$

where p_α is the classical equilibrium pressure,

$$-p_\alpha = \hat{\rho}_\alpha^2 \frac{\partial \psi_\alpha}{\partial \hat{\rho}_\alpha}, \qquad M < \alpha \leq N, \tag{58}$$

where $\hat{\rho}_\alpha$ is the mass density of constituent (6), and the thermodynamic pressure is represented as the derivative of free energy per unit mass for each fluid constituent. Moreover, the solid species are considered to be isotropic hyperelastic. In a hyperelastic body, the Piola-Kirchhoff stress is the derivative of a scalar function W called strain energy density. Therefore, the second Piola-Kirchhoff stress is given by,

$$\mathbf{S}_\alpha = \det \mathbf{F}_\alpha \mathbf{F}_\alpha^{-1} \mathbf{T}_\alpha \mathbf{F}_\alpha^{-T} = \frac{\partial W_\alpha}{\partial \mathbf{C}_\alpha}, \qquad 1 < \alpha \leq M, \tag{59}$$

where $\mathbf{C}_\alpha = \mathbf{F}_\alpha^T \mathbf{F}_\alpha$ is the right Cauchy-Green deformation tensor and $W_\alpha = W_\alpha(\mathbf{C}_\alpha, \phi_\alpha)$ represents the strain energy function for the α-th solid constituent. The strain energy density and elastic free energy are related through the mass density of a constituent in the reference configuration, $W_\alpha = \rho_\alpha^0 \phi_\alpha^0 \psi_\alpha^{\text{els}}$. Considering $\Psi_\alpha^{\text{els}} = \Psi_\alpha^{\text{els}}(\mathbf{F}_\alpha, \phi_\alpha)$ one can derive[10],

$$\frac{\partial \Psi^{\text{els}}}{\partial \mathbf{F}_\alpha} = 2 \frac{1}{\det \mathbf{F}_\alpha} \mathbf{F}_\alpha \mathbf{S}_\alpha \mathbf{F}_\alpha^T, \qquad 1 < \alpha \leq M.$$

An important class of diffuse-interface or phase-field models of Cahn-Hilliard type are characterized by a Helmholtz free energy that consists of a double-well potential function for $\Psi^{\text{chm}} = \Psi^{\text{chm}}(\phi_1, \cdots, \phi_N)$ called a "coarse-grain" free energy, and an interfacial energy of the form,

$$\Psi^{\text{int}} = \Psi^{\text{int}}(\nabla\phi_1, \cdots, \nabla\phi_N) = \sum_\alpha \frac{\epsilon_\alpha}{2} |\nabla \phi_\alpha|^2, \tag{60}$$

where ϵ_α (sometime referred to as the Landau-Ginzburg constants) characterizes the interface thickness. Interfacial energy (60) models longer range interactions among the components by representing the effects of large gradients in concentrations that occur at interface regions between different constituents.

The effect of energy due to taxis-inducing chemical and molecular species is included in the free energy by [33, 140],

$$\Psi^{\text{taxis}}(\phi_1, \cdots, \phi_N) = \sum_\alpha \phi_\alpha \sum_{\beta=1}^{L} \eta_{\alpha\beta} c_\beta, \tag{61}$$

[10]The kinematic of biological growth of the solid species along with the constitutive laws are discussed in the following section.

where c_β, $1 \leq \beta \leq L$, are the concentrations of chemical factors that may induce taxis (e.g., various sources of nutrient) and $\eta_{\alpha\beta}$ is the taxis coefficient. In particular, (61) accounts for the reaction between concentrations of various vital nutrients in the mixture (such as oxygen or glucose) and the constituent α. This relation enables describing complex invasive behavior of a tumor observed in *in vivo*. Here, taxis refers to directional migration toward particular chemical or molecular species (i.e., chemotaxis) gradients or toward adhesion site gradients (i.e., haptotaxis). In a chemotaxis scenario, cells migrate in the direction of increased nutrient concentration [67]. The movement of the nutrient towards the tumor can be seen as an active transport of the nutrient [49]. Garcke et al. [49] studied the effects of chemotaxis and active transport on the tumor growth. Through numerical experiments, they verified the jump on the nutrient concentration at the tumor interface due to the active transport. The experiments also demonstrate that higher the chemotatic term ($\eta_{\alpha\beta}$) leads to a faster formation and evolution of the fingers [49]. In vascular models of tumor growth (e.g., [8, 88]), this accounts for the endothelial cells moving up the concentration gradient of vascular endothelial growth factor (VEGF). VEGF is a pro-angiogenic factor released by tumor cells in an effort to recruit new vasculature to support further tumor growth [109].

2.8.2 Rate of Dissipation Potential

As discussed in section 2.6, energetic-dissipative decomposition of the thermodynamic conjugate forces results in the development of an energy dissipation rate. Here the dissipation energy potential can be considered as the summation of dissipations due to viscosity $\mathcal{D}^{\text{vis}}$ and diffusion $\mathcal{D}^{\text{diff}}$,

$$\mathcal{D} \;=\; \mathcal{D}^{\text{vis}} + \mathcal{D}^{\text{diff}} \geq 0.$$

For hyperelastic solid constituents,

$$\mathcal{D}^{\text{vis}}\left(\mathbf{D}_1, \cdots, \mathbf{D}_M, \phi_1, \cdots, \phi_M\right) = 0,$$

where $\mathbf{D}_\alpha$ is defined in (12) and we assume the internal viscosity of fluid species can be described by a dissipation potential as a general isotropic, second-order tensor function of deformation rate,

$$\mathcal{D}^{\text{vis}}\left(\mathbf{D}_{M+1}, \cdots, \mathbf{D}_N, \phi_{M+1}, \cdots, \phi_N\right) = \sum_\alpha \frac{1}{2} A_\alpha |\mathbf{D}_\alpha|^2, \quad M < \alpha \leq N, \tag{62}$$

where $A_\alpha(\phi_\alpha)$ is the shear viscosity of fluid species. The above relation results in a dissipative counterpart of the Cauchy stress,

$$\mathbf{T}_\alpha^{dis} = A_\alpha \mathbf{D}_\alpha, \quad M < \alpha \leq N. \tag{63}$$

Cahn-Hilliard type equations are considered in this formulation for characterizing the energy dissipation due to diffusion,

$$\mathcal{D}^{\text{diff}}\left(\mathbf{D}_1, \cdots, \mathbf{D}_N, \phi_1, \cdots, \phi_N, \mu_1, \cdots, \mu_N\right) = \sum_\alpha \nabla\mu_\alpha \cdot \mathbf{M}_\alpha \cdot \nabla\mu_\alpha \tag{64}$$

where μ_α is the chemical potential and $\mathbf{M}_\alpha = \mathbf{M}_\alpha(\mathbf{C}_\alpha, \phi_\alpha)$ is the positive semi-definite mobility tensor. Using the frame-indifference principle discussed in appendix A.1, it can be shown that $\mathbf{M}_\alpha$ is symmetric and invariant under a change in frame.

2.8.3 Energetic and Dissipative Forces

From the functional forms of Ψ and $\mathcal{D}$, one can derive relations for the thermodynamic forces. From (48), the energetic micro-stress $\boldsymbol{\xi}_\alpha$ has the form

$$\boldsymbol{\xi}_\alpha = \epsilon_\alpha \nabla \phi_\alpha. \tag{65}$$

Using (49) and (54), the Cauchy stress for solid and fluid constituents can be derived as

$$\mathbf{T}_\alpha = \mathbf{T}_\alpha^{en} + \mathbf{T}_\alpha^{dis} = \begin{cases} \frac{2}{\det \mathbf{F}_\alpha} \mathbf{F}_\alpha \mathbf{S}_\alpha \mathbf{F}_\alpha^T & - \quad \epsilon_\alpha \nabla \phi_\alpha \otimes \nabla \phi_\alpha \quad , \quad 1 < \alpha \leq M \\ \\ p_\alpha \mathbf{I} + A_\alpha \mathbf{D}_\alpha & - \quad \epsilon_\alpha \nabla \phi_\alpha \otimes \nabla \phi_\alpha \quad , \quad M < \alpha \leq N \end{cases} \tag{66}$$

The $\boldsymbol{\xi}_\alpha$ enters in (18) and (19) as a flux and divergence term, respectively. This suggests that $\boldsymbol{\xi}_\alpha$ is a stress-type quantity and associated with the interaction forces at the interface of the constituents. From (65), one can argue that the microstress $\boldsymbol{\xi}$ accounts for cell adhesion due to volume fraction changes at the interface of each constituent. The term ϵ_α represents the thickness of the interface (i.e., how sharp is the interface between the phases). In biological processes involved in tumor growth, this term is directly related to the cell-cell adhesion [34, 93]. Sharp interfaces (i.e, ϵ_α close to zero with α indicating tumor constituent) can model cells with high adhesion such some epithelial tumors [132] and increasing the value of interface thickness enables mimicking the behavior of cells with low adhesion and higher motility as glioblastoma and stromal cells [79, 93, 113]. This relation suggests that stronger cell-cell adhesion results in sharper interfaces and more compact morphology. The first term in the Cauchy stress of solid constituents in (66) reflects the hyperelastic deformation with growth. However, the microforce balance of (19) and the nonlocal microstress $\boldsymbol{\xi}$ results in another term in the Cauchy stress; i.e., $\epsilon_\alpha \nabla \phi_\alpha \otimes \nabla \phi_\alpha$. In biological processes, this term mimics surface tension-like cell-adhesion forces in the Cauchy stress and exists in the absence of elastic deformation (see Appendix B for the evolution of this counterpart of the Cauchy stress).

Another dissipative thermodynamic force is the mass flux that can be derived from (55) and (64) as,

$$\mathbf{J}_\alpha = -\mathbf{M}_\alpha \cdot \nabla \mu_\alpha. \tag{67}$$

Assuming (67) holds, the equation describing the evolution of species content (recall (21)) becomes,

$$\frac{\partial \rho_\alpha \phi_\alpha}{\partial t} + \nabla \cdot (\rho_\alpha \phi_\alpha \mathbf{v}_\alpha) = S_\alpha - \nabla \cdot (\mathbf{M}_\alpha \cdot \nabla \mu_\alpha). \tag{68}$$

Making use of (50), the chemical potential can be derived as,

$$\rho_\alpha \mu_\alpha = \frac{\partial \Psi^{\text{els}}}{\partial \phi_\alpha} + \frac{\partial \Psi^{\text{chm}}}{\partial \phi_\alpha} + \sum_{\beta=1}^{L} \eta_{\alpha\beta} c_\beta - \epsilon_\alpha \Delta \phi_\alpha - \tau_\alpha, \tag{69}$$

where Δ denotes the spatial Laplacian operator (i.e., $\Delta = \nabla \cdot \nabla$). Relation (69) indicates the dependency of μ_α on volume fractions[11].

Equation (68) represents a system of N fourth-order, parabolic partial differential equations of the Cahn-Hilliard type. These equations along with the macro-force balance (15), together with appropriate boundary and initial conditions, characterize a general coupled phase-field and elastic deformation, continuum mixture model of a complex media consisting of multiple solid and fluid species. The constituents can be compressible, the fluid species are non-Newtonian, the solid constituents are isotropic hyperelastic, and the effects of diffusion of chemical or biological constituents due to chemo- or bio-taxis as well as surface effects due to gradients in concentrations are taken into account.

To apply such general models in a meaningful manner to simulate tumor growth, several specific details are needed. These include specific forms of the constitutive equations for each constituent along with the inclusion of growth effects due to mass exchange and deformation. These are discussed in detail in the next section.

3 A Four-Constituent Phase-Field Model of Tumor Growth

In this section, the general multi-species theory laid down in section 2 is adapted to simulate major features of the growth of tumors in a microenvironment. Lima et al. [88] developed a hybrid 10-constituent phase-field model without accounting for mechanical deformation and growth strain. Here, the avascular counterpart of this hybrid phase-field model is employed as the basis for deriving a coupled formulation for diffusion and large elastic deformation. Thus, the mixture considered here consists of four constituent volume fractions: tumor cell, ϕ_T, nutrient-rich extracellular water, ϕ_σ, nutrient-poor extracellular water, ϕ_{σ_0}, and healthy cell, ϕ_C. In [86, 88], proliferative, hypoxic, and necrotic cells are considered as separate constituents that must satisfy their own balance law. In this formulation, for simplicity, the tumor volume fraction accounts for proliferative cell, hypoxic, and necrotic cells. Moreover, the saturation condition of the mixture $\phi_T + \phi_\sigma + \phi_{\sigma 0} + \phi_C$, is enforced by rescaling the volume fractions. The solid $s = \phi_T + \phi_C$ and fluid $w = \phi_\sigma + \phi_{\sigma_0}$ are assumed to vary from 0 to 1 depending on a constant C by defining $s = C$ and $w = 1 - C$; i.e., in other word, the values of ϕ_t and ϕ_σ are normalized so as to take on values between 0 and 1.

[11] While most of the phase transformation theories of the type considered here are consistent with the dependency of the chemical potential on volume fractions, in some special situations the chemical potential cannot be expressed as a function of volume fraction [46, 47].

Next the functional forms of the primary free energy and dissipation potential of the mixture are described. The tumor cells (proliferative, hypoxic, and necrotic) have similar adhesive properties and they prefer to adhere to one another [33, 87], causing a segregation from healthy cells. This behavior of separation among phases, typical of binary Cahn-Hilliard systems, is modeled by a double-well potential and a capillary interfacial energy. The presence of a nutrient-rich volume fraction in the mixture contributes to an increase of the system energy through a quadratic term and interacts chemotactically with tumor cells, yielding a directional movement towards nutrient supply [88, 140]. These assumptions yield the following chemical and interface components of the Helmholtz free energy energy of the system:

$$\Psi^{\text{chm}}(\phi_T, \phi_\sigma) = \kappa\phi_T^2(1-\phi_T)^2 + \frac{1}{2\delta_\sigma}\phi_\sigma^2, \tag{70}$$

$$\Psi^{\text{int}}(\nabla\phi_T, \nabla\phi_\sigma) = \frac{\epsilon_T^2}{2}|\nabla\phi_T|^2, \tag{71}$$

where the coefficient $\kappa > 0$ in the quadratic double-well function is an energy scale giving rise to a well-delineated phase separation of the tumor and the host tissues. In (70), δ_σ is a coefficient that controls the increase of energy due to nutrient and the interfacial surface energy due to spatial concentration gradient is defined using an interaction length parameter ϵ_T. In particular, ϵ_T controls the interface among tumor cells and other constituents. The effect of energy due to taxis-inducing chemical and molecular species is addressed through,

$$\Psi^{\text{taxis}}(\phi_T, \phi_\sigma) = -\chi_0\phi_T\phi_\sigma, \tag{72}$$

where $\chi_0 > 0$ is a constant governing the relative strength of the interaction between tumor cells and nutrient.

We take into account a Cahn-Hilliard type energy dissipation due to diffusion, such as

$$\mathcal{D}^{\text{diff}} = \nabla\mu_T \cdot \mathbf{M}_T \cdot \nabla\mu_T + \nabla\mu_\sigma \cdot \mathbf{M}_\sigma \cdot \nabla\mu_\sigma, \tag{73}$$

where the mobility tensor for nutrient rich water is

$$\mathbf{M}_\sigma = \frac{1}{\delta_\sigma}M_\sigma\mathbf{I}, \tag{74}$$

where M_σ is a constant describing the mobility of extracellular water and $\mathbf{M}_T = M_T\mathbf{I}$ is the mobility of tumor cells. The coupling effect of deformation on the tumor mass transfer results in the dependency of tumor mobility and mass exchange on a measure of deformation. Modeling this dependency is discussed in the following section. Finally, the energy dissipation due to viscosity is considered to be, [112]

$$\mathcal{D}^{\text{vis}} = \frac{1}{2}A_\sigma|\mathbf{D}_\sigma|^2, \tag{75}$$

where A_σ is an extracellular water viscosity coefficient.

3.1 Kinematics of Hyperelastic, Growing Solid Tumor

The mechanical stresses of a solid tumor have fundamental implications for both its growth [68] and response to treatment [137]. For example, it has been shown that compression of cancer cells reduces their proliferation rate, induces apoptosis, and enhances their invasive and metastatic potential. Thus, tumors that manifest higher stress levels may have lower growth rates and a higher tendency to metastasize [25, 28, 38, 74, 75, 80, 85, 133]. Moreover, the force applied by the surrounding tissue during growth of a tumor can alter both tumor expansion and shape [68, 70, 136, 137, 139]. Here we consider two mechanisms participating in the mechanical behavior of a tumor: (i) *the externally applied stress* due to mechanical interactions among the solid components of the growing tumor and the surrounding tissue, and (ii) *the growth-induced stress* due to proliferating cancer cells.

Stylianopoulos et al [122, 123] identified an additional growth-induced residual stress that accumulates in tumors due to internal forces among the constituents. On the basis of *ex vivo* experimental data, they developed a biexponential model to describe this stress. Determining parameters of this model requires specific experiments to measure the residual stretch ratio. Later, the same investigators indicated that their measurements of residual stress in various tumor types showed residual stress were negligible compared to stress due to other mechanisms [133].

To model the effect of growth on the mechanical behavior of tumors, it is considered here that the deformation gradient is produced by the mass growth and deformation due to externally applied and growth induced stress. Consequently, the deformation gradient of the tumor $\mathbf{F}_T$ accepts following decomposition (see, e.g., [52]),

$$\mathbf{F}_T = \mathbf{F}_T^S \mathbf{F}_T^G, \tag{76}$$

where $\mathbf{F}_T^S$ is the elastic component of the deformation gradient tensor and accounts for mechanical interactions with other constituents such as surrounding normal tissue, and $\mathbf{F}_T^G$ is the counterpart representing tumor growth and describing the change in mass. Assuming the elasticity parameters are independent of volume fraction,

$$\mathbf{T}_T = \frac{\partial \Psi^{\text{els}}}{\partial \mathbf{F}_T} - \epsilon_T \nabla \phi_T \otimes \nabla \phi_T = \frac{\partial \Psi^{\text{els}}}{\partial \mathbf{F}_T^S} : \frac{\partial \mathbf{F}_T^S}{\partial \mathbf{F}_T} - \epsilon_T \nabla \phi_T \otimes \nabla \phi_T, \tag{77}$$

where

$$\frac{\partial \mathbf{F}_T^S}{\partial \mathbf{F}_T} = \frac{\partial \mathbf{F}_T (\mathbf{F}^G)^{-1}}{\partial \mathbf{F}_T} = \mathbf{I} \otimes (\mathbf{F}^G)^{-1}. \tag{78}$$

We consider a compressible Neo-Hookean material for the tumor material[12] that is a commonly used constitutive model for elastic response of soft tissue [48, 94, 133]. The

[12]There is a general agreement in the literature that the elastic response of the soft biological tissues is highly nonlinear [37], with the linear strain limit around 0.1% [18]. This elastic response is often modeled as hyperelastic, as in many experimental studies the elastic behavior of the tissues resembles that of rubberlike materials and polymers [43, 95]. The Neo-Hookean was one of the earlier models for simulating soft tissues [106] and it is still employed in recent studies [24]. Other hyperelastic models

strain energy function is,

$$W = \frac{G_T}{2}\left(I_{C_1}^S - 3\right) + \frac{K_T}{2}\left(J_T^S - 1\right)^2, \tag{79}$$

where G_T and K_T are shear and bulk modulus, respectively, and I_{C1}^S is the first invariant of the right Cauchy-Green deformation tensor defined as,

$$I_{C_1}^S = \mathrm{tr}(\mathbf{C}_T^S), \tag{80}$$

where $\mathbf{C}_T^S = (\mathbf{F}_T^S)^T\mathbf{F}_T^S$. In (79), J_T^S is a volume change measure,

$$J_T^S = \sqrt{\det(\mathbf{C}_T^S)} = \det(\mathbf{F}_T^S). \tag{81}$$

From (66) and the specific form of strain energy (79), a relation for the Cauchy stress is obtained as,

$$\mathbf{T}_T = \left(\frac{G_T}{J_T^{S^{5/3}}}\left(\mathbf{B}_T^S - \frac{1}{3}tr(\mathbf{B}_T^S)\mathbf{I}\right) + K_T(J_T^S - 1)\mathbf{I}\right)(\mathbf{F}_T^G)^{-T} - \epsilon_T\nabla\phi_T \otimes \nabla\phi_T, \tag{82}$$

where $\mathbf{B}_T^S = \mathbf{F}_T^S(\mathbf{F}_T^S)^T$ is the left Cauchy-Green deformation tensor. The following relations can be also derived for the components of (82),

$$J_T^S = J_T \det\left((\mathbf{F}_T^G)^{-1}\right), \tag{83}$$

$$\mathbf{B}_T^S = \mathbf{B}_T(\mathbf{F}_T^G)^{-1}(\mathbf{F}_T^G)^{-T}, \tag{84}$$

$$\det(\mathbf{B}_T^S) = \det(\mathbf{B}_T)\cdot\det\left((\mathbf{F}_T^G)^{-1}(\mathbf{F}_T^G)^{-T}\right). \tag{85}$$

The remaining derivation related to Ψ^{els} is to evaluate the effect of deformation on the chemical potential (69). Taking into account that $\mathbf{F}^G$ can be a function of volume fraction, one can write,

$$\frac{\partial\Psi^{\mathrm{els}}}{\partial\phi} = \frac{\partial\Psi^{\mathrm{els}}}{\partial\mathbf{F}_T} : \frac{\partial\mathbf{F}_T}{\partial\mathbf{F}_T^G} : \frac{\partial\mathbf{F}_T^G}{\partial\phi} \tag{86}$$

---

are employed for soft biological tissues, including adopting rubberlike materials models such as Ogden model [104, 105] and MooneyRivlin model [98, 114] or extending them; e.g., Cloots model [31], Hrapko model [71], Bilston model [19], and Prevost model [110]. Another common assumption is that soft biological tissues are incompressible, while some models do not feature this assumption [31, 82, 110]. In addition, experiments have consistently shown that the tissues may exhibit viscoelastic behavior, their responses are highly sensitive to the loading rate and loading history [29]. The choice of constitutive model depends on the physiological phenomenon of interest. Choosing the "best" model for tumor growth based on physical motivation, practical relevance, and measurements observation to select the model is beyond the scope of this paper. Without loss of generality, current formulation consider a Neo-Hookean type hyperelastic model to account for the highly nonlinear elastic behavior. The tumor tissue is assumed to be compressible, since the porous nature of tumor may cause a significant compressibility when fluid locally migrates into or out of the tissue. It is also assumed that the tumor growth is an extremely slow phenomena (compared to fast phenomena associated high loading rates; e.g., traumatic brain injury [31]) and it is sufficient to consider a time-independent model.

where

$$\frac{\partial \mathbf{F}_T}{\partial \mathbf{F}_T^G} = \mathbf{F}_T^S \otimes \mathbf{I}. \tag{87}$$

The multiplicative decomposition (76) is based on introducing an intermediate unstressed configuration by elastic distressing of the current configuration $\mathcal{B}_t$ to zero stress[13].

Skalak et al [118, 119] cast the kinematics of growth into the mathematical theory of finite strain continuum mechanics through the notion of "volumetric growth". However, considering the kinematic effect of growth alone, where material is added to or lost from the body, might lead to incompatible adjacent neighborhoods of the body in Euclidean space and $\mathbf{F}^G$ cannot then be expressed as the gradient of a vector field[14]. In (76) both $\mathbf{F}^G$ and $\mathbf{F}^S$ are incompatible, but their multiplicative decomposition is compatible by construction. This multiplicative framework has been widely employed to model certain features of biological growth, (e.g., [4, 5, 56, 92, 125, 141]). Nevertheless, some investigators, (e.g., [15, 72]), argued against such a decomposition based on the mass gain or loss during growth. They pointed out that if the mapping between configurations is defined only by the deformation, in the case of biological growth, the notion of a fixed reference configuration vanishes. Such a fundamental deficiency is valid for the theories of growth that consider tissue as a single-constituent solid continuum. However, the growth models based on mixture theory, where different species can possess different natural configurations, removes the challenge encountered in identifying reference configurations for the growing tissue [3].

3.1.1 Deformation Feedback on the Tumor Mobility and Mass Exchange

Prior to presenting an evolution relation for the growth tensor, we first postulate the way deformation is coupled to the diffusion equation. To account for the restriction of tumor expansion produced by the surrounding tissues, one might consider the dependency of diffusion on deformation [50]. Such hypothesis testing using *in vivo* data is shown to greatly improve predictability of computational models [70, 87, 137, 138] in addressing the experimental observations. Most of the previous models considered the dependency of the mobility tensor (i.e., the diffusion coefficient in reaction-diffusion models) to a stress quantity. However, the principle of material frame-indifference (see Appendix A.2) shows that the mass flux can be a function of the right Cauchy-Green deformation tensor or its invariants, volume fraction, and gradient of chemical potential, such as

$$\mathbf{J}_T = \mathbf{J}_T(\mathbf{C}_T, \phi_T, \nabla \mu_T). \tag{88}$$

Thus, from (67) and by considering the dependency of the tumor mobility tensor on the volume fraction [86, 88], we postulate the following form describing tumor mobility,

[13]The deformation gradient decomposition (76) is analogous to the decomposition of elasto-plastic deformation gradient into its elastic and plastic parts (see, e.g., [62]).

[14]The decomposition of the deformation gradient into elastic and growth parts in (76) was first introduced in biomechanics by Rodrigez et al. [116] to address the effects of incompatible growth.

$\mathbf{M}_T = M_T\mathbf{I}$[15].,

$$M_T = \lambda_T^{\text{mob}}\phi_T^2(1-\phi_T)^2. \tag{89}$$

The double-well functional form of the dependency to the volume fraction in (89) ensures the mobility is always positive and avoids possible inconsistency in the phase field model [39, 67][16]. Moreover, the inhibitory effect of the surrounding tissue on tumor growth is mimicked by an exponential decay, such as

$$\lambda_T^{\text{mob}} = \alpha_T^{\text{mob}}\exp(-\gamma_T^{\text{mob}}J_T), \tag{90}$$

where α_T^{mob} and γ_T^{mob} are constants and $J_T = \sqrt{\det(\mathbf{C}_T)}$ is a measure of volume change.

Additionally, it is assumed that the mass exchange terms among the mixture constituents are governed by the following source terms

$$S_T = -S_\sigma = \lambda_T^{\text{pa}}\phi_T(1-\phi_T)\phi_\sigma. \tag{91}$$

The relations for source terms accounts for the biophysical processes including: (i) the proliferating tumor cells grow continuously when consuming nutrient and (ii) tumor cells decay due at the natural apoptosis. The constant rate of the cellular mitosis minus the apoptosis is indicated by λ_T^{pa}, characterizing the growth in solid phase. Part of the dead cells are degraded for reuse and ultimately increase the nutrient-rich extracellular water volume fraction. We thus assume that growth evolution in the mass balance, as the process of mass addition and loss, is directly related to the both tumor and nutrient-rich extracellular water volume fractions. To account for the mechanical effects of decreasing the rate of tumor cell proliferation with increasing the surrounding tissue stress, we consider the following relation for λ_T^{pa}:

$$\lambda_T^{\text{pa}} = \alpha_T^{\text{pa}}\exp(-\gamma_T^{\text{pa}}J_T), \tag{92}$$

where α_T^{pa} and γ_T^{pa} are constants controlling decay of the growth stretch with increasing tumor volume.

3.1.2 Constitutive Relations for Tumor Growth

The continuum mechanics treatment of growth introduces $\mathbf{F}^G$ as a new unknown that is neither governed by a new balance law nor can be found based on thermodynamic arguments. Thus, a constitutive relation must be postulated for the evolution law of growth in relation to physical, biological, and chemical effects. Proposing an evolution relation for growth can follow two general approaches. Motivated from engineering

[15]It should be noted that the relation $\nabla\mu_\alpha \cdot \mathbf{J}_\alpha \leq 0$ obtained from the rate of dissipation potential of each constituent ensures no matter how large the deformation, it cannot induce a flow of mass in the absence of a volume fraction gradient.

[16]Lee et al. [83, 84] showed that the long-time behavior of Cahn-Hilliard equation with a quadratic degenerate mobility, i.e., $M_T = 1-\phi_T^2$, does not reduce to surface diffusion as its long-time, sharp interface limit.

materials modeling, micromechanically-motivated evolution equations might be considered for growing tissue. However, this approach encounters additional challenges in describing biological growth due to the requirement of *in vivo* characterization of living tissue and strong dependency of the growth law on the type of tissue under consideration. Additionally, micro-mechanical based models might lead to a large number of model parameters and challenges the predictive capability of the model due to the lack of experimental observations to calibrate and validate the model. Another approach consists of hypothesizing phenomenological laws based on experimental observations. Such models result in the development of theories that can be effectively informed by specific experiments from which model parameters can be evaluated[17]. Since the aim of the current formulation is to develop a tumor model that can be ultimately informed by typical imaging data of tumor evolution, we follow the later approach.

Tumor growth is taken to be anisotropic and the growth component of the deformation gradient is given by

$$\mathbf{F}_T^G = \Lambda_T^G \boldsymbol{\Omega}, \tag{93}$$

where Λ_T^G is the growth stretch ratio and

$$\boldsymbol{\Omega} = \begin{bmatrix} \lambda_1 & & \\ & \lambda_2 & \\ & & \lambda_3 \end{bmatrix}, \qquad \lambda_1^2 + \lambda_2^2 + \lambda_3^2 = 1 \tag{94}$$

is the anisotropy tensor, with λ_1, λ_2, and λ_3 being anisotropic growth multipliers [9, 10, 12, 13] and isotropic growth (see, e.g., [123, 141]) corresponds to $\boldsymbol{\Omega} = \mathbf{I}$. Such anisotropic growth allows preferential expansion of tumor in the direction of low stress and enables stress-relaxation even in absence of viscose dissipation, a phenomena that is observed experimentally (see, e.g., [68]).

If the mass balance equation is not included in the formulation, the evolution of the growth stretch ratio[18] can be related to the induced pressure expressed in terms of the trace of the second Piola-Kirchhoff stress [92, 125], von Mises stress [122, 123], or the Mandel stress [69]. However, more realistic representation of the biophysical process of growing tumor in a microenvironment, is to account for both diffusion and deformation as well as their coupling responses. In this setting, the growth stretch ratio Λ_T^G and creation or degradation rate of the solid tumor constituent through mass transfer, must be explicitly related to one another. We presented a relation among the growth tensor evolution and the mass exchange terms in the Appendix C. According to (145), an evolution equation for the growth stretch ratio can be obtained as,

$$\frac{1}{\Lambda_T^G}\frac{\partial \Lambda_T^G}{\partial t} = \frac{1}{3}\lambda_T^{\mathrm{pa}}\phi_T(1-\phi_T)\phi_\sigma. \tag{95}$$

[17] For instance, in many physiological systems one can consider the notion of homeostatic, indication that growth occurs in a way that minimizes the difference between the actual stress and a preferred stress, to propose a differential law for the evolution of the growth [3].

[18] In the absence of mass transport, the biological growth is modeled solely based on the evolution of the growth stretch ratio, see, e.g., [69, 107, 133].

As oppose to the phenomenological evolution equations of growth stretch (e.g., [107, 122, 123, 133]), the relation (95) is derived based on physically and mathematically consistent framework (inline with [6, 100]) without the requirement of introducing additional model parameters.

In current formulation, the feedback of deformation on the tumor mobility and source term is consider through a function of volume change. Even in absence of other biological and chemical effects, there is no general agreement in the literature on whether growth processes relate best to stress or strain [3]. Here we argue that the stress is an unobservable quantity and does not directly appear in observational data to support or contradict any particular hypothesis with respect to an explicit form of the stress tensor. Thus, in the relations of tumor mobility (90), tumor mass exchange (92), and consequently evolution equation of the growth stretch ratio (95), we consider a representative measure of the tumor deformation J_T, as increasing/decreasing the tumor volume correlates with the increasing/decreasing of the surrounding tissue induced stress to the solid tumor.

3.2 Summary of Governing Equations

Using the macro-force balance (15) and neglecting the body forces, the governing equation for deformation of tumor and nutrient rich water reduces to,

$$\begin{aligned} \frac{\partial \rho_T \phi_T \mathbf{v}_T}{\partial t} + \nabla \cdot (\rho_T \phi_T \mathbf{v}_T \otimes \mathbf{v}_T) &= \nabla \cdot \mathbf{T}_T, & (96)\\ \frac{\partial \rho_\sigma \phi_\sigma \mathbf{v}_\sigma}{\partial t} + \nabla \cdot (\rho_\sigma \phi_\sigma \mathbf{v}_\sigma \otimes \mathbf{v}_\sigma) &= \nabla \cdot \mathbf{T}_\sigma, & (97) \end{aligned}$$

where

$$\begin{aligned} \mathbf{T}_T &= \left(\frac{G_T}{J_T^{S^{5/3}}} \left(\mathbf{B}_T^S - \frac{1}{3} tr(\mathbf{B}_T^S)\mathbf{I} \right) + K_T (J_T^S - 1)\mathbf{I} \right) \frac{1}{\Lambda_T^G} \mathbf{\Omega}^{-1} \\ &- \epsilon_T \nabla \phi_T \otimes \nabla \phi_T, & (98)\\ \mathbf{T}_\sigma &= -p_\sigma \phi_\sigma \mathbf{I} + \frac{1}{2} A_\sigma (\nabla \mathbf{v}_\sigma + \nabla \mathbf{v}_\sigma^T). & (99) \end{aligned}$$

The species mass balance relations (21) for two constituents are,

$$\begin{aligned} \frac{\partial \rho_T \phi_T}{\partial t} + \nabla \cdot (\rho_T \phi_T \mathbf{v}_T) &= S_T - \nabla \cdot (\mathbf{M}_T \cdot \nabla \mu_T) & (100)\\ \frac{\partial \rho_\sigma \phi_\sigma}{\partial t} + \nabla \cdot (\rho_\sigma \phi_\sigma \mathbf{v}_\sigma) &= S_\sigma - \nabla \cdot (\mathbf{M}_\sigma \cdot \nabla \mu_\sigma) & (101) \end{aligned}$$

where S_T and S_σ are defined in (91), $\mathbf{M}_\sigma$ is defined in (74), the form of $\mathbf{M}_T$ is presented

in (89). The chemical potentials, neglecting the external microforce, are defined as:

$$\begin{aligned}\rho_T\mu_T &= 2\kappa\phi_T(2\phi_T^2 - 3\phi_T + 1) - \chi_0\phi_\sigma - \epsilon_T^2\Delta\phi_T \\ &\quad + \frac{\partial\Lambda_T^G}{\partial\phi_T}(\mathbf{T}_T + \epsilon_T\nabla\phi_T \otimes \nabla\phi_T) : \mathbf{F}_T^S, \qquad (102)\\ \rho_\sigma\mu_\sigma &= 2\frac{1}{\delta_\sigma}\phi_\sigma - \chi_0\phi_T. \qquad (103)\end{aligned}$$

The above partial differential equations (96), (97), (100), and (101), characterize the coupled diffusion and hyperelastic deformation of tumor growth. Additionally, Ambrosi and Mollica [5] argue that in the case of biological tissues, the characteristic velocities are so small ($\mathbf{v}_T \approx 0$ and $\mathbf{v}_\sigma \approx 0$) that the system can be conveniently described as quasi-static. This assumption results in a simpler system of partial differential equation that (96) - (101) to be solved using finite elemenet methods.

4 Conclusions

In this work, we have developed a general mixture theory for a complex mass of multiple constituents. The local species mass balance results in a system of N fourth-order parabolic partial differential equations of the Cahn-Hilliard type. These equations along with the macro-force balance, together with appropriate boundary and initial conditions, characterize a general coupled phase-field and elastic deformation, continuum mixture model of a complex media consisting of multiple solid and fluid species. The constituents can be compressible, the fluid species are non-Newtonian, the solid constituents are isotropic hyperelastic, and the effects of diffusion of chemical or biological constituents due to chemo- or bio-taxis as well as surface effects due to gradients in concentrations are taken into account.

We then specialized the general framework to describe the response of a mixture consisting of four constituent volume fractions: tumor cells, nutrient-rich extracellular water, nutrient-poor extracellular water, and healthy cells. We were particularly interested in modeling the mechanical aspects of the tumor growth and their link with tumor progression. In this regard, the growth effects and its interaction with the deformation are included in this model through decomposition of the tumor deformation gradient into elastic and growth counterparts. The tumor growth counterpart of the deformation gradient is a new unknown that is neither governed by a new balance law nor can be found based on thermodynamic arguments. Thus, a constitutive relation must be postulated for the evolution law of growth in relation to physical, biological, and chemical effects. Perhaps, identification of appropriate evolution equations for the growth tensor is one of the most challenging problems in biomechanics. Here, we postulate phenomenological constitutive models accounting for the mechanical effect of decreasing the rate of tumor cell proliferation with increasing the tumor volume. In this regard, the mobility tensor and mass exchange source term in the diffusion equations of the tumor constituent are considered as an exponential decay function of the tumor

of volume change indicating the increase/decreas of induced pressure from surrounding tissues. Both the diffusion source term and the growth tensors characterize the cancer cell proliferation and apoptosis. As a result of this physical feature, an evolution equation is derived for the growth stretch ration as a function of the source term. Although the mathematical arguments for the exponential decay evolution equations for mass transfer are fairly intuitive, the law is arguably a starting point for describing such a complex biological event. Future insight through micromechanical models of phenomena on the cellular and sub-cellular levels, are required as well as much experimental *in vivo* data to propose a meaningful constitutive model with clear biomechanical interpretations.

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Appendices

A Frame-Indifference Principle

As noted before, $\mathcal{B}_t$ is the region of mixture evolves during the motion and is termed *observed space* or *current configuration* while $\mathcal{B}$ serves to label material points and is termed *reference space*. Granted this dichotomy, spatial points $\mathbf{x}$ and spatial vectors belong to the observed space, while material points $\mathbf{X}$ and material vectors belong to the reference space.

The frame-indifference is a basic principle in continuum mechanics that states material points and material vectors are invariant under changes in frame[19]. It is clear that a change of frame affects the observed space and it does not affect the reference space. In particular, a change of frame at a fixed time t transforms (maps) a spatial points $\mathbf{x}_\alpha$ to the spatial points,

$$\mathbf{x}^*_\alpha = \mathcal{F}(\mathbf{x}) = \mathbf{y}(t) + \mathbf{Q}(t)\mathbf{x}_\alpha \tag{104}$$

where $\mathcal{F}(\mathbf{x})$ is a rigid transformation, $\mathbf{y}(t)$ is an arbitrary spatial point, $\mathbf{Q}(t)$ is a rigid body frame-rotation holding the properties $\mathbf{Q}\mathbf{Q}^T = 1$ and $\det(\mathbf{Q}) = 1$, and the rate at which the new frame is spinning represents by a skew tensor,

$$\mathbf{\Omega}(t) = \dot{\mathbf{Q}}(t)\mathbf{Q}^T(t), \tag{105}$$

and is called frame-spin. In general the scalar field a, vector field $\mathbf{a}$, and tensor field $\mathbf{A}$ are said to be frame-indifferent with respect to Euclidean transformation if

$$a^* = a, \qquad \mathbf{a}^* = \mathbf{Q}\mathbf{a}, \qquad \mathbf{A}^* = \mathbf{Q}\mathbf{A}\mathbf{Q}^T, \tag{106}$$

where superscript $(\cdot)^*$ indicates the entities in the new frame.

The motion $\mathcal{X}_\alpha$ (recall (1)) transforms according to

$$\mathcal{X}^*_\alpha(\mathbf{X}_\alpha, t) = \mathbf{y}(t) + \mathbf{Q}(t)\mathcal{X}_\alpha(\mathbf{X}_\alpha, t), \tag{107}$$

and the gradient of (107) with respect to $\mathbf{X}_\alpha$ results in a transformation law for the deformation gradient,

$$\mathbf{F}^*_\alpha(\mathbf{X}_\alpha, t) = \mathbf{Q}(t)\mathbf{F}_\alpha(\mathbf{X}_\alpha, t). \tag{108}$$

From (108) one can show the field $\mathbf{C}_\alpha$ is invariant,

$$\mathbf{C}^*_\alpha = (\mathbf{Q}\mathbf{F}_\alpha)^T\mathbf{Q}\mathbf{F}_\alpha = \mathbf{F}^T_\alpha\mathbf{F}_\alpha = \mathbf{C}_\alpha \tag{109}$$

[19] According to Truesdell and Noll [127]: "The position of an event can be specified only if a frame of reference, or observer, is given. Physically, a frame of reference is a set of objects whose mutual distances change comparatively little in time $\cdots$ Only if such a frame is given for all times does it make sense to compare the positions of a particle at different times, and only then can we speak about velocities, accelerations, etc. of a particle $\cdots$"

Having (107) along with (8) yields a transformation for the velocity field $\mathbf{v}_\alpha(\mathbf{x}_\alpha, t)$ such as,

$$\mathbf{v}^*_\alpha(\mathbf{x}^*, t) = \mathbf{Q}(t)\mathbf{v}_\alpha(\mathbf{x}_\alpha, t) + \dot{\mathbf{y}}(t) + \dot{\mathbf{Q}}(t)\mathbf{x}_\alpha, \tag{110}$$

and the velocity gradient of each constituent transforms according to

$$\mathbf{L}^*_\alpha(\mathbf{x}^*_\alpha, t) = \nabla^* \cdot \mathbf{v}^*_\alpha(\mathbf{x}^*_\alpha, t). \tag{111}$$

Using (104) along with the chain-rule to differentiation with respect to $\mathbf{x}$, results in

$$\mathbf{L}^*_\alpha(\mathbf{x}^*_\alpha, t) = \mathbf{Q}(t)\mathbf{L}_\alpha(\mathbf{x}_\alpha, t)\mathbf{Q}^T(t) + \mathbf{\Omega}(t). \tag{112}$$

A.1 Virtual Internal Power

Here we show the consequence of the requirement that the virtual internal power be invariant under changes of frame. According to (37) the internal virtual power is expressed as

$$\mathcal{P}_{\text{int}} = \sum_\alpha \int_{\mathcal{R}_t} \left(\mathbf{T}_\alpha : \tilde{\mathbf{L}}_\alpha - \pi_\alpha \frac{d^\alpha \tilde{\phi}_\alpha}{dt} + \boldsymbol{\xi}_\alpha \cdot \nabla \left(\frac{d^\alpha \tilde{\phi}_\alpha}{dt} \right) \right) \mathrm{d}V(\mathbf{x}), \tag{113}$$

and thus the internal power in the new frame can be represent by

$$\mathcal{P}^*_{\text{int}} = \sum_\alpha \int_{\mathcal{R}^*_t} \left(\mathbf{T}^*_\alpha : \tilde{\mathbf{L}}^*_\alpha - \pi^*_\alpha \frac{d^\alpha \tilde{\phi}^*_\alpha}{dt} + \boldsymbol{\xi}^*_\alpha \cdot \nabla^* \left(\frac{d^\alpha \tilde{\phi}^*_\alpha}{dt} \right) \right) \mathrm{d}V(\mathbf{x}^*). \tag{114}$$

Frame-indifference requires that

$$\mathcal{P}_{\text{int}} = \mathcal{P}^*_{\text{int}}. \tag{115}$$

Substituting (112) and (110) into (114) and considering the scalar fields such as the π_α and volume fraction ϕ_α are invariant,

$$\pi^*_\alpha = \pi_\alpha \qquad , \qquad \tilde{\phi}^*_\alpha = \tilde{\phi}_\alpha, \tag{116}$$

yields a relation for the internal power in the new frame,

$$\mathcal{P}^*_{\text{int}} = \sum_\alpha \int_{\mathcal{R}^*_t} \left(\mathbf{T}^*_\alpha : [\mathbf{Q}\mathbf{L}_\alpha\mathbf{Q}^T + \mathbf{\Omega}] - \pi_\alpha \frac{d^\alpha \tilde{\phi}_\alpha}{dt} + \boldsymbol{\xi}^*_\alpha \cdot \nabla \left(\frac{d^\alpha \tilde{\phi}^*_\alpha}{dt} \right) \right) \mathrm{d}V(\mathbf{x}^*). \tag{117}$$

From (104) and considering the Jacobian of the transformation $\mathcal{F}$ satisfies $\det(\nabla\mathcal{F}) = \det(\mathbf{Q}) = 1$, one can change the variable of integration in (117) from $\mathbf{x}^*$ to $\mathbf{x}$. Since the spatial region $\mathcal{R}_t$ is arbitrary, (115) is equivalent to satisfying following relations,

$$\mathbf{T}_\alpha : \tilde{\mathbf{L}}_\alpha = \mathbf{T}^*_\alpha : [\mathbf{Q}\tilde{\mathbf{L}}_\alpha\mathbf{Q}^T + \mathbf{\Omega}], \tag{118}$$

$$\boldsymbol{\xi}^*_\alpha \cdot \nabla^* \frac{d^\alpha \tilde{\phi}_\alpha}{dt} = \boldsymbol{\xi}_\alpha \cdot \nabla \frac{d^\alpha \tilde{\phi}_\alpha}{dt}. \tag{119}$$

Relation (118) can be expressed as

$$\mathbf{T}_\alpha : \tilde{\mathbf{L}}_\alpha = [\mathbf{Q}^T \mathbf{T}^*_\alpha \mathbf{Q}] : \tilde{\mathbf{L}}_\alpha + \mathbf{T}^*_\alpha : \mathbf{\Omega}. \tag{120}$$

Without loss of generality, one may consider a change of frame in which the $\mathbf{Q}$ is constant and thus frame-spin $\mathbf{\Omega}$ vanishes. This implies

$$[\mathbf{T}_\alpha - \mathbf{Q}^T \mathbf{T}^*_\alpha \mathbf{Q}] : \tilde{\mathbf{L}}_\alpha = 0, \qquad \forall\, \tilde{\mathbf{L}}_\alpha, \tag{121}$$

and

$$\mathbf{T}^*_\alpha = \mathbf{Q} \mathbf{T}_\alpha \mathbf{Q}^T, \qquad \forall\, \mathbf{Q}. \tag{122}$$

From (122) one can conclude that *Cauchy stress for each species* $\mathbf{T}_\alpha$ *is frame-indifferent.* Moreover, substituting (122) in (120), yields

$$\mathbf{T}^*_\alpha : \mathbf{\Omega} = 0, \tag{123}$$

and from (105) one may assume that $\mathbf{\Omega}$ is an arbitrary skew tensor, resulting in $\mathbf{T}^* = \mathbf{T}^{*T}$ and using (122), yields

$$\mathbf{T}_\alpha = \mathbf{T}^T_\alpha, \tag{124}$$

indicating that *Cauchy stress for each species* $\mathbf{T}_\alpha$ *is symmetric.* Additionally using chain-rule $\nabla(\cdot) = \mathbf{Q}\nabla^*(\cdot)$, in relation (119) indicates the *microforce* $\boldsymbol{\xi}_\alpha$ *is invariant under change of frame*,

$$\boldsymbol{\xi}^*_\alpha = \mathbf{Q}\boldsymbol{\xi}_\alpha. \tag{125}$$

A.2 Mass Flux

Guided by the form of the free energy (53), one may assume that the species flux $\mathbf{J}_\alpha$ has the form,

$$\mathbf{J}_\alpha = \mathbf{J}_\alpha(\mathbf{F}_\alpha, \phi_\alpha, \nabla\mu_\alpha). \tag{126}$$

Since flux is a material vector field, it is invariant under a change of frame,

$$\mathbf{J}^*_\alpha = \mathbf{J}_\alpha. \tag{127}$$

Also, because the deformation gradient transforms according to (108), $\mathbf{J}_\alpha$ must satisfy

$$\mathbf{J}_\alpha(\mathbf{F}_\alpha, \phi_\alpha, \nabla\mu_\alpha) = \mathbf{J}_\alpha(\mathbf{Q}\mathbf{F}_\alpha, \phi_\alpha, \nabla\mu_\alpha); \qquad \forall\, \mathbf{Q},\ \mathbf{F}_\alpha,\ \phi_\alpha. \tag{128}$$

Considering the polar decomposition of the deformation gradient, $\mathbf{F}_\alpha = \mathbf{R}_\alpha \mathbf{U}_\alpha$, in which $\mathbf{R}_\alpha$ is an orthogonal tensor ($\mathbf{R}_\alpha \cdot \mathbf{R}^T_\alpha = \mathbf{I}$) and $\mathbf{U}_\alpha$ is a symmetric tensors called the right stretch tensor. The fact that $\mathbf{Q}$ is arbitrary, allows one to choose $\mathbf{Q} = \mathbf{U}^T_\alpha$. Having $\mathbf{Q}\mathbf{F}_\alpha = \mathbf{U}_\alpha$, (128) specializes to

$$\mathbf{J}_\alpha(\mathbf{F}_\alpha, \phi_\alpha, \nabla\mu_\alpha) = \mathbf{J}_\alpha(\mathbf{U}_\alpha, \phi_\alpha, \nabla\mu_\alpha), \tag{129}$$

and replacing $\mathbf{U}_\alpha$ by $\sqrt{\mathbf{C}_\alpha}$ in (129), one may therefore express species flux as a function of $\mathbf{C}_\alpha$. This shows that if the constitutive equation (126) is to be frame-indifferent, it must reduce to constitutive equation of the specific form

$$\mathbf{J}_\alpha = \mathbf{J}_\alpha(\mathbf{C}_\alpha, \phi_\alpha, \nabla\mu_\alpha). \tag{130}$$

B Numerical Experiments: Stress Due to Microstress

As discussed in section 2.7.3, presence of a nonlocal microstress,

$$\boldsymbol{\xi}_T = \epsilon_T \nabla \phi_T, \tag{131}$$

results in existence of a Cauchy stress term even in the absence of elastic deformation of the tumor,

$$\mathbf{T}_T = \epsilon_T \nabla \phi_T \otimes \nabla \phi_T. \tag{132}$$

In this appendix, we describe numerical experiments performed for simulating the evolution of this stress during tumor growth with different interface thicknecess. In this regard, the governing equations of the model, summarized in section 3.2, are solved numerically using mixed finite element method. In particular, the effects of elastic deformation are ignored that reduces system of partial differential equations to solving (100) and (101) are solved numerically.

The numerical study consists of a unit circle in the middle of which a tumor is implanted at $t = 0$. In specific, the initial conditions are:

$$\begin{aligned}
\phi_T &= 0.9 \exp\left[-100\left(x^2 + y^2\right)\right], && (133)\\
\phi_\sigma &= 0.8 \cos\left(\pi x y\right), && (134)\\
\mu_T &= 2\kappa\phi_T\left(2\phi_T^2 - 3\phi_T + 1\right) - \chi_0\phi_\sigma - \epsilon_T^2 \Delta\phi_T. && (135)
\end{aligned}$$

On the boundary of the domain, flux-free conditions are prescribed,

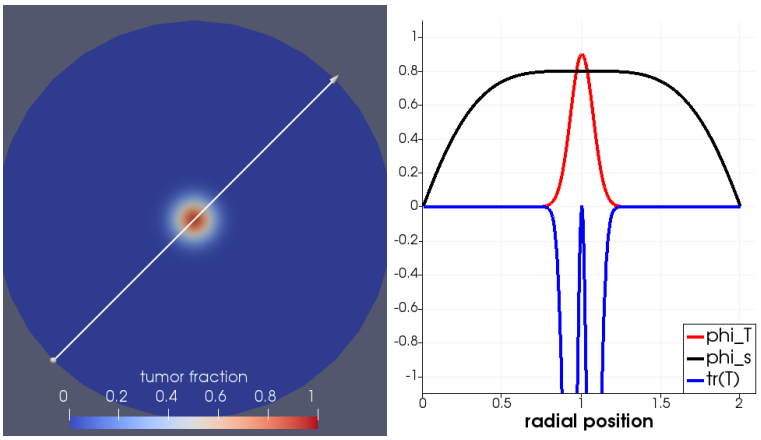
$$\begin{aligned}
\frac{\partial \mu_T}{\partial \mathbf{n}} &= 0, \text{ on } \partial\Omega && (136)\\
\frac{\partial \mu_\sigma}{\partial \mathbf{n}} &= 0, \text{ on } \partial\Omega && (137)\\
\frac{\partial \phi_T}{\partial \mathbf{n}} &= 0, \text{ on } \partial\Omega, && (138)
\end{aligned}$$

where $\mathbf{n}$ is the outward normal vector to the boundary. The problem is solved using the numerical scheme proposed by [88] with uniform a step size $\Delta t = 0.0001$. Other parameters are $\lambda_p = 0.5, \lambda_A = 0, \delta_\sigma = 1, M_T = 200, M_s = 1, \kappa = 0.045$, and $\chi_0 = 0.035$.

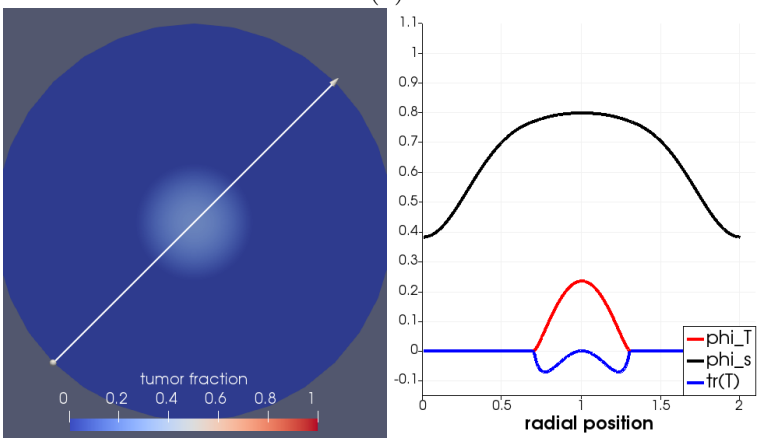
In Figures 1 and 2, we plot the trace of the Cauchy stress,

$$\mathrm{tr}(\mathbf{T}) = -\frac{1}{\epsilon_T}||\boldsymbol{\xi}_T||_2^2, \tag{139}$$

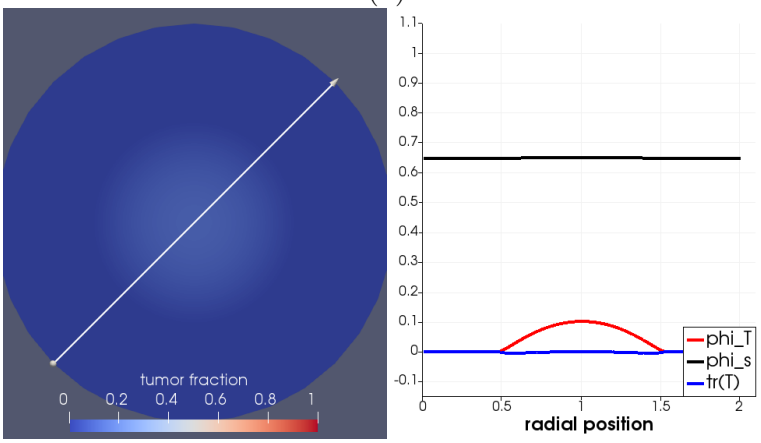
at multiple time points for $\epsilon_T = 0.005$ and 0.05. With larger ε_T, the trace of the Cauchy stress is initially larger in magnitude but decays quickly. At $t = 1$, the magnitude $|\mathrm{tr}(\mathbf{T})|$ is less than 2% of its initial value. On the other hand, when $\epsilon_T = 0.005$, the Cauchy stress gradually increases in magnitude while the spread of the tumor is much slower.



(a)



(b)



(c)

Figure 1: Simulation results for tumor growth with a moderate interface parameter $\epsilon_T = 0.05$. Time evolution of tumor volume fraction ϕ_T, extracellular water volume fraction ϕ_T, and a measure of Cauchy stress $\mathrm{tr}(\mathbf{T})$ in the absence of elastic deformation (132) at (a) $t = 0$, (b) $t = 0.02$, and (c) $t = 1.0$.

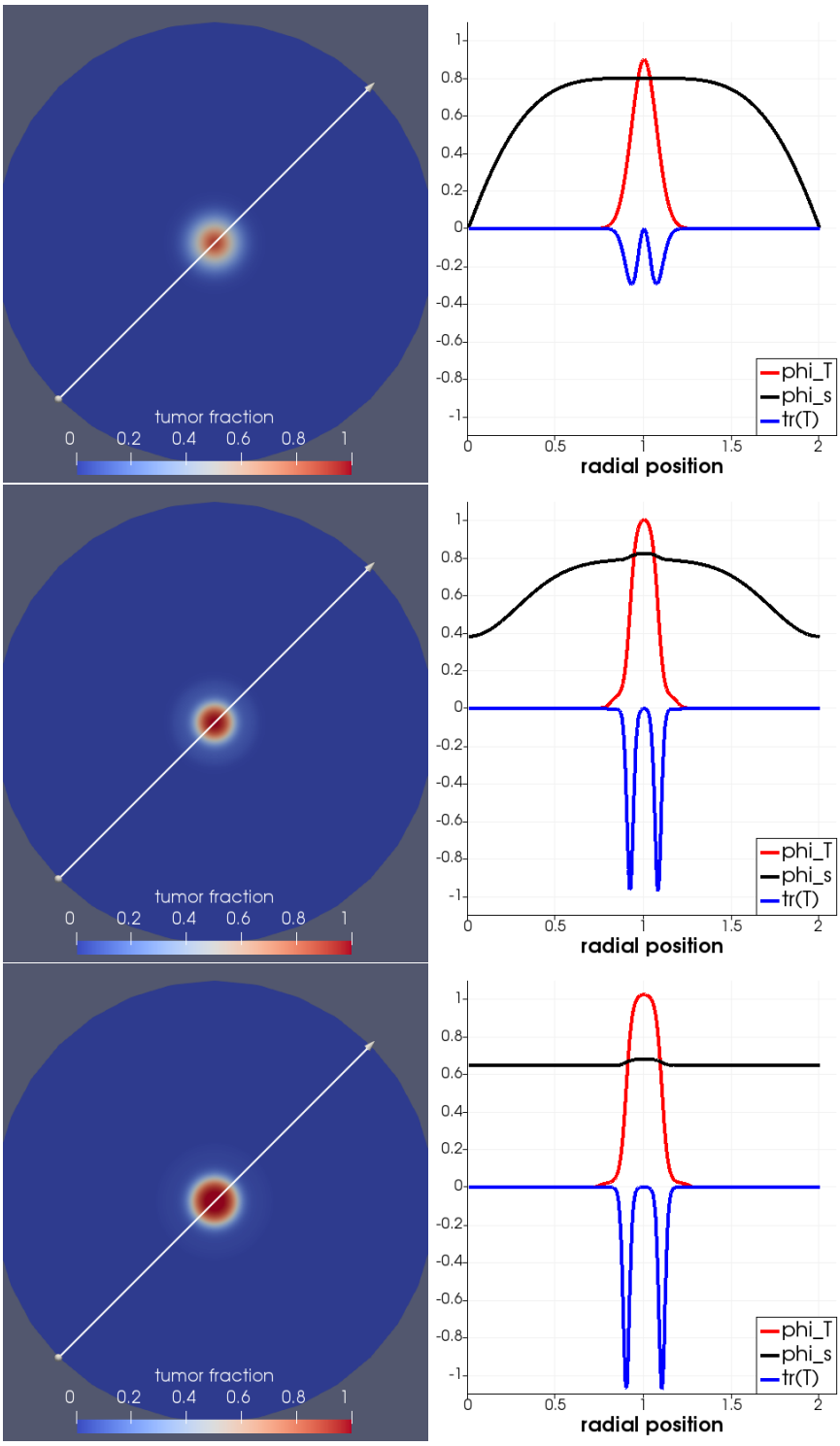


Figure 2: Simulation results for tumor growth with a sharp interface parameter $\epsilon_T = 0.005$. Time evolution of tumor volume fraction ϕ_T, extracellular water volume fraction ϕ_T, and a measure of Cauchy stress $\mathrm{tr}(\mathbf{T})$ in the absence of elastic deformation (132) at (a) $t = 0$, (b) $t = 0.02$, and (c) $t = 1.0$.

C Growth Tensor and Mass Exchange Rate

The fundamental governing equation of biological growth, as the process of mass addition and loss, is the mass balance written in terms of the order parameter, i.e., volume fraction in current formulation. This diffusion equation is necessary to address the physical phenomena involved in macroscopic growth. In case of coupled diffusion-deformation formulation, an evolution equation of the growth tensor must be consistent with the growth characterization through the mass transfer equation (i.e., mass supply and flux). Here we derive a relation between growth tensor $\mathbf{F}_T^G$ and mass exchange rate under the isotropic growth assumption[20],

$$\mathbf{F}_T^G = \Lambda_T^G \mathbf{I}. \tag{140}$$

Considering a two phase mixture with volume v in which a solid phase (tumor) undergoes pure growth process $\mathbf{F}_T^S = 0$. In this case, the volume occupied by tumor constituent increases from initial value $v_T^0 = v_T(t_0)$ to a volume $v_T(t)$ in time t. The volume change due to this growth process is,

$$J_T^G = \frac{dv_T}{dv_T^0}. \tag{141}$$

Following (140), the change in the tumor volume can be also represent as,

$$J_T^G = \det(\mathbf{F}_T^G) = \left(\Lambda_T^G\right)^3. \tag{142}$$

Equating above relations along with the definition of tumor volume fraction (**??**), results in following relation consistent with the formulation developed by Garikipati et al. [51, 52, 100],

$$\Lambda_T^G = \left(\frac{\rho_T \phi_T}{\rho_T^0 \phi_T^0}\right)^{1/3}, \tag{143}$$

where $\phi_T^0 = \phi_T(t_0)$ and $\rho_T^0 = \rho_T(t_0)$.

Additionally, the tumor mass balance under quasi-static assumption is

$$\frac{\partial \rho_T \phi_T}{\partial t} = S_T - \nabla \cdot (\mathbf{M}_T \cdot \nabla \mu_T). \tag{144}$$

Substituting $\rho_T \phi_T$ from (143) into above relation, one can find an evolution equation for growth stretch ratio as,

$$\rho_T^0 \phi_T^0 \frac{\partial \left(\Lambda_T^G\right)^3}{\partial t} = \rho_T \phi_T \left(S_T - \nabla \cdot (\mathbf{M}_T \cdot \nabla \mu_T)\right). \tag{145}$$

The above equation provides a consistent framework to determine the growth tensor evolution equation from functional forms of S_T and M_T postulated based upon bio-physical phenomena. Similar relation is presented by Ambrosi and Mollica using a mathematical consistent derivations based on natural configuration argument and Lagrangian form of the mass balance(for more details see [5, 6]).

[20]The assumption of isotropic/homogeneous growth is only valid for small avascular tumors. For vascular tumors, that display heterogeneous anisotropic growth, the growth tensor must be anisotropic.

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