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GENERAL DIFFUSE-INTERFACE THEORIES AND AN APPROACH TO PREDICTIVE TUMOR GROWTH MODELING

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While a large and growing literature exists on mathematical and computational models of tumor growth, to date tumor growth models are largely qualitative in nature, and fall far short of being able to provide predictive results important in life-and-death decisions. This is largely due to the enormous complexity of evolving biological and chemical processes in living tissue and the complex interactions of many cellular and vascular constituents in living organisms. Several new technologies have emerged, however, which could lead to significant progress in this important area: (i) the development of so-called phase-field, or diffuse-interface models, which can be developed using continuum mixture theory, and which provide a general framework for modeling the action of multiple interacting constituents. These are based on generalizations of the Cahn–Hilliard models for spinodal decomposition, and have been used recently in certain tumor growth theories; (ii) the emergence of predictive computational methods based on the use of statistical methods for calibration, model validation, and uncertainty quantification; (iii) advances in imaging, experimental cell biology, and other medical observational methodologies; and (iv) the advent of petascale computing that makes possible the resolution of features at scales and at speeds that were unattainable only a short time in the past.

Here we develop a general phenomenological thermomechanical theory of mixtures that employs phase-field or diffuse interface models of surface energies and reactions and which provides a framework for generalizing existing theories of the types that are in use in tumor growth modeling. In principle, the framework provides for the effects of M solid constituents, which may undergo large deformations, and for the effect of $N - M$ fluid constituents, which could include highly nonlinear, non-Newtonian fluids. We then describe several special cases which have the potential of providing acceptable models of tumor growth. We then describe the beginning steps of the development of Bayesian methods for statistical calibration, model validation, and uncertainty quantification, which, with further work, could produce a truly predictive tool for studying tumor growth. In particular, we outline the processes of statistical calibration and validation that can be employed to determine if tumor growth models, drawn from the broad class of models developed here, are valid for prediction of key quantities of interest critical to making decisions on various medical protocols. We also describe how

uncertainties in such key quantities of interest can be quantified in ways that can be used to establish confidence in predicted outcomes.

Keywords: Mixture theory; diffuse-interface; predictive models; tumor growth; Bayesian statistics; calibration and validation; uncertainty quantification.

AMS Subject Classification: 92B99, 62F15

1. Introduction

Our general goal is to develop predictive phenomenological models of the evolution and interaction of a complex mass of numerous constituents making up living tissue in which one constituent, a tumor mass, may grow or decline due to various physical and biological effects. By a predictive model, we mean one which has been subjected to a meaningful validation process and for which uncertainties in predictions in key quantities of interest can be quantified. We will take up this aspect of the analysis later in connection with Bayesian methods of statistical calibration and validation.

Work directed at mathematical modeling of tumor growth can be found in the literature throughout the last century, but only recently have the models shifted focus from mimicking growth rates from nutrient diffusion in avascular tumors to monitoring changes in tumor behavior resulting from more complex phenomena. This is due to the many discoveries concerning mechanisms now known to be critical to tumor growth: angiogenesis, cell movement, cell mutations, etc. A comprehensive history has been compiled by Araujo and McElwain[7] and several surveys of models have also appeared in recent years, i.e. those compiled in Wodarz and Komarova,[77] Bellomo, Chaplain and De Angelis,[12] and Preziosi.[63] A review of the foundations of cancer modeling has recently been contributed by Bellomo, Li and Maini.[14] These indicate that the majority of models can be placed in two categories: discrete or cellular automata models and continuum models. Deterministic models have been developed to specifically investigate metastasis,[67,74] cell−cell adhesion and motility,[36,35,54] angiogenesis,[6] and growth.[50,51] Such models have the advantage of capturing individual cell behavior, but are clearly limited in the size of tumor they can simulate. Despite recent developments in high performance computing, it is unlikely that such models will be able to capture a realistic tumor, as a small visible tumor will have on the order of 10^{10} cells. In contrast, continuum models are able to capture the evolution and growth of large tumors but must average over individual cell behaviors. Governing equations for such models have been developed based on empirical laws[22,26] and by first principles through continuum mechanics.[7,19,20,76] There have also been attempts to capitalize on both the benefits of the discrete models and the continuum models by creating hybrid models where the cells are treated in a discrete manner and the microenvironment and nutrients are characterized through a continuum.[5] While a few models attempt in some way to capture multiscale events and may be clinically relevant,[41] the vast majority of models

produce results that are primarily qualitative and are not capable of providing patient-specific predictions. The component most notably absent in all of these models, however, is the ability to quantify the uncertainty in the prediction.

This paper looks specifically at continuum models and a first consideration is the difficult and long-standing problem of modeling the interaction of different material bodies or different phases of materials. This problem has been the focus of research in mechanics for many years and is at the heart of classical approaches for treating free boundary problems, variational inequalities, the behavior of porous media, particle suspensions, phase transitions, and other phenomena involving the characterization of interface conditions when one or more bodies interact with one another or when fronts separating one medium from another propagate over time.

One general approach to modeling multiphase materials is provided by the so-called diffuse-interface or phase-field models, in which the interface between phases is handled automatically as a feature of the solution, and is spread out over boundary layers between phases. In general, such models are obtained by incorporating gradients in concentrations of various constituents in the Helmholtz or Gibbs free energy functionals for a multiphase material so as to approximate surface energies at interfaces. The most notable model of this type is the now classical Cahn−Hilliard model of binary phase separation[24] in which the free energy contains gradients in concentrations multiplied by parameters which characterize the thickness of smoothed interfaces between the phases.

The idea of modeling the interface between dissimilar phases as a smooth transition zone where field variables vary continuously across an interfacial region is not new. Such models were used by van der Waals over a century ago[75]; the Ginzburg−Landau model of superconductivity[45] employed ideas related to diffuse interfaces a half-century later, and the Cahn−Hilliard model[24] appeared over a half-century ago. In recent years, phase-field models have provided important frameworks for characterizing microstructure evolution at the mesoscale, solidification, grain growth, dislocation dynamics, and many other multiphase phenomena in materials science, metallurgy, chemistry, and chemical engineering. Extensive surveys of the work on phase-field models in these areas have been published, for example by Boettinger *et al.*,[15] Chen,[27] and Moelans *et al.*[56]; see also the books of Emmerich[38] and Khachaturyan.[52] Various phase-field models of multiphase flows are derived in Ganeson and Brenner,[43] Kim and Lowengrub,[53] Lowengrub and Truskinovsky,[55] and Papatzacos.[60] Only recently, however, has this concept been applied to tumor growth by Cristini, Li, Lowengrub and Wise,[30] Frieboes, Lowengrub, Wise, Zheng, Macklin, Bearer and Cristini,[41] and others. In these papers the authors demonstrate the capability models produced under this framework have for producing qualitatively accurate results for modeling the growth of gliomas. One aim of this paper is to consider the generalization and extension of the mathematical models in Refs. 30, 41, 53, 55, 76 in the predictive modeling context such that quantitatively accurate results can be produced.

As with other types of models, the appropriate choice of model parameters is heavily related to the predictive capability of the model. In general, tumor growth models will make use of a growth parameter, a death parameter, a mobility type parameter, and a parameter relating growth with the concentration of nutrients. Naturally, these parameters will be different in different tumors and due to mutations will possibly take on drastically different values even throughout a single tumor. *In vitro* and *in vivo* experiments are often performed to determine approximate values of these parameters. However, even if ideal experiments are performed to determine model parameters, the method of obtaining the data and then projecting it into the parameter value is by no means exact. Error is inherent in each step. One major source of error arises in the assumption that results from *in vitro* experiments, where data is usually generated, are true reflections of *in vivo* behavior. Thus, cell doubling times observed in *in vitro* experiments for mitosis rates could be a gross over (or under) estimate. Further, cell staining is not always clear, i.e. the stains could be "blurry", and the projection of cell counts from a few samples of cell cultures to the parameter value is not a well-defined operation. The quantification of such error is necessary for any predictive tool, but the error coming from the issues just described is difficult to determine and quantify as it arises from more than just an imprecise measuring device.

While it is the intent of this paper to demonstrate the derivation of a general class of thermodynamically consistent continuum models as a first step to predictive modeling of tumor growth, we acknowledge the possibility of physical phenomena at the smaller scales, i.e. the molecular and the cellular scales, that should also be modeled. The landmark paper by Hanahan and Weinburg[47] outlines the seven key characteristics of a malignant tumor: genetic instability, self-sufficiency in growth signals, insensitivity to antigrowth signals, evasion of apoptosis, limitless proliferation potential, sustained angiogenesis, and tissue invasion. Each of these events is clearly directed by events happening at the molecular and cellular scales and drastically impacts the overall behavior of the tumor. The review paper by Bellomo and Delitala[13] also emphasizes the need for multiscale modeling and describes in detail a few example models at the smaller scales. As the content of this paper will not dwell on these subjects, we refer the reader to this paper and the references within for further details. It should be noted that the continuum models presented here are not expected to be in conflict with smaller scale models. Certainly, future directions in continuum modeling will include the development of multiscale models which use models of the smaller scale events to improve the mapping procedure from experiments to model parameters. As a first step, the methods of statistical calibration presented in this paper are meant to provide a tumor specific homogenization of the behavior coming from these scales. While this methodology currently does not account for spontaneous mutations and alterations in tumor behavior, it does represent a significant step in characterizing individual tumors. These ideas will be described in further detail in Secs. 6 and 7.

In Sec. 2, following the Introduction, we develop a general continuum theory of mixtures with diffuse-interface effects that describes the thermomechanical 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. Thermal effects and heat transfer are also included. The theory thus generalizes those found in the literature. Our work in this section is inspired by and follows several aspects of the work of Bowen[16] and of the more recent work of Cristini, Li, Lowengrub and Wise[30] and Frieboes *et al.*[41] In Sec. 3, we introduce specific forms of constitutive equations for mixtures of M solids and $N - M$ fluids (or gases) which cover mixtures undergoing large elastic deformations and containing non-Newtonian viscous fluids. A development of diffuse-interface models of the Cahn−Hilliard type is given in Sec. 4, and several special cases covered by the theory are taken up in Sec. 5, including the theories in Ref. 30 and others. In Sec. 6, we describe a Bayesian-based theory of statistical calibration, validation, and uncertainty quantification that is fundamental to creating a predictive model of tumor growth. Section 7 outlines an example of statistical calibration and validation as related to a tumor growth model. Brief comments summarizing the work are given at the conclusion of the presentation. We note that in the final implementation of models taken from the class we consider here, we arrive at stochastic systems that require the full arsenal of developing methods for statistical sampling, uncertainty quantification, and finding solutions of stochastic equations. We also mention that such continuum models are not in conflict with those based on models of cellular behavior as these types of models depict phenomena at smaller scales which when appropriately averaged could yield vital information on many constitutive functions at the heart of continuum models.

2. Diffuse-Interface Models of Multi-Constituent Mixtures

The theoretical framework of our approach to modeling tumor growth is founded in the continuum theory of mixtures. The literature on this subject is very rich, dating back to the early work on simple mixtures of Fick[40] and Darcy[31] and progressing to the general continuum theories advanced by Truesdell,[70,71] Truesdell and Toupin,[73] Müller,[57] Eringen and Ingram,[39] and others. The important and comprehensive review article of Bowen[16] and the monograph of Rajagopal and Tao[65] provide detailed accounts of the theory and a fuller review of the relevant literature on the subject as it stood in the mid-'90s. 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,[32,33] Coussy,[29] Pinder and Gray,[62] Bowen[17,18] and Papatzacos.[60]

It can be said that few applications of mixture theory rest on a single mathematical model, as most are based on approximations brought about through many simplifying assumptions, the validities of which are rarely addressed in a systematic way. The development of diffuse-interface models based on mixture theory involve an additional level of complexity as is discussed below. We next record the basic

equations governing the behavior of a general continuum mixture of N constituents and then develop a general diffuse-interface version by closing the system through a special choice of constitutive equations.

2.1. *A continuum theory of mixtures*

The fundamental idea underlying mixture theory is that a material body $\mathcal{B}$ can be composed of N constituent species $\mathcal{B}_1, \mathcal{B}_2, \ldots, \mathcal{B}_N$ that occupy a common portion of physical space at the same time. We establish a fixed reference configuration so that the spatial position of a material point is defined by the motion

$$\mathbf{x} = \boldsymbol{\chi}_\alpha(\mathbf{X}_\alpha, t), \tag{2.1}$$

where $\mathbf{X}_\alpha$ is the position of a particle in the αth constituent in its reference configuration, and $\mathbf{x}$ is the spatial position occupied by the particle at time t. The deformation gradient is defined by

$$\mathbf{F}_\alpha = \mathrm{GRAD}\, \boldsymbol{\chi}_\alpha(\mathbf{X}_\alpha, t), \tag{2.2}$$

where GRAD denotes the material gradient. Each spatial position is occupied by N such particles, and each constituent is assigned a mass density $\hat{\rho}_\alpha$, which is regarded as a function of $(\mathbf{x}, t)$, representing the mass of the αth constituent per unit volume of the mixture. Then the mass density of the mixture is

$$\rho(\mathbf{x}, t) = \sum_{\alpha=1}^{N} \hat{\rho}_\alpha(\mathbf{x}, t). \tag{2.3}$$

The mass concentration of the αth constituent is defined by:

$$c_\alpha = c_\alpha(\mathbf{x}, t) = \hat{\rho}_\alpha / \rho. \tag{2.4}$$

Clearly,

$$\sum_{\alpha=1}^{N} c_\alpha = 1. \tag{2.5}$$

For a differential volume dv containing a point $(\mathbf{x}, t)$, let dv_α be the proportion occupied by constituent α. The quantity $\varphi_\alpha(\mathbf{x}, t) = dv_\alpha / dv$ is the volume fraction of the αth constituent at that point. We also have

$$\sum_{\alpha=1}^{N} \varphi_\alpha = 1. \tag{2.6}$$

The densities, ρ_α, defined so that

$$\hat{\rho}_\alpha(\mathbf{x}, t) = \rho_\alpha(\mathbf{x}, t)\varphi_\alpha(\mathbf{x}, t), \tag{2.7}$$

represent the mass of the αth constituent per unit volume of the constituent. Thus,

$$\rho c_\alpha = \rho_\alpha \varphi_\alpha = \hat{\rho}_\alpha. \tag{2.8}$$

It is further assumed that each constituent moves with velocity

$$\mathbf{v}_\alpha = \frac{\partial \boldsymbol{\chi}_\alpha}{\partial t}(\mathbf{X}_\alpha, t) = \frac{\partial \boldsymbol{\chi}_\alpha}{\partial t}(\boldsymbol{\chi}_\alpha^{-1}(\mathbf{x}_\alpha, t), t) = \mathbf{v}_\alpha(\mathbf{x}, t) \tag{2.9}$$

and that the mixture velocity $\mathbf{v}$ is the mass-averaged velocity,

$$\mathbf{v} = \frac{1}{\rho}\sum_{\alpha=1}^{N} \rho_\alpha \varphi_\alpha \mathbf{v}_\alpha. \tag{2.10}$$

The diffusion velocity is defined by

$$\mathbf{u}_\alpha = \mathbf{v}_\alpha - \mathbf{v}. \tag{2.11}$$

Clearly,

$$\sum_{\alpha=1}^{N} \rho_\alpha \varphi_\alpha \mathbf{u}_\alpha = 0. \tag{2.12}$$

We distinguish between two types of material-time derivatives when describing the response relative to the spatial frame of reference, one relative to the motion of the mixture, denoted $d(\cdot)/dt$, and the other relative to the motion of each constituent, denoted $d^\alpha(\cdot)/dt$. Thus, if ϕ is any differentiable function of $\mathbf{x}$ and t, we write

$$\frac{d\phi}{dt} = \frac{\partial \phi}{\partial t} + \mathbf{v}\cdot\nabla\phi \quad \text{and} \quad \frac{d^\alpha \phi}{dt} = \frac{\partial \phi}{\partial t} + \mathbf{v}_\alpha \cdot \nabla\phi \tag{2.13}$$

with ∇ being the spatial gradient.

2.2. *The balance laws for mixtures*

Each of the N constituents must satisfy its own balance laws which differ from those of classical continuum mechanics due to the presence of interaction terms representing the exchange of mass, momentum, and energy between constituents. For a general mixture occupying an open region Ω in $\mathbb{R}^3$ over a time interval $(0, T)$, the volume fractions, or mass concentrations, and other independent field variables must satisfy the following local forms of the balance laws for all α, $1 \le \alpha \le N$, all $\mathbf{x} \in \Omega$, and $t \in (0, T)$.

Balance of mass:

$$\frac{\partial \rho_\alpha \varphi_\alpha}{\partial t} + \nabla\cdot(\rho_\alpha \varphi_\alpha \mathbf{v}_\alpha) = \gamma_\alpha - \nabla\cdot\mathbf{j}_\alpha \tag{2.14}$$

or

$$\rho \frac{dc_\alpha}{dt} = -\nabla\cdot\mathbf{h}_\alpha + \gamma_\alpha, \tag{2.15}$$

where γ_α is the mass supplied to constituent α by other constituents and $\mathbf{j}_\alpha$ is the mass flux due to changes in the chemical potential defined in terms of gradients in

concentrations and changes in nutrient concentrations, and

$$\mathbf{h}_\alpha = \mathbf{j}_\alpha + \rho_\alpha \varphi_\alpha \mathbf{u}_\alpha. \tag{2.16}$$

The term $\rho_\alpha \varphi_\alpha \mathbf{u}_\alpha$ represents the change in mass concentration due to the relative motion of the αth constituent to the motion of the mixture. The mass flux $\mathbf{j}_\alpha$ is generally not present in classical formulations of mixture theory, such as that developed in Bowen,[16] Rajagopal and Tao,[66] and others: similar terms are present in the formulations proposed by Cristini, Li, Lowengrub and Wise.[30] The balance law (2.15) shows that in the absence of mass supplied and mass fluxes from other constituents into constituent α, the concentrations of each constituent is constant.

Balance of linear momentum:

$$\rho_\alpha \varphi_\alpha \frac{d^\alpha \mathbf{v}_\alpha}{dt} = \nabla \cdot \mathbf{T}_\alpha + \rho_\alpha \varphi_\alpha \mathbf{b}_\alpha + \hat{\mathbf{p}}_\alpha, \tag{2.17}$$

where $\mathbf{T}_\alpha$ is the partial Cauchy stress tensor, $\mathbf{b}_\alpha$ is the body force per unit mass, and $\hat{\mathbf{p}}_\alpha$ is the momentum supplied by other constituents to the αth constituent.

Balance of angular momentum:

$$\mathbf{M}_\alpha = \mathbf{T}_\alpha - \mathbf{T}_\alpha^T \tag{2.18}$$

with $\mathbf{M}_\alpha$ the intrinsic moment of momentum vector for constituent α. The partial stress tensor is thus, in general, unsymmetric.

Balance of energy:

$$\rho_\alpha \varphi_\alpha \frac{d^\alpha e_\alpha}{dt} = \operatorname{tr} \mathbf{T}_\alpha^T \mathbf{L}_\alpha - \nabla \cdot \mathbf{q}_\alpha + \rho_\alpha \varphi_\alpha r_\alpha + \hat{\varepsilon}_\alpha + \Upsilon_\alpha. \tag{2.19}$$

Here e_α is the internal energy per unit mass, $\mathbf{L}_\alpha$ is the velocity gradient, $\mathbf{L}_\alpha = \nabla \mathbf{v}_\alpha$, $\mathbf{q}_\alpha$ is the heat flux vector, r_α is the heat supplied per unit mass per unit time, and $\hat{\varepsilon}_\alpha$ is the energy supplied to constituent α by other constituents. The remaining term,

$$\Upsilon_\alpha = \sum_{\beta=1}^{N} \nabla \cdot \left(\boldsymbol{\sigma}_{\alpha\beta} \frac{d^\alpha \varphi_\beta}{dt} \right) + \sum_{\beta=1}^{L} \zeta_{\alpha\beta} \frac{d^\alpha m_\beta}{dt}, \tag{2.20}$$

is critical in making the connection between mixture theory and phase-field or diffuse-interface models.

The quantity $\boldsymbol{\sigma}_{\alpha\beta}$ is a generalized surface traction that is conjugate to time-changes in species volume fractions on constituent interfaces. It was introduced in a slightly different form in the paper of Kim and Lowengrub[53] and Lowengrub and Truskinovsky[55] and a different version appears in the tumor growth models of Wise *et al.*[76] and Cristini, Lowengrub and Wise.[30] It represents a simplification of models of surface traction and interface relations encountered in the study of the evolution of phase boundaries, as discussed, for example, by Gurtin and McFadden[46]; see also the book by Joseph and Renardy[48] for a description of surface stresses on interfaces between viscous fluids. This term represents the contribution to the change in energy due to actions of surface tensions or adhesion between cell concentrations due to

time-rates-of-change of each mass concentration on the surface of the full mixture, and results from a surface power defined by a surface integral,

$$\int_{\partial\omega}\left(\sum_{\beta}\boldsymbol{\sigma}_{\alpha\beta}\frac{d^{\alpha}\varphi_{\beta}}{dt}\right)\cdot\mathbf{n}\,ds$$

$\mathbf{n}$ being a unit outward normal to the boundary $\partial\omega$ of ω, an arbitrary subdomain of Ω.

In the remaining term in (2.19), m_β denotes a concentration of a nutrient species so that $m_\beta\varphi_\alpha$ defines the reaction between various nutrients in the mixture (such as oxygen) and the constituent φ_α, and $\zeta_{\alpha\beta}$ denotes the chemical or biological forces conjugate to changes in nutrient concentrations. According to Ref. 30, this term in the energy balance provides a means to account for the diffusion of chemical or biological constituents due to chemo- or bio-taxis. These effects were introduced in the tumor growth models of Cristini *et al.*[30] and Wise, Lowengrub, Frieboes and Cristini.[76]

The second law of thermodynamics:

$$\sum_{\alpha=1}^{N}\left\{\rho_\alpha\varphi_\alpha\frac{d^{\alpha}\eta_\alpha}{dt}-\frac{1}{\theta_\alpha}\rho_\alpha\varphi_\alpha r_\alpha+\Gamma_\alpha\eta_\alpha+\nabla\cdot(\mathbf{H}_\alpha-\rho_\alpha\varphi_\alpha\eta_\alpha\mathbf{u}_\alpha)\right\}\geq 0. \tag{2.21}$$

Here η_α is the entropy per unit mass, Γ_α is the total mass supplied,

$$\Gamma_\alpha=\gamma_\alpha-\nabla\cdot\mathbf{j}_\alpha, \tag{2.22}$$

$\mathbf{H}_\alpha$ is the entropy flux in the αth constituent, and θ_α is its absolute temperature. If we introduce the Helmholtz free energy ψ_α for constituent α, defined by

$$\psi_\alpha=e_\alpha-\theta_\alpha\eta_\alpha, \tag{2.23}$$

then, introducing (2.19) into (2.21) and making use of (2.23) gives

$$\begin{aligned}\sum_{\alpha=1}^{N}\Bigg\{\frac{1}{\theta_\alpha}\Bigg[&-\rho_\alpha\varphi_\alpha\frac{d^{\alpha}\psi_\alpha}{dt}-\rho_\alpha\varphi_\alpha\eta_\alpha\frac{d^{\alpha}\theta_\alpha}{dt}+\operatorname{tr}\mathbf{T}_\alpha^{T}\mathbf{L}_\alpha-\nabla\cdot\mathbf{q}_\alpha\\&+\hat{\varepsilon}_\alpha+\sum_{\beta=1}^{N}\nabla\cdot\left(\boldsymbol{\sigma}_{\alpha\beta}\frac{d^{\alpha}\varphi_\beta}{dt}\right)+\sum_{\beta=1}^{L}\zeta_{\alpha\beta}\frac{d^{\alpha}m_\beta}{dt}\Bigg]\\&+\Gamma_\alpha\eta_\alpha+\nabla\cdot(\mathbf{H}_\alpha-\rho_\alpha\varphi_\alpha\eta_\alpha\mathbf{u}_\alpha)\Bigg\}\geq 0.\end{aligned} \tag{2.24}$$

Equations (2.14), (2.17)–(2.19), and inequality (2.24) describe the balance laws and the second law of thermodynamics (the entropy inequality with entropy rates replaced by rates of change of the Helmholtz free energy), for a constituent α in a mixture of N constituents. This system is closed by the addition of appropriate constitutive equations, which put constraints on the physical processes that can be performed on the mixture. But there are other constraints imposed by the requirements that the above axioms of balance and entropy for the constituents must be consistent with those for the mixture as a whole. We record these constraints next.

Balance laws for the mixture. The continuum balance laws for the mixture are defined by the system

$$\left.\begin{aligned}
&\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \mathbf{v}) = 0; \\
&\rho \frac{d\mathbf{v}}{dt} = \nabla \cdot \mathbf{T} + \rho \mathbf{b}; && (\mathbf{T} = \mathbf{T}^T) \\
&\rho \frac{de}{dt} = \operatorname{tr} \mathbf{TL} - \nabla \cdot \mathbf{q} + \rho r + \sum_{\alpha=1}^{N} (\Upsilon_\alpha + \rho_\alpha \varphi_\alpha \mathbf{b}_\alpha \cdot \mathbf{u}_\alpha); \\
&\rho \frac{d\eta}{dt} - \sum_{\alpha=1}^{N} \left(\frac{1}{\theta_\alpha} \rho_\alpha \phi_\alpha r_\alpha - \nabla \cdot \mathbf{H}_\alpha \right) \geq 0; && (\psi = e - \theta\eta)
\end{aligned}\right\}, \tag{2.25}$$

where ρ, $\mathbf{T}$, $\mathbf{b}$, e, $\mathbf{q}$ and η are the mass density, the Cauchy stress, the body force per unit mass, the internal energy per unit mass, the heat flux, the entropy density for the mixture, and Υ_α is defined in (2.20). Note that the body-force term in $(2.25)_3$ vanishes when there is no diffusion or when $\mathbf{b}_1 = \mathbf{b}_2 = \cdots = \mathbf{b}_N = \mathbf{b}$, as pointed out by Bowen.[16] If we sum the constituent balance laws over all N constituents, the sums are compatible with (2.25) if

$$\left.\begin{aligned}
&\mathbf{T} = \sum_{\alpha=1}^{N} (\mathbf{T}_\alpha - \rho_\alpha \varphi_\alpha \mathbf{u}_\alpha \otimes \mathbf{u}_\alpha); && \mathbf{M} = \sum_{\alpha=1}^{N} \mathbf{M}_\alpha; \\
&e = \frac{1}{\rho} \sum_{\alpha=1}^{N} \left(\rho_\alpha \varphi_\alpha e_\alpha + \frac{1}{2} \rho_\alpha \varphi_\alpha \mathbf{u}_\alpha \cdot \mathbf{u}_\alpha \right); && \mathbf{b} = \frac{1}{\rho} \sum_{\alpha=1}^{N} \rho_\alpha \varphi_\alpha \mathbf{b}_\alpha; \\
&\eta = \frac{1}{\rho} \sum_{\alpha=1}^{N} \rho_\alpha \varphi_\alpha \eta_\alpha; && r = \frac{1}{\rho} \sum_{\alpha=1}^{N} \rho_\alpha \varphi_\alpha r_\alpha; \\
&\mathbf{q} = \sum_{\alpha=1}^{N} \left(\mathbf{q}_\alpha - \mathbf{T}_\alpha^T \mathbf{u}_\alpha + \rho_\alpha \varphi_\alpha e_\alpha \mathbf{u}_\alpha + \frac{1}{2} \rho_\alpha \varphi_\alpha \mathbf{u}_\alpha (\mathbf{u}_\alpha \cdot \mathbf{u}_\alpha) \right)
\end{aligned}\right\} \tag{2.26}$$

and, very importantly, the following conditions hold:

$$\left.\begin{aligned}
&\sum_{\alpha=1}^{N} \Gamma_\alpha = \sum_{\alpha=1}^{N} (\gamma_\alpha - \nabla \cdot \mathbf{j}_\alpha) = 0; \\
&\sum_{\alpha=1}^{N} (\Gamma_\alpha \mathbf{u}_\alpha + \hat{\mathbf{p}}_\alpha) = 0; \\
&\sum_{\alpha=1}^{N} \mathbf{M}_\alpha = 0; \\
&\sum_{\alpha=1}^{N} \left[\hat{\varepsilon}_\alpha + \hat{\mathbf{p}}_\alpha \cdot \mathbf{u}_\alpha + \Gamma_\alpha \left(e_\alpha + \frac{1}{2} \mathbf{u}_\alpha \cdot \mathbf{u}_\alpha \right) \right] = 0.
\end{aligned}\right\} \tag{2.27}$$

Whatever the mixture, the mass, momentum, and energy supplied to a constituent for any internal energy e_α and diffusive velocity $\mathbf{u}_\alpha$ must satisfy (2.27). The energy

constraint, $(2.27)_4$, was introduced by Truesdell and Toupin,[73] see also Bowen.[16] Note that in the present development, the definition of mass supply per constituent is different from most other developments (such as in Ref. 53) and is defined by (2.22). We observe that by taking $(2.27)_1$ and $(2.27)_2$ into account, the fourth sum in (2.27) can be written:

$$\sum_{\alpha=1}^{N}\left[\hat{\varepsilon}_\alpha+\hat{\mathbf{p}}_\alpha\cdot\mathbf{v}_\alpha+\Gamma_\alpha\left(e_\alpha+\frac{1}{2}\mathbf{v}_\alpha\cdot\mathbf{v}_\alpha\right)\right]=0. \tag{2.28}$$

Single temperature case. It is often reasonable to assume that all N constituents experience the same temperature $\theta=\theta(\mathbf{x},t)$ at a point $\mathbf{x}$ in the mixture at time t:

$$\theta=\theta_1=\theta_2=\cdots=\theta_N. \tag{2.29}$$

Hereafter, we shall assume that this constraint on the temperature holds.

An alternate form of (2.24) is obtained if, in addition to (2.29), we work with the Helmholtz free energy per unit volume Ψ_α instead of ψ_α:

$$\Psi_\alpha=\rho_\alpha\varphi_\alpha\psi_\alpha. \tag{2.30}$$

One can show that (see Ref. 16, p. 32):

$$\rho_\alpha\varphi_\alpha\frac{d^\alpha\psi_\alpha}{dt}=\frac{d\Psi_\alpha}{dt}-\Gamma_\alpha\psi_\alpha+\Psi_\alpha\mathrm{tr}\,\mathbf{L}_\alpha. \tag{2.31}$$

Returning to (2.24), we shall take for the entropy flux:

$$\mathbf{H}_\alpha=\frac{\mathbf{q}_\alpha}{\theta}+\rho_\alpha\varphi_\alpha\eta_\alpha\mathbf{u}_\alpha+\mathbf{J}_\alpha. \tag{2.32}$$

Here $\mathbf{q}_\alpha/\theta$ is the standard entropy flux due to the influx of heat at an absolute temperature θ, $\rho_\alpha\varphi_\alpha\eta_\alpha\mathbf{u}_\alpha$ is the entropy flux due to the relative motion of the mixture to constituent α, and $\mathbf{J}_\alpha$ is the entropy flux due to chemical reactions, adhesion, and surface gradients in concentrations of volume fraction and will be defined more precisely below.

With (2.29)−(2.32) in force, and eliminating the energy supply $\hat{\varepsilon}_\alpha$ using (2.28), the entropy (Clausius−Duhem) inequality (2.24) assumes the form

$$\begin{aligned}\sum_{\alpha=1}^{N}\Bigg\{\frac{1}{\theta}\Bigg[&-\frac{d^\alpha\Psi_\alpha}{dt}-\rho_\alpha\varphi_\alpha\eta_\alpha\frac{d^\alpha\theta}{dt}+\mathrm{tr}(\mathbf{T}_\alpha^T-\Psi_\alpha\mathbf{I})\mathbf{L}_\alpha+\sum_{\beta=1}^{L}\zeta_{\alpha\beta}\frac{d^\alpha m_\beta}{dt}\\&+\sum_{\beta=1}^{N}\nabla\cdot\left(\boldsymbol{\sigma}_{\alpha\beta}\frac{d^\alpha\varphi_\beta}{dt}\right)-\left(\hat{\mathbf{p}}_\alpha+\frac{1}{2}\Gamma_\alpha\mathbf{v}_\alpha\right)\cdot\mathbf{v}_\alpha\Bigg]\\&-\frac{1}{\theta^2}\mathbf{q}_\alpha\cdot\mathbf{g}+\nabla\cdot\mathbf{J}_\alpha\Bigg\}\geq 0.\end{aligned} \tag{2.33}$$

We will return to this inequality after introducing general assumptions on the forms of constitutive equations.

3. General Forms of Constitutive Equations

We now close the system by introducing constitutive equations for the dependent variables: free energy, Cauchy stress, internal energy or entropy, heat flux, and the momentum. Since from the outset, we have ignored electromagnetic effects, we confine our attention hereafter to nonpolar materials, so that $\mathbf{M}_\alpha = 0$ and the partial stress tensors $\mathbf{T}_\alpha$ are symmetric. Throughout, we insist that the constitutive equations obey the restrictions imposed by the classical axiom of material frame indifference (as in Ref. 73).

Symbolically, we wish to supply frame indifferent constitutive equations for the thermomechanical fields

$$(\Psi_\alpha, \mathbf{T}_\alpha, \eta_\alpha, \mathbf{q}_\alpha, \hat{\mathbf{p}}_\alpha), \quad 1 \le \alpha \le N \tag{3.1}$$

in terms of an array $\mathbf{\Lambda}_\alpha$ of independent state variables, with equations for other quantities, such as $\boldsymbol{\sigma}_{\alpha\beta}$, $\zeta_{\alpha\beta}$, $\mathbf{j}_\alpha$, $\mathbf{J}_\alpha$ determined by requiring consistency with the second law of thermodynamics for the mixture.

We shall assume that the mixture consists of M solid constituents and $N - M$ fluid components, each of which may be heterogeneous, but which are pointwise isotropic. The M solid constituents are assumed to be heterogeneous isotropic hyperelastic materials, capable of undergoing large deformations, but extensions to anisotropic cases and even inelastic materials are readily handled. The partial stresses for the fluid phases are assumed to consist of the sum of an equilibrium stress $\mathbf{T}^e_\alpha$, which is characterized as that of a simple fluid (see Truesdell and Noll[72]) and a non-equilibrium thermoviscous stress $\mathbf{T}^v_\alpha$, the form of which must be consistent with the principle of material frame indifference and the entropy inequality. Thus, we take

$$\mathbf{\Lambda}_\alpha = \begin{cases} (\boldsymbol{X}_\alpha; \theta, \mathbf{g}, \mathbf{C}_\alpha, \boldsymbol{\varphi}, \nabla\boldsymbol{\varphi}, \hat{\mathbf{m}}_\alpha) & \text{for } \alpha \le M, \\ (\boldsymbol{x}_\alpha; \theta, \mathbf{g}, \mathbf{F}_\alpha, \boldsymbol{\varphi}, \nabla\boldsymbol{\varphi}, \hat{\mathbf{m}}_\alpha) & \text{for } M < \alpha \le N, \end{cases} \tag{3.2}$$

where

$$\left.\begin{aligned} &\mathbf{g} = \nabla\theta, \\ &\mathbf{C}_\alpha = \mathbf{F}_\alpha^T \mathbf{F}_\alpha, \\ &\boldsymbol{\varphi} = (\varphi_1, \varphi_2, \ldots, \varphi_N), \\ &\nabla\boldsymbol{\varphi} = (\nabla\varphi_1, \nabla\varphi_2, \ldots, \nabla\varphi_N), \\ &\hat{\mathbf{m}}_\alpha = (m_1\varphi_\alpha, m_2\varphi_\alpha, \ldots, m_L\varphi_\alpha), \end{aligned}\right\} \tag{3.3}$$

$\mathbf{C}_\alpha$ being the right Cauchy–Green deformation tensor. Due to (2.6), the φ_α's are not independent, so we take, in general,

$$\varphi_N = 1 - \sum_{\alpha=1}^{N-1} \varphi_\alpha. \tag{3.4}$$

In $(3.2)_2$, the dependence on $\mathbf{F}_\alpha$ is understood in a special way: for a simple fluid, $\mathbf{T}^e_\alpha$ and $\mathbf{q}_\alpha$ can depend on $\mathbf{F}_\alpha$ only through $\det \mathbf{F}_\alpha$ or through the mass density $\hat{\rho}_\alpha$

(see, e.g. Batra[11]). Under these conventions, we have:

$$\left.\begin{aligned}
&\Psi_\alpha = \Psi_\alpha(\mathbf{\Lambda}_\alpha), && 1 \le \alpha \le N,\\
&\mathbf{T}_\alpha = \mathbf{T}^e_\alpha + \mathbf{T}^v_\alpha, && 1 \le \alpha \le N,\\
&\mathbf{T}^e_\alpha = \mathbf{T}^{e_*}_\alpha(\mathbf{\Lambda}_\alpha), && 1 \le \alpha \le N,\\
&\mathbf{T}^v_\alpha = \mathbf{T}^{v_*}_\alpha(\mathbf{\Lambda}_\alpha), && M < \alpha \le N.
\end{aligned}\right\} \tag{3.5}$$

Using for simplicity the notation $d^\alpha(\cdot)/dt = (\dot{\cdot})$, it follows that

$$\begin{aligned}
\frac{d^\alpha \Psi_\alpha}{dt} = {} & \frac{\partial \Psi_\alpha}{\partial \theta}\dot{\theta} + \frac{\partial \Psi_\alpha}{\partial \mathbf{g}} \cdot \dot{\mathbf{g}} + \frac{\partial \Psi_\alpha}{\partial(\mathbf{C}_\alpha, \mathbf{F}_\alpha)} : \mathbf{D}_\alpha \\
& + \sum_{\beta=1}^{N} (\mu_{\alpha\beta}\dot{\varphi}_\beta + \nabla \cdot \boldsymbol{\sigma}_{\alpha\beta}\dot{\varphi}_\beta) + \sum_{\gamma=1}^{L} \frac{\partial \Psi_\alpha}{\partial(m_\gamma \varphi_\alpha)} \varphi_\alpha \dot{m}_\gamma \\
& + \sum_{\beta=1}^{N} \frac{\partial \Psi_\alpha}{\partial \nabla \varphi_\beta} \otimes (\nabla \dot{\varphi}_\beta - \nabla \mathbf{v}_\alpha \cdot \nabla \varphi_\beta)
\end{aligned} \tag{3.6}$$

with

$$\frac{\partial \Psi_\alpha}{\partial(\mathbf{C}_\alpha, \mathbf{F}_\alpha)} : \mathbf{D}_\alpha = \begin{cases} \dfrac{\partial \Psi_\alpha}{\partial \mathbf{C}_\alpha} : \dot{\mathbf{C}}_\alpha = 2\mathbf{F}^T_\alpha \dfrac{\partial \Psi_\alpha}{\partial \mathbf{C}_\alpha} \mathbf{F}_\alpha : \mathbf{D}_\alpha, & \alpha \le M, \\ \dfrac{\partial \Psi_\alpha}{\partial \mathbf{F}_\alpha} : \dot{\mathbf{F}}_\alpha = \dfrac{\partial \Psi_\alpha}{\partial \mathbf{F}_\alpha} \mathbf{F}^T_\alpha : \mathbf{D}_\alpha, & M < \alpha \le N, \end{cases} \tag{3.7}$$

where we have used the identities,

$$\left.\begin{aligned}
&\dot{\mathbf{C}}_\alpha = 2\mathbf{F}^T_\alpha \mathbf{D}_\alpha \mathbf{F}_\alpha, \\
&\mathbf{D}_\alpha = \frac{1}{2}(\nabla \mathbf{v}_\alpha + (\nabla \mathbf{v}_\alpha)^T), \\
&\dot{\overline{\nabla \varphi_\alpha}} = \nabla \dot{\varphi}_\alpha - \nabla \varphi_\alpha \cdot \nabla \mathbf{v}_\alpha,
\end{aligned}\right\} \tag{3.8}$$

and $\mu_{\alpha\beta}$ is the chemical potential

$$\mu_{\alpha\beta} = \frac{\partial \Psi_\alpha}{\partial \varphi_\beta} + \delta_{\alpha\beta} \sum_{\gamma=1}^{L} \frac{\partial \Psi_\alpha}{\partial(m_\gamma \varphi_\alpha)} m_\gamma - \nabla \cdot \boldsymbol{\sigma}_{\alpha\beta}. \tag{3.9}$$

Using another identity,

$$\begin{aligned}
\frac{d^\alpha \varphi_\beta}{dt} &= \dot{\varphi}_\beta \\
&= \frac{1}{\rho_\beta}\left[(\gamma_\beta - \nabla \cdot \mathbf{j}_\beta) - \varphi_\beta \frac{d^\alpha \rho_\beta}{dt} + (\mathbf{v}_\alpha - \mathbf{v}_\beta) \cdot \nabla(\rho_\beta \varphi_\beta) - \rho_\beta \varphi_\beta \operatorname{tr} \mathbf{L}_\beta\right],
\end{aligned} \tag{3.10}$$

where we have introduced (2.13) and (2.14); replace $\dot{\varphi}_\beta$ in the term $\sum_\beta \mu_{\alpha\beta}\dot{\varphi}_\beta$ by (3.10) and introduce the result into (2.33) to obtain

$$\sum_{\alpha=1}^{N}\Bigg\{\frac{1}{\theta}\Bigg[-\left(\frac{\partial\Psi_\alpha}{\partial\theta}+\rho_\alpha\varphi_\alpha\eta_\alpha\right)\dot{\theta}-\frac{\partial\Psi_\alpha}{\partial\mathbf{g}}\cdot\dot{\mathbf{g}}+\operatorname{tr}\Bigg[\mathbf{T}_\alpha-\left(\Psi_\alpha-\sum_{\beta=1}^{N}\varphi_\alpha\mu_{\beta\alpha}\right)\mathbf{I}$$
$$-\frac{\partial\Psi_\alpha}{\partial(\mathbf{C}_\alpha,\mathbf{F}_\alpha)}+\sum_{\beta=1}^{N}\frac{\partial\Psi_\alpha}{\partial\nabla\varphi_\beta}\otimes\nabla\varphi_\beta\Bigg]\mathbf{L}_\alpha+\sum_{\beta=1}^{N}\left(\boldsymbol{\sigma}_{\alpha\beta}-\frac{\partial\Psi_\alpha}{\partial\nabla\varphi_\beta}\right)\nabla\dot{\varphi}_\beta$$
$$+\sum_{\beta=1}^{N}\left(\boldsymbol{\zeta}_{\alpha\beta}-\frac{\partial\Psi_\alpha}{\partial(m_\beta\varphi_\alpha)}\varphi_\alpha\right)\dot{m}_\beta-\Bigg(\hat{\mathbf{p}}_\alpha+\frac{1}{2}\Gamma_\alpha\mathbf{v}_\alpha-\sum_{\beta=1}^{N}\Bigg[\frac{1}{\rho_\beta}\mu_{\alpha\beta}\nabla(\rho_\beta\varphi_\beta)$$
$$-\frac{1}{\rho_\alpha}\mu_{\beta\alpha}\nabla(\rho_\alpha\varphi_\alpha)\Bigg]\Bigg)\cdot\mathbf{v}_\alpha\Bigg]+R_\alpha-\frac{1}{\theta^2}\mathbf{g}\cdot\mathbf{q}_\alpha-\sum_{\beta=1}^{N}\nabla\left(\frac{\mu_{\alpha\beta}}{\rho_\beta}\right)\cdot\mathbf{j}_\beta\Bigg\}\geq 0, \tag{3.11}$$

where

$$R_\alpha=-\sum_{\beta=1}^{N}\frac{\mu_{\alpha\beta}}{\rho_\beta}\left[\gamma_\beta-\varphi_\beta\frac{d^\alpha\rho_\beta}{dt}\right] \tag{3.12}$$

and we have taken

$$\mathbf{J}_\alpha=-\sum_{\beta=1}^{N}\frac{\mu_{\alpha\beta}}{\rho_\beta}\mathbf{j}_\beta. \tag{3.13}$$

Invoking the classical Coleman and Noll[28] argument, since the rates in (3.11) can be varied arbitrarily, for (3.11) to hold it is sufficient that:

$$\left.\begin{aligned}
&\frac{\partial\Psi_\alpha}{\partial\theta}=-\rho_\alpha\varphi_\alpha\eta_\alpha,\\
&\frac{\partial\Psi_\alpha}{\partial\mathbf{g}}=\mathbf{0},\\
&\boldsymbol{\sigma}_{\alpha\beta}=\frac{\partial\Psi_\alpha}{\partial\nabla\varphi_\beta},\\
&\zeta_{\alpha\beta}=\frac{\partial\Psi_\alpha}{\partial(m_\beta\varphi_\alpha)}\varphi_\alpha,\\
&\mathbf{T}^e_\alpha=\left(\Psi_\alpha-\sum_{\beta=1}^{N}\mu_{\beta\alpha}\varphi_\alpha\right)\mathbf{I}+\frac{\partial\Psi_\alpha}{\partial(\mathbf{C}_\alpha,\mathbf{F}_\alpha)}-\sum_{\beta=1}^{N}\frac{\partial\Psi_\alpha}{\partial\nabla\varphi_\beta}\otimes\nabla\varphi_\beta
\end{aligned}\right\} \tag{3.14}$$

and

$$\sum_{\alpha=1}^{N}\Bigg\{\mathbf{T}_{\alpha}^{v*}(\mathbf{\Lambda}_{\alpha}):\mathbf{D}_{\alpha}+R_{\alpha}-\sum_{\beta=1}^{N}\nabla\left(\frac{\mu_{\beta\alpha}}{\rho_{\alpha}}\right)\cdot\mathbf{j}_{\alpha}-\frac{1}{\theta}\Bigg[\hat{\mathbf{p}}_{\alpha}+\frac{1}{2}\Gamma_{\alpha}\mathbf{v}_{\alpha}$$
$$-\sum_{\beta=1}^{N}\left(\frac{1}{\rho_{\beta}}\mu_{\alpha\beta}\nabla(\rho_{\beta}\varphi_{\beta})-\frac{1}{\rho_{\alpha}}\mu_{\beta\alpha}\nabla(\rho_{\alpha}\varphi_{\alpha})\right)\Bigg]\cdot\mathbf{v}_{\alpha}\Bigg\}\geq 0. \tag{3.15}$$

The first term on the left-hand side of inequality (3.15) can always be made non-negative by placing appropriate restrictions on the form of the constitutive equations for the viscous or dissipative part of the partial stress, as we show below. For the bracketed term in (3.15) to be non-negative, it is sufficient to take

$$\hat{\mathbf{p}}_{\alpha}=-\frac{1}{2}\Gamma_{\alpha}\mathbf{v}_{\alpha}+\sum_{\beta=1}^{N}\left(\frac{1}{\rho_{\beta}}\mu_{\alpha\beta}\nabla(\rho_{\beta}\varphi_{\beta})-\frac{1}{\rho_{\alpha}}\mu_{\beta\alpha}\nabla(\rho_{\alpha}\varphi_{\alpha})\right)-\lambda_{\alpha}\mathbf{v}_{\alpha} \tag{3.16}$$

with $\lambda_{\alpha}>0$. But there are infinitely many choices of such relations. Bowen[16] (p. 39), for example, has suggested as a typical constitutive equation for the momentum supply

$$\hat{\mathbf{p}}_{\alpha}=-\sum_{\beta=1}^{N}(\lambda_{\alpha\beta}\nabla(\rho_{\beta}\varphi_{\beta})+A_{\alpha\beta}\mathbf{v}_{\beta}-B_{\alpha}\mathbf{g}), \tag{3.17}$$

where $\lambda_{\alpha\beta}$, $A_{\alpha\beta}$, B_{α} are functions of $(\theta,\rho_1\varphi_1,\ldots,\rho_N\varphi_N)$. In the paper by Cristini *et al.*,[41] $\hat{\mathbf{p}}_{\alpha}$ is chosen to be of a form similar to (3.16) so as to reduce the momentum-supply term [in square brackets in (3.15)] to a non-negative contribution (in our case, to $\theta^{-1}\lambda_{\alpha}\mathbf{v}_{\alpha}\cdot\mathbf{v}_{\alpha}$). See also Araujo and McElwain.[7]

If we demand that the mass-supply-rate R_{α} in (3.12) be non-negative, then we can interpret $R_{\alpha}\geq 0$ as a constraint on the rate at which the constituent mass densities ρ_{β} can change for given thermodynamic potential $\mu_{\alpha\beta}$, given mass supply γ_{β}, and volume fraction ϕ_{β}.

Returning to the last term on the right-hand side of inequality (3.15), we render it non-negative by introducing the constitutive equation for total mass flux,

$$\mathbf{j}_{\alpha}=-\sum_{\beta=1}^{N}M_{\beta\alpha}(\boldsymbol{\varphi},\mathbf{m}_{\alpha})\nabla(\mu_{\beta\alpha}/\rho_{\alpha}), \tag{3.18}$$

where $M_{\beta\alpha}$ is a symmetric positive-semi-definite matrix, possibly dependent on the volume fractions $\boldsymbol{\varphi}=(\varphi_1,\varphi_2,\ldots,\varphi_N)$ and the taxis factors $m_1\varphi_{\alpha},m_2\varphi_{\alpha},\ldots,m_L\varphi_{\alpha}$, called the mobility of the mixture. The last term on the left-hand side of (3.15) is then always non-negative. Reviewing the derivation of (3.15) and assuming that $\hat{\mathbf{p}}_{\alpha}$ is given by (3.16), one can argue that the mobility $M_{\beta\alpha}$ can conceivably be negative definite if we demand that

$$\sum_{\alpha=1}^{N}\sum_{\beta=1}^{N}(\rho_{\beta}^{-1}\mu_{\alpha\beta}\gamma_{\beta}-\nabla(\mu_{\alpha\beta}/\rho_{\beta})\cdot\mathbf{j}_{\beta})\geq 0. \tag{3.19}$$

However, the question of existence of solutions of the governing balance equations may then become an issue.

Partial stress and heat flux. Returning to (3.14) and recalling the notation introduced in (3.3), we observe that the mechanical part of the equilibrium partial stress $\hat{\mathbf{T}}_\alpha^e$ (that in response to deformation and flow) can be written as

$$\left.\begin{aligned} \hat{\mathbf{T}}_\alpha^e &= 2\mathbf{F}_\alpha^T \frac{\partial \Psi_\alpha}{\partial \mathbf{C}_\alpha}\mathbf{F}_\alpha = \frac{1}{\det \mathbf{F}_\alpha}\mathbf{F}_\alpha \mathbf{S}_\alpha \mathbf{F}_\alpha^T, \quad \alpha \le M, \\ \hat{\mathbf{T}}_\alpha^e &= \frac{\partial \Psi_\alpha}{\partial \mathbf{F}_\alpha}\mathbf{F}_\alpha^T = \frac{\partial \Psi_\alpha}{\partial \hat{\rho}_\alpha}\frac{\partial \hat{\rho}_\alpha}{\mathbf{F}_\alpha^T} = -\pi_\alpha, \qquad M < \alpha \le N, \end{aligned}\right\} \tag{3.20}$$

where $\rho_{0\alpha}\varphi_{0\alpha} = \hat{\rho}_{0\alpha}$ is the mass density of the αth constituent in the reference configuration, $\mathbf{S}_\alpha$ is the partial second Piola–Kirchhoff stress tensor,

$$\mathbf{S}_\alpha = \det \mathbf{F}_\alpha \mathbf{F}_\alpha^{-1}\hat{\mathbf{T}}_\alpha \mathbf{F}_\alpha^{-T} = 2\frac{\partial W_\alpha}{\partial \mathbf{C}_\alpha}, \quad \alpha \le M \tag{3.21}$$

with $W_\alpha = \hat{\rho}_{0\alpha}\psi_\alpha$, and π_α is the thermodynamic pressure,

$$\pi_\alpha(\theta, \hat{\rho}_\alpha, \boldsymbol{\varphi}, \mathbf{m}_\alpha) = -\hat{\rho}_\alpha^2 \frac{\partial \psi_\alpha}{\partial \hat{\rho}_\alpha}, \quad M < \alpha \le N. \tag{3.22}$$

In (3.20), W_α represents the stored energy function for the αth constituent, $\alpha \le M$.

Hereafter, we assume that the M solid constituents of the mixture are isotropic and hyperelastic so that W_α represents a stored energy function for the αth constituent. To comply with the requirement of frame indifference, we take W_α to be a differentiable function of the principal invariants $\mathrm{I}_{\mathbf{C}_\alpha}^\alpha$, $\mathrm{II}_{\mathbf{C}_\alpha}^\alpha$, $\mathrm{III}_{\mathbf{C}_\alpha}^\alpha$ of $\mathbf{C}_\alpha$. Then

$$\mathbf{S}_\alpha = \frac{\partial W_\alpha}{\partial \mathrm{I}_{\mathbf{C}_\alpha}^\alpha}\mathbf{I} + \frac{\partial W_\alpha}{\partial \mathrm{II}_{\mathbf{C}_\alpha}^\alpha}(\operatorname{tr}\mathbf{C}_\alpha^{-1}\mathbf{I} - \mathbf{C}_\alpha^{-T}\operatorname{Cof}\mathbf{C}_\alpha) + \frac{\partial W_\alpha}{\partial \mathrm{III}_{\mathbf{C}_\alpha}^\alpha}\operatorname{Cof}\mathbf{C}_\alpha, \tag{3.23}$$

where $\operatorname{Cof}\mathbf{C}_\alpha$ is the cofactor tensor of $\mathbf{C}_\alpha$. Let $\mathbf{w}_\alpha$ denote the displacement of particle $\mathbf{X}_\alpha$ from the reference configuration of the αth constituent: $\mathbf{w}_\alpha = \boldsymbol{\chi}_\alpha(\mathbf{X}_\alpha, t) - \mathbf{X}_\alpha$. Then $\mathbf{C}_\alpha$ can be expressed as a function of the displacement gradients,

$$\hat{\mathbf{H}}_\alpha = \operatorname{GRAD}\mathbf{w}_\alpha, \quad \mathbf{C}_\alpha = \mathbf{I} + \hat{\mathbf{H}}_\alpha \tag{3.24}$$

and (3.23) can, in general, be expressed as a function of $\hat{\mathbf{H}}_\alpha$. If $\hat{\rho}_{0\alpha} = \rho_{0\alpha}\varphi_{0\alpha}$ is the mass density of the αth constituent in the reference configuration, then the momentum balance for the M solid constituents can be written as

$$\rho_{0\alpha}\varphi_{0\alpha}\frac{\partial^2 \mathbf{w}_\alpha}{\partial t^2} = \operatorname{Div}(\det \mathbf{F}_\alpha \mathbf{T}_\alpha \mathbf{F}_\alpha^{-T}) + \rho_{0\alpha}\varphi_{0\alpha}\mathbf{b}_{0\alpha} + \mathbf{P}_{0\alpha}, \quad \alpha \le M, \tag{3.25}$$

$\mathbf{b}_{0\alpha}$ being the body force and $\mathbf{P}_{0\alpha}$ the momentum supplied in the reference configuration and $\mathbf{T}_\alpha$ is now given by (3.14) for $\alpha \le M$.

We shall assume that the dissipative partial stress is representable as a general isotropic second-order tensor function of the deformation rate $\mathbf{D}_\alpha$ and the

temperature gradient $\mathbf{g}$

$$\begin{aligned}\mathbf{T}_\alpha^{v*}(\mathbf{\Lambda}_\alpha) &= \mathbf{T}_\alpha^{v*}(\theta, \mathbf{D}_\alpha, \mathbf{g}, \boldsymbol{\varphi}, \mathbf{m}_\alpha)\\ &= A_{1\alpha}\mathbf{D}_\alpha + A_{2\alpha}\mathbf{D}_\alpha^2 + A_{3\alpha}\mathbf{g}\otimes\mathbf{g}\\ &\quad + A_{4\alpha}(\mathbf{g}\otimes\mathbf{D}_\alpha\mathbf{g}) + A_{5\alpha}(\mathbf{g}\otimes\mathbf{D}_\alpha^2\mathbf{g})\end{aligned} \tag{3.26}$$

and that likewise the heat flux is an isotropic vector-valued function,

$$\begin{aligned}\mathbf{q}_\alpha &= \mathbf{q}_\alpha^*(\theta, \mathbf{D}_\alpha, \mathbf{g}, \boldsymbol{\varphi}, \mathbf{m}_\alpha)\\ &= -k_{1\alpha}\mathbf{g} - k_{2\alpha}\mathbf{D}_\alpha\mathbf{g} - k_{3\alpha}\mathbf{D}_\alpha^2\mathbf{g},\end{aligned} \tag{3.27}$$

where the viscosities $A_{i\alpha}$, $i = 1, 2, \ldots, 5$ are functions of position $\mathbf{x}$ and of possibly θ, $\hat{\rho}_\alpha$, $\operatorname{tr}\mathbf{D}_\alpha^2$, $\operatorname{tr}\mathbf{D}_\alpha^3$, $\mathbf{g}$, $\mathbf{D}_\alpha\mathbf{g}$, $\boldsymbol{\varphi}$, $\mathbf{m}_\alpha$ and $\mathbf{g}\cdot\mathbf{D}_\alpha^2\mathbf{g}$, and the thermal conductivities $k_{j\alpha}$, $j = 1, 2, 3$, may likewise be functions of these variables. The material functions $A_{i\alpha}$, $i = 1, 2, \ldots, 5$ are chosen so that $\operatorname{tr}\mathbf{T}_\alpha^{v*}(\mathbf{\Lambda}_\alpha)\mathbf{D}_\alpha \geq 0$ in (3.15) and likewise $k_{1\alpha}$, $k_{2\alpha}$, and $k_{3\alpha}$ must be such that $-\theta^2\mathbf{g}\cdot\mathbf{q}_\alpha \geq 0$ in (3.15). It is also understood that for $\alpha \leq M$, we replace $\mathbf{g}$ by $\mathbf{G}_\alpha = \mathbf{F}_\alpha^T\mathbf{g}$, the material temperature gradient for constituent α.

Introducing (3.20)−(3.23) into $(3.5)_2$, we arrive at the constitutive equations for partial stress:

$$\mathbf{T}_\alpha = \begin{cases} \left(\Psi_\alpha - \displaystyle\sum_{\beta=1}^{N}\mu_{\beta\alpha}\varphi_\alpha\right)\mathbf{I} + (\det\mathbf{F}_\alpha)^{-1}\mathbf{F}_\alpha\mathbf{S}_\alpha\mathbf{F}_\alpha^T \\ \qquad\qquad - \displaystyle\sum_{\beta=1}^{N}\frac{\partial\Psi_\alpha}{\partial\nabla\varphi_\beta}\otimes\nabla\varphi_\beta, \quad \alpha \leq M, \\ \left(\Psi_\alpha - \displaystyle\sum_{\beta=1}^{N}\mu_{\beta\alpha}\varphi_\alpha - \pi_\alpha\right)\mathbf{I} + \mathbf{T}_\alpha^{v*}(\mathbf{D}_\alpha, \mathbf{g}) \\ \qquad\qquad - \displaystyle\sum_{\beta=1}^{N}\frac{\partial\Psi_\alpha}{\partial\nabla\varphi_\beta}\otimes\nabla\varphi_\beta, \quad M < \alpha \leq N, \end{cases} \tag{3.28}$$

where $\mathbf{S}_\alpha$ is given by (3.23) and $\mathbf{T}_\alpha^{v*}(\mathbf{D}_\alpha, \mathbf{g})$ by (3.26). The relations (3.28) generalize those in the study of Araujo and McElwain[7] involving a single linearly elastic isotropic solid and a viscous fluid.

We remark that further simplifications in choosing forms of the constitutive equations are possible if we invoke the "Principle of Phase Separation" advocated by Passman, Nunziato, and Walsh[61] and employed by Araujo and McElwain.[8] According to this principle, material-specific dependent variables of a given phase (e.g. stress, free energy, etc.) depend only on the independent variables of that phase while the interaction variables (e.g. mass flux, momentum supply) depend on all independent variables. Rajagopal and Tao[65] attribute this idea to Adkins[1] and argue that a careful study would cast doubt on the status of this hypothesis as a principle since "the internal state of the one mathematical continuum unlike the associated

state of its physical phase depends upon the state of another mathematical concentration".

Growth effects. The inclusion of growth effects due to mass exchange and deformation had been considered in tumor growth models by several authors; see in particular the works of Ambrosi and Mollica,[3,4] Araujo and McElwain,[7] Preziosi and Farina,[63] and Byrne and Preziosi[21] and the book edited by Preziosi.[64] In Araujo and McElwain,[7] growth in the volume fractions of the solid phases ($\alpha \leq M$) takes the form of the change in gradients $\partial\varphi_\alpha/\partial\mathbf{F}_\alpha$ due to mass exchange. In our model, this is characterized by

$$\begin{aligned}\frac{d^\alpha}{dt}(\rho_\alpha\varphi_\alpha \det\mathbf{F}_\alpha) &= \det\mathbf{F}_\alpha[(\gamma_\alpha - \nabla\cdot\mathbf{j}_\alpha) + \rho_\alpha\varphi_\alpha \mathrm{tr}\,\mathbf{L}_\alpha - \rho_\alpha\varphi_\alpha \mathrm{tr}\,\mathbf{L}_\alpha] \\ &= \Gamma_\alpha \det\mathbf{F}_\alpha. \end{aligned} \tag{3.29}$$

Thus,

$$\rho_\alpha\varphi_\alpha \det\mathbf{F}_\alpha = U_\alpha, \tag{3.30}$$

where

$$U_\alpha = \rho_{0\alpha}\phi_{0\alpha} + \int_0^t \Gamma_\alpha(\mathbf{X}_\alpha, s)\det\mathbf{F}_\alpha(\mathbf{X}_\alpha, s)ds. \tag{3.31}$$

Then

$$\frac{\partial\rho_\alpha\varphi_\alpha}{\partial\mathbf{F}_\alpha} = (\det\mathbf{F}_\alpha)^{-1}\frac{\partial U_\alpha}{\partial\mathbf{F}_\alpha} - \rho_\alpha\varphi_\alpha \mathrm{Cof}\,\mathbf{F}_\alpha, \tag{3.32}$$

where $\mathrm{Cof}\,\mathbf{F}_\alpha$ is the cofactor tensor of $\mathbf{F}_\alpha$ $(=\det\mathbf{F}_\alpha\mathbf{F}_\alpha^{-T})$, and

$$\mathbf{S}_\alpha = 2\frac{\partial\Psi_\alpha}{\partial\mathbf{C}_\alpha} = \mathbf{F}_\alpha^{-1}\left(\rho_\alpha\varphi_\alpha\frac{\partial\Psi_\alpha}{\partial\mathbf{F}_\alpha} + \Psi_\alpha(\det\mathbf{F}_\alpha)^{-1}\frac{\partial U_\alpha}{\partial\mathbf{F}_\alpha} - \rho_\alpha\varphi_\alpha\mathrm{Cof}\,\mathbf{F}_\alpha\right). \tag{3.33}$$

Similar growth effects can be derived for the fluid constituents. Hereafter, we assume that such effects are implicit in the terms involving $\mathbf{S}_\alpha$ and π_α.

Summary. We collect principal results derived up to this point in Table 1. Note that since we have invoked as a constraint on constituent temperatures that $\theta_1 = \theta_2 = \cdots = \theta_N = \theta$, it makes sense to formulate an energy equation for the entire mixture as the sum of the individual constituent balance laws to acquire a single equation for a single temperature.

4. Diffuse-Interface Models

An important class of diffuse-interface or phase-field models of materials of the Cahn–Hilliard type is characterized by a Helmholtz free energy for each constituent of the form

$$\Psi_\alpha = \Psi_{0\alpha}(\mathbf{\Lambda}^0_\alpha) + \varphi_\alpha\sum_{\beta=1}^{L} a_{\alpha\beta}m_\beta + \sum_{\beta=1}^{N}\frac{\varepsilon_{\alpha\beta}}{2}|\nabla\varphi_\beta|^2, \tag{4.1}$$

Table 1. General governing equations for a mixture composed of N constituents of which M are solids and $N - M$ are fluids.

Balance of mass

$$\frac{\partial \rho_\alpha \varphi_\alpha}{\partial t} + \nabla \cdot (\rho_\alpha \varphi_\alpha \mathbf{v}_\alpha) = \gamma_\alpha - \nabla \cdot \mathbf{j}_\alpha$$

Balance of linear momentum

$$\rho_\alpha \varphi_\alpha \frac{d^\alpha \mathbf{v}_\alpha}{dt} = \nabla \cdot \mathbf{T}_\alpha + \rho_\alpha \varphi_\alpha \mathbf{b}_\alpha + \hat{\mathbf{p}}_\alpha$$

Balance of energy

$$-\rho\theta \frac{d}{dt}\left(\frac{1}{\rho}\sum_{\alpha=1}^{N}\frac{\partial \Psi_\alpha}{\partial \theta}\right) = \sum_{\alpha=1}^{N}\Bigg\{\operatorname{tr}\mathbf{T}_\alpha^{v_*}(\mathbf{\Lambda}_\alpha)\mathbf{D}_\alpha - \left(\hat{\mathbf{p}}_\alpha + \frac{1}{2}\Gamma_\alpha \mathbf{v}_\alpha\right)\cdot \mathbf{v}_\alpha + \sum_{\beta=1}^{N}\rho_\beta^{-1}\mu_{\alpha\beta}\left(\nabla \cdot \mathbf{j}_\alpha + \nabla(\rho_\beta\varphi_\beta)\cdot \mathbf{v}_\alpha - \gamma_\beta + \varphi_\beta \frac{d^\alpha \rho_\beta}{dt}\right) - \nabla \cdot \mathbf{q}_\alpha^*(\mathbf{\Lambda}_\alpha) - \theta \nabla \cdot (\rho_\alpha \varphi_\alpha \eta_\alpha \mathbf{u}_\alpha)\Bigg\} + \rho r$$

Constitutive equations

$$\frac{\partial \Psi_\alpha}{\partial \theta} = -\rho_\alpha \varphi_\alpha \eta_\alpha, \quad \boldsymbol{\sigma}_{\alpha\beta} = \frac{\partial \Psi_\alpha}{\partial \nabla \varphi_\beta}, \quad \zeta_{\alpha\beta} = \frac{\partial \Psi_\alpha}{\partial (m_\beta \varphi_\alpha)}\varphi_\alpha$$

$$\mathbf{T}_\alpha = \left(\Psi_\alpha - \sum_{\beta=1}^{N}\mu_{\beta\alpha}\varphi_\alpha - X_\alpha\right)\mathbf{I} + Y_\alpha - \sum_{\beta=1}^{N}\frac{\partial \Psi_\alpha}{\partial \nabla \varphi_\beta}\otimes \nabla \varphi_\beta$$

$$\text{where } \begin{cases} X_\alpha = 0 & Y_\alpha = (\det \mathbf{F}_\alpha)^{-1}\,\mathbf{F}_\alpha \mathbf{S}_\alpha \mathbf{F}_\alpha^T \quad \alpha \le M \\ X_\alpha = \pi_\alpha & Y_\alpha = \mathbf{T}_\alpha^{v_*}(\mathbf{\Lambda}_\alpha) \qquad\qquad\quad M < \alpha \le N \end{cases}$$

$$\mathbf{T}_\alpha^{v_*}(\mathbf{\Lambda}_\alpha) = A_{1\alpha}\mathbf{D}_\alpha + A_{2\alpha}\mathbf{D}_\alpha^2 + A_{3\alpha}\mathbf{g}\otimes\mathbf{g} + A_{4\alpha}\mathbf{g}\otimes\mathbf{D}_\alpha\mathbf{g} + A_{5\alpha}\mathbf{g}\otimes\mathbf{D}_\alpha^2\mathbf{g}$$

$$\mathbf{q}_\alpha^*(\mathbf{\Lambda}_\alpha) = -k_{1\alpha}\mathbf{g} - k_{2\alpha}\mathbf{D}_\alpha\mathbf{g} - k_{3\alpha}\mathbf{D}_\alpha^2\mathbf{g}$$

$$\mathbf{S}_\alpha = \mathbf{F}_\alpha^{-1}\left(\rho_\alpha\varphi_\alpha\frac{\partial \Psi_\alpha}{\partial \mathbf{F}_\alpha} + \Psi_\alpha(\det \mathbf{F}_\alpha)^{-1}\frac{\partial U_\alpha}{\partial \mathbf{F}_\alpha} - \rho_\alpha\varphi_\alpha \operatorname{Cof}\mathbf{F}_\alpha\right)$$

$$U_\alpha = \rho_{0\alpha}\phi_{0\alpha} + \int_0^t (\gamma_\alpha - \nabla\cdot\mathbf{j}_\alpha)(\mathbf{X}_\alpha, s)\det\mathbf{F}_\alpha(\mathbf{X}_\alpha, s)ds$$

$$\hat{\mathbf{p}}_\alpha = -\frac{1}{2}\Gamma_\alpha\mathbf{v}_\alpha + \sum_{\beta=1}^{N}(\rho_\beta^{-1}\mu_{\alpha\beta}\nabla(\rho_\beta\varphi_\beta) - \rho_\alpha^{-1}\mu_{\beta\alpha}\nabla(\rho_\alpha\varphi_\alpha)) - \lambda_\alpha\mathbf{v}_\alpha$$

$$\mathbf{j}_\alpha = -\sum_{\beta=1}^{N}M_{\alpha\beta}(\boldsymbol{\varphi}, \mathbf{m}_\alpha)\nabla(\mu_{\alpha\beta}/\rho_\alpha)$$

$$\mu_{\alpha\beta} = \frac{\partial \Psi_\alpha}{\partial \varphi_\beta} + \delta_{\alpha\beta}\sum_{\gamma=1}^{L}m_\gamma\zeta_{\alpha\beta}/\varphi_\alpha - \nabla\cdot\boldsymbol{\sigma}_{\alpha\beta}$$

where

$$\mathbf{\Lambda}_\alpha^0 = \begin{cases}(\mathbf{X}_\alpha; \theta, \mathbf{C}_\alpha, \boldsymbol{\varphi}), & \alpha \le M, \\ (\mathbf{x}_\alpha = \boldsymbol{\chi}_\alpha(\mathbf{X}_\alpha, t); \theta, \mathbf{F}_\alpha, \boldsymbol{\varphi}), & M < \alpha \le N. \end{cases} \tag{4.2}$$

The addition of the second term in (4.1) is inspired by the work of Cristini *et al.*[30] and describes a linear dependence of the free energy on the "concentrations (m_β) of

taxis-inducing chemical and molecular species". The $a_{\alpha\beta}$ are taxis coefficients. The last term in (4.1) represents the effects of large gradients in concentrations that occur at interface regions between different constituents. We shall assume that the $\varepsilon_{\alpha\beta}$ are constants. Papatzacos[60] refers to these parameters as the Landau−Ginzburg constants.

With (4.1) in force, we have via (3.14)

$$\left.\begin{aligned} \boldsymbol{\sigma}_{\alpha\beta} &= \varepsilon_{\alpha\beta}\nabla\varphi_\beta, \\ \zeta_{\alpha\beta} &= a_{\alpha\beta}\varphi_\alpha, \\ \mu_{\alpha\beta} &= f_{\alpha\beta} - \varepsilon_{\alpha\beta}\Delta\varphi_\beta, \end{aligned}\right\} \tag{4.3}$$

where

$$f_{\alpha\beta} = f_{\alpha\beta}(\boldsymbol{\Lambda}^0{}_\alpha, \mathbf{m}) = \frac{\partial\Psi_{0\alpha}}{\partial\varphi_\beta} + \delta_{\alpha\beta}\sum_{\gamma=1}^{L} a_{\alpha\gamma}m_\gamma \tag{4.4}$$

and Δ denotes the spatial Laplacian operator ($\Delta = \nabla\cdot\nabla$). Assuming (3.18) holds, the equations describing the evolution of mass concentrations (recall (2.14)) become

$$\frac{\partial\rho_\alpha\varphi_\alpha}{\partial t} = \nabla\cdot\left(\sum_{\beta=1}^{N} M_{\alpha\beta}(\boldsymbol{\varphi}, \boldsymbol{m}_\alpha)\nabla(f_{\alpha\beta} - \varepsilon_{\alpha\beta}\Delta\varphi_\beta)/\rho_\beta\right) + \gamma_\alpha - \nabla\cdot(\rho_\alpha\varphi_\alpha\mathbf{v}_\alpha). \tag{4.5}$$

This represents a system of N fourth-order-in-space, parabolic partial differential equations of the Cahn−Hilliard type. For $\alpha \le M$, the momentum equations for this case become

$$\begin{aligned} \rho_{0\alpha}\varphi_{0\alpha}\frac{\partial^2\mathbf{w}_\alpha}{\partial t^2} = \operatorname{Div}\mathbf{F}_\alpha\Bigg\{ &\det\mathbf{F}_\alpha\mathbf{F}_\alpha^{-1}\left[\left(\Psi_\alpha - \sum_{\beta=1}^{N}(f_{\beta\alpha} - \varepsilon_{\alpha\beta}\Delta\varphi_\beta)\varphi_\alpha\right)\mathbf{I}\right] \\ &+ \mathbf{S}_\alpha - \det\mathbf{F}_\alpha\mathbf{F}_\alpha\left(\sum_{\beta=1}^{N}\varepsilon_{\alpha\beta}\nabla\varphi_\beta\otimes\nabla\varphi_\beta\right)\mathbf{F}_\alpha^{-T}\Bigg\} \\ &+ \rho_{0\alpha}\varphi_{0\alpha}\mathbf{b}_{0\alpha} + \hat{\mathbf{P}}_{0\alpha}, \end{aligned} \tag{4.6}$$

and for $M < \alpha \le N$

$$\begin{aligned} \rho_\alpha\varphi_\alpha\frac{d^\alpha\mathbf{v}_\alpha}{dt} = \nabla\cdot\Bigg[&\left(\Psi_\alpha - \hat{\rho}_\alpha\pi_\alpha - \sum_{\beta=1}^{N}(f_{\beta\alpha} - \varepsilon_{\alpha\beta}\Delta\varphi_\beta)\varphi_\alpha\right)\mathbf{I} \\ &+ \mathbf{T}_\alpha^{v_*}(\mathbf{D}_\alpha, \mathbf{g}) - \sum_{\beta=1}^{N}\varepsilon_{\alpha\beta}\nabla\varphi_\beta\otimes\nabla\varphi_\beta\Bigg] + \rho_\alpha\varphi_\alpha\mathbf{b}_\alpha + \hat{\mathbf{p}}_\alpha. \end{aligned} \tag{4.7}$$

For the momentum supply, (3.16) reduces to

$$\begin{aligned} \hat{\mathbf{p}}_\alpha = -\frac{1}{2}\Gamma_\alpha\mathbf{v}_\alpha + \sum_{\beta=1}^{N}\Bigg[&\frac{1}{\rho_\beta}(f_{\alpha\beta} - \varepsilon_{\alpha\beta}\Delta\varphi_\beta)\nabla(\rho_\beta\varphi_\beta) \\ &- \frac{1}{\rho_\alpha}(f_{\beta\alpha} - \varepsilon_{\beta\alpha}\Delta\varphi_\alpha)\nabla(\rho_\alpha\varphi_\alpha)\Bigg] - \lambda_\alpha\mathbf{v}_\alpha. \end{aligned} \tag{4.8}$$

In (4.6), $\mathbf{S}_\alpha$ is given in (3.23), and $\hat{\mathbf{P}}_{0\alpha}$ is the momentum supplied to the αth constituent referred to in the reference configuration. In (4.7), $\mathbf{T}_\alpha^{v_*}(\mathbf{D}_\alpha, \mathbf{g})$ is given by (3.26). Finally, the energy balance equation now takes the specific form

$$
\begin{aligned}
-\rho\theta \frac{d}{dt}\left(\rho^{-1}\sum_{\alpha=1}^{N}\frac{\partial \Psi_\alpha}{\partial \theta}\right) = \sum_{\alpha=1}^{N}\Bigg\{ & \operatorname{tr}\mathbf{T}_\alpha^{v_*}(\mathbf{\Lambda}_\alpha)\mathbf{D}_\alpha - \left(\hat{\mathbf{p}}_\alpha + \frac{1}{2}\Gamma_\alpha \mathbf{v}_\alpha\right)\cdot \mathbf{v}_\alpha \\
& - \nabla\cdot \mathbf{q}_\alpha^*(\mathbf{\Lambda}_\alpha) + \sum_{\beta=1}^{N}\rho_\beta^{-1}\left(f_{\alpha\beta} - \varepsilon_{\alpha\beta}\Delta\varphi_\beta\right) \\
& \times\left(\nabla\cdot \mathbf{j}_\alpha + \nabla\left(\rho_\beta\varphi_\beta\right)\cdot \mathbf{v}_\alpha - \gamma_\beta + \varphi_\beta \frac{d^\alpha \rho_\beta}{dt}\right) \\
& - \theta\nabla\cdot\left(\rho_\alpha\varphi_\alpha\eta_\alpha \mathbf{u}_\alpha\right)\Bigg\} + \rho r, \qquad (4.9)
\end{aligned}
$$

where $\mathbf{q}_\alpha^*(\mathbf{\Lambda}_\alpha)$ is defined by (3.27), $\psi_\alpha = \Psi_\alpha/\rho_\alpha\varphi_\alpha$ and $f_{\alpha\beta}$ is defined in (4.4).

Since $\mathbf{j}_\alpha$ is determined by (3.18) for given thermodynamic potentials $\mu_{\alpha\beta}$, the remaining quantities that need to be defined are the mass supply γ_α and the energy supply ε_α. These quantities must, in general, be determined through a separate relation that characterizes the mass supply and energy supply as functions of the concentration of nutrients.

Equations (4.5)−(4.9), together with appropriate boundary and initial conditions, characterize a general diffuse-interface, continuum mixture model of the thermomechanical behavior of a complex media consisting of multiple solid and fluid constituents. The constituents can be compressible, the fluid species non-Newtonian, and effects of taxis-inducing chemical and molecular species and surface effects due to gradients in concentrations are taken into account.

To apply such general models in meaningful simulations, several additional developments are needed. First, we must define more specific forms of the constitutive equations and, in general, simplify the system to make it tractable. This involves simplifying assumptions. But with each such assumption, a possible loss in predictability of the model arises. Ultimately, the predictability of the model will depend on three things: the validity of the theory itself and its ability to yield meaningful abstractions of actual physical events, the availability of data on model parameters, including their uncertainty, and the availability of observational data through experiments, tests, and imaging, and their uncertainties. All of these components form the basis of Bayesian methods for calibration and validation, which we take up in Sec. 6. Ultimately, we must also solve the equations governing the model. This, of course, is a formidable challenge.

5. Examples and Special Cases

As can be seen from Table 1, the particular form of the Helmholtz Free Energy ultimately defines many of the constitutive equations. Thus, different forms of the

free energy define different specialized models. Various specialized models can be found in the literature which can be deduced from our general theory through a sequence of simplifying assumptions. We describe here a few such special cases, although many others could be cited. We note that it is often assumed that the constituents are incompressible and that the mixture is isothermal. This first assumption renders ρ_α constant for all α while the second assumption eliminates the need to solve the energy equation and thus implies no specific form for $\mathbf{q}_\alpha^*$ is needed.

5.1. *A reduced model of isothermal, Newtonian or Stokesian fluids*

We consider as an example the special case of a model of a mixture of four incompressible viscous fluids with $\rho_1 = \rho_2 = \rho_3 = \rho_4 = \rho$ and with mass supplied in proportion to the respective volume fractions φ_α: $\gamma_\alpha = a_\alpha \varphi_\alpha$, $a_\alpha =$ constant. We consider isothermal processes for which the free energy per unit volume is given by

$$\Psi_\alpha = \frac{c_\alpha}{8}\varphi_\alpha^2(\varphi_\alpha - 1)^2 + \frac{\varepsilon}{2}|\nabla\varphi_\alpha|^2, \quad 1 \le \alpha \le 4 \tag{5.1}$$

with $c_\alpha > 0$ and it is understood that $\phi_4 = 1 - \phi_1 - \phi_2 - \phi_3$. In this case,

$$\mu_{\alpha\beta} = \mu_\alpha = \frac{c_\alpha}{4}\left(2\varphi_\alpha^3 - 3\varphi_\alpha^2 + \varphi_\alpha\right) - \varepsilon\Delta\varphi_\alpha. \tag{5.2}$$

We assume constant mobility M which is the same for each constituent so that

$$\mathbf{j}_\alpha = -M\nabla\mu_\alpha = -M\Big(\frac{c_\alpha}{4}\nabla\left(2\varphi_\alpha^3 - 3\varphi_\alpha^2 + \varphi_\alpha\right) - \varepsilon\nabla\Delta\varphi_\alpha\Big). \tag{5.3}$$

Thus, the mass balance equations are

$$\rho\frac{\partial\varphi_\alpha}{\partial t} = a\varphi_\alpha + M\frac{c_\alpha}{4}\Delta(2\varphi_\alpha - 3\varphi_\alpha^2 + \varphi_\alpha) - \varepsilon M\Delta^2\varphi_\alpha - \rho\nabla\cdot(\varphi_\alpha\mathbf{v}_\alpha). \tag{5.4}$$

The equilibrium Cauchy partial stress is

$$\mathbf{T}_\alpha^e(\varphi_\alpha) = \mathbf{F}_\alpha^e(\varphi_\alpha) - p_\alpha\mathbf{I}, \tag{5.5}$$

with

$$\mathbf{F}_\alpha^e = -\sum_{\beta=1}^{4}\mu_\beta\varphi_\alpha\mathbf{I} - \varepsilon\nabla\varphi_\alpha\otimes\nabla\varphi_\alpha, \tag{5.6}$$

where p_α is the hydrostatic pressure ($p_\alpha = \pi_\alpha - \Psi_\alpha$ in $(3.28)_2$). For the viscous part of the partial stress, we first consider an isotropic Newtonian fluid,

$$\mathbf{T}_\alpha^{v*} = 2\nu_\alpha(\varphi_\alpha)\mathbf{D}_\alpha, \tag{5.7}$$

where $\nu_\alpha(\varphi_\alpha)$ is the viscosity and $\operatorname{tr}\mathbf{D}_\alpha = 0$. Thus, the balance of momentum equations are

$$\rho_\alpha\varphi_\alpha\frac{d^\alpha\mathbf{v}_\alpha}{dt} = \nu_\alpha(\varphi_\alpha)\Delta\mathbf{v}_\alpha - \nabla p_\alpha + \hat{\mathbf{p}}_\alpha - \nabla\cdot\mathbf{F}_\alpha^e. \tag{5.8}$$

Now other special cases of interest can be deduced from (5.8). First, the momentum supply can be equated with a vector proportional to the difference between $\mathbf{v}_\alpha$ and the velocities of other constituents

$$\hat{\mathbf{p}}_\alpha = d_\alpha \left(\mathbf{v}_\alpha - \sum_{\beta=1}^{N} \mathbf{v}_\beta \right), \tag{5.9}$$

where d_α is a "drag" coefficient (see Rajagopal[66]). Next, assuming slow motions of a mixture of fluid constituents, we ignore inertial effects and set the left-hand side of (5.8) to zero. We arrive at a Stokesian (or Brinkman)-type model:

$$-\nu(\varphi_\alpha)\Delta \mathbf{v}_\alpha + \nabla p_\alpha + d_\alpha \left(\mathbf{v}_\alpha - \sum_{\beta=1}^{4} \mathbf{v}_\beta \right) - \nabla \cdot \mathbf{F}^e_\alpha(\varphi_\alpha) = 0. \tag{5.10}$$

Finally, if we assume the fluids are inviscid, we obtain a generalized form of Darcy's law,

$$d_\alpha \mathbf{v}_\alpha = -\nabla p_\alpha + d_\alpha \sum_{\beta=1}^{4} \mathbf{v}_\beta + \nabla \cdot \mathbf{F}^e_\alpha(\varphi_\alpha). \tag{5.11}$$

The pressure p_α can be characterized by a collection of Poisson problems obtained by taking the divergence of terms in (5.11):

$$-\Delta p_\alpha = \nabla \cdot \left[d_\alpha \left(v_\alpha - \sum_{\beta=1}^{4} \mathbf{v}_\beta \right) - \nabla \cdot \mathbf{F}^e_\alpha(\varphi_\alpha) \right]. \tag{5.12}$$

Thus, in this case the three volume fractions, four velocities and four pressures are governed by the system of equations (5.4), (5.8) and (5.12).

We can add to (5.1) a term involving a nutrient supply, such as $m_\alpha = b_\alpha m \varphi_\alpha$, $b_\alpha =$ constant and $m = m(\mathbf{x}, t)$. Then the chemical potential takes the form

$$\mu_\alpha = b_\alpha m + \frac{c_\alpha}{4}\left(2\varphi_\alpha^3 - 3\varphi_\alpha^2 + \varphi_\alpha\right) - \varepsilon \Delta \varphi_\alpha, \tag{5.13}$$

and (5.4), (5.5), (5.8), (5.10) and (5.11) are modified accordingly to depend now on m. We must append to the system an additional equation describing the evolution of m such as the diffusion equation

$$\frac{\partial m}{\partial t} = -\nabla \cdot D \nabla m - \sum_{\alpha=1}^{4} \sigma m \varphi_\alpha, \tag{5.14}$$

where D is a diffusion coefficient and σ is a reaction coefficient, possibly dependent on the φ_α.

5.2. *N-phase Navier–Stokes–Cahn–Hilliard model*

For the next example in this section, the model proposed by Kim and Lowengrub in Ref. 53 is considered. In this formulation, one writes the mass and momentum

balance equations in terms of the mass concentrations rather than volume fractions. The development also deviates from that in Sec. 4 in that it is assumed that all the constituents are incompressible, the mixture is isothermal, body forces are negligible, and $\gamma_\alpha = 0$ for all α. Note that these assumptions should imply π_α as defined in Eq. (3.22) is such that

$$\pi_\alpha(\theta, \hat{\rho}_\alpha, \boldsymbol{\varphi}, \mathbf{m}_\alpha) = \pi_\alpha(\boldsymbol{\varphi}, \mathbf{m}_\alpha). \tag{5.15}$$

Then π_α becomes a multiplier associated with the incompressibility constraint and is analogous to the classical hydrostatic pressure. In the development in Ref. 53, formulations of balance laws for the full mixture are considered as opposed to constituents. These include the specification of forms of the constitutive equations, such quantities as the free energy, i.e. Ψ_α in all equations in Table 1 is replaced with Ψ, and similarly with the velocity $\mathbf{v}$, the symmetric part of the velocity gradient $\mathbf{D}$, and the mixture thermodynamic pressure π. The form of the Helmholtz free energy in Ref. 53 is taken to be of the form

$$\Psi(c_1, \ldots, c_N, \nabla c_1, \ldots, \nabla c_N) = F(c_1, \ldots, c_N) + \sum_{\beta=1}^{N} \frac{\varepsilon_\beta^2}{4} |\nabla c_\beta|^2. \tag{5.16}$$

Further, for $\mathbf{T}_\alpha^{v_*}(\mathbf{D}_\alpha, \mathbf{c})$ the constitutive equation for an isotropic Newtonian fluid with mass concentration-dependent viscosity is considered:

$$\mathbf{T}_\alpha^{v_*}(\mathbf{D}_\alpha, \mathbf{c}) = \eta(\mathbf{c}) \left(\mathbf{D} - \frac{2}{3} (\nabla \cdot \mathbf{v}) \mathbf{I} \right), \tag{5.17}$$

where the viscosity is now a function of the concentration $\mathbf{c}$ of a species: $\rho c_\alpha = \rho_\alpha \varphi_\alpha$, $\mathbf{c} = (c_1, \ldots, c_N)$.

This set of assumptions results in the following governing equations

$$\begin{cases} \rho \dot{c}_\alpha = \nabla \cdot (M \nabla \mu_\alpha), \\ \rho \dot{\mathbf{v}} = -\nabla \pi - \nabla \cdot \left(\dfrac{\rho}{2} \displaystyle\sum_{\alpha=1}^{N} \varepsilon_\alpha^2 \nabla c_\alpha \otimes \nabla c_\alpha \right) + \nabla \cdot \mathbf{T}_\alpha^{v*}, \\ \nabla \cdot \mathbf{v} = \displaystyle\sum_{\alpha=1}^{N} a_\alpha \nabla \cdot (M \nabla \mu_\alpha), \\ \mu_\alpha = \dfrac{\partial \Psi}{\partial c_\alpha} + a_\alpha \pi - \dfrac{1}{\rho} \nabla \cdot \left(\dfrac{\rho \varepsilon_\alpha^2}{2} \nabla c_\alpha \right), \end{cases} \tag{5.18}$$

where $\dot{(\cdot)} = \partial(\cdot)/\partial t + \mathbf{v} \cdot \nabla(\cdot)$ and $a_\alpha = \rho_\alpha^{-1}$. Numerical solutions of this system restricted to three constituents for two- and three-dimensional domains are discussed in Ref. 53.

5.3. *Two-phase tumor model: Elastic solid with inviscid fluid*

The third case to be considered is that presented by Araujo and McElwain in Ref. 8 which specifically looks at modeling the growth of tumors with a mixture consisting

of an elastic solid and an inviscid fluid, denoted by ϕ_s and ϕ_f respectively. These authors also make the assumption that the constituents are incompressible and that the mixture is isothermal.

This model does not fall into the category of diffuse interface as it does not include as an independent variable the gradients of the volume fractions for the Helmholtz free energy. Instead they use the Principle of Phase Separation discussed earlier, and take as their constitutive assumption

$$\Psi_\alpha = f(\theta, \mathbf{F}_s, \operatorname{Grad} \mathbf{F}_s, \mathbf{v}_f - \mathbf{v}_s). \tag{5.19}$$

Before writing the form of the free energy, the strain tensor for the solid is considered as decomposed into two parts, one part due to growth, $\mathbf{E}_G$, and the other part due to stress $\mathbf{E}_S$. That is

$$\mathbf{E}^s = \mathbf{E}^s_S + \mathbf{E}^s_G. \tag{5.20}$$

With this in mind, the form of the free energy density is written with the following linearized elastic form:

$$\psi_s(\mathbf{E}_S) = \psi_s(\mathbf{I}) + \sigma_0(\operatorname{tr} \mathbf{E}^s_S) + \frac{1}{2}\lambda_0(\operatorname{tr} \mathbf{E}^s_S)^2 + \mu_0 \operatorname{tr}(\mathbf{E}^s_S \mathbf{E}^s_S). \tag{5.21}$$

$\mathbf{E}^s_G$ is expressed as

$$\mathbf{E}^s_G = g\mathbf{A}, \quad \mathbf{A} := \begin{bmatrix} \gamma_1 & 0 & 0 \\ 0 & \gamma_2 & 0 \\ 0 & 0 & \gamma_3 \end{bmatrix}. \tag{5.22}$$

This formulation leads to the following set of constitutive equations:

$$\left.\begin{aligned} \mathbf{T}_s &= -\phi_s P\mathbf{I} + \lambda \operatorname{tr} \mathbf{E}_s \mathbf{I} - g\mathbf{A}, \\ \mathbf{T}_f &= -\phi_f P\mathbf{I}, \\ \mathbf{p}_s &= P\nabla\phi_s + \kappa(\mathbf{v}_f - \mathbf{v}_s), \\ \mathbf{p}_f &= P\nabla\phi_f + \kappa(\mathbf{v}_f - \mathbf{v}_s), \end{aligned}\right\} \tag{5.23}$$

where $P = \pi - \rho\psi_f$. We note that the form of the momentum supply postulated here is not equivalent with that in Table 1, but in Ref. 8 it is shown that this form is also thermodynamically consistent. Finally, it is assumed that the mass exchange term is of the form

$$\gamma_s = \beta\rho\phi_s m, \tag{5.24}$$

where β is a constant and m is a nutrient concentration.

By further ignoring inertia and body forces, these constitutive equations lead to the following closed system of equations ($\phi_s = \text{const.}$):

$$\left.\begin{aligned} \phi_s\rho\nabla \cdot \mathbf{v}_s &= \beta\rho\phi_s c, \\ \nabla \cdot \mathbf{T}_s &= -\kappa(\mathbf{v}_f - \mathbf{v}_s), \\ (1-\phi_s)\nabla P &= -\kappa(\mathbf{v}_f - \mathbf{v}_s). \end{aligned}\right\} \tag{5.25}$$

We note that this model has reduced the momentum equation for the fluid to a form of Darcy's law.

5.4. *Two-phase diffuse-interface tumor model*

In the paper by Cristini *et al.*,[30] the specific mixture being modeled consists of one solid, φ_T, and one fluid, φ_W, representative of the tumor tissue and extracellular fluid respectively. In many aspects, this model can be viewed as an extension of that proposed by Kim and Lowengrub in Ref. 53, as many assumptions are the same, but to include important biophysical effects, the free energy functional is expanded to include effects of a representative nutrient, such as oxygen. In this case, Eq. (4.1) is assumed to be of the form

$$\Psi_T = c_0\varphi_T^2(\varphi_T - 1)^2 + a_T\varphi_T m + \frac{\varepsilon_T}{2}|\nabla\varphi_T|^2, \tag{5.26}$$

where $c_0 = 9/200$.

Another key difference is that Cristini *et al.* do not assume that $\gamma_\alpha = 0$. Instead, empirical equations are employed to characterize the mass exchange. Further, the system of governing equations is augmented by an equation describing the evolution of the nutrient m. Finally, as a simplifying assumption, convective velocities are neglected. These assumptions lead to the following system of governing equations:

$$\left.\begin{aligned} &\frac{\partial\varphi_T}{\partial t} = \nabla\cdot\left(M\varphi_T^2\nabla\mu\right) + \gamma_T,\\ &\mu = 2c_0\left(2\varphi_T^3 - 3\varphi_T^2 + \varphi_T\right) - a_T m - \varepsilon_T^2\Delta\varphi_T,\\ &\frac{\partial m}{\partial t} = 0 = \nabla\cdot(D(\varphi_T)\nabla m) - m\varphi_T,\\ &\gamma_T = \lambda_P m\varphi_T - \lambda_A\varphi_T, \end{aligned}\right\} \tag{5.27}$$

where M, χ and ε are constants and λ_P and λ_A are constants representing the proliferation and apoptosis (cell death) rates respectively.

Numerical simulations of this system for problems set on two- and three-dimensional domains are presented in Ref. 30.

6. Statistical Calibration, Validation, and Uncertainty Quantification

The successful use of computational models to predict physical events depends on several fundamental concepts and processes. Firstly, there is the mathematical model itself: the manifestation of a scientific theory cast in mathematical structures that are intended to provide a meaningful abstraction of reality. For a given theoretical framework, such as the framework of mixture theory discussed earlier, there are infinitely many models, each differentiated from another by the specific parameters that define the model: the coefficients, solution domains, boundary and initial conditions.

Secondly, the particular features of the physical event of interest that are targets of the prediction must be clearly specified in advance. These are the quantities of

interest, the "QoI's". A model suitable for predicting one QoI with sufficient accuracy may be completely unsuitable for another. The notion of QoI's thus recognizes that it is not simply the global solution of a system of partial differential equations that is the goal of a computation, but particular features or functions of the solution that are key to decision making or discovery and understanding of physical events.

Thirdly, there is the fact that for predictability, experimental observations must be made for two fundamental purposes: (1) to determine (or, at least, to reduce uncertainty in) the parameters of the model for the specific physical environment in which the events of interest take place and (2) to determine, if only subjectively, if the model is capable of faithfully predicting the quantities of interest with sufficient accuracy. The first of these is called the process of *calibration*. In general, it involves solving an inverse problem as it determines model parameters indirectly by correlating model predictions with quantities measured in laboratory tests. The second process is the process of *validation*. In general, validation also involves a comparison of model predictions with experimental observations, but the observations are usually conducted on more complex problem domains than those for the calibration process, and are designed to depict as clearly as possible features similar to the target QoI's to be predicted. The comparison of validation experiments with model predictions can never actually validate the model as new experiments may lead to results in conflict with validation predictions. Thus, we can only hope to proceed with a prediction if the validation process does not lead to results which invalidate the model. A model that is "not invalidated" by virtue of validation experiments is often referred to as a "valid" model, clearly an abuse of language and a designation based on purely subjective decisions on the correlation of predictions and observations.

One should note that calibration, validation, and the ultimate prediction are done on different solution domains using different boundary and initial conditions, generally in a hierarchy of ascending complexity from calibration to validation to prediction. This is depicted in the prediction pyramid shown in Fig. 1. This hierarchy suggests that the model parameters can be separated into two categories: the *scenario parameters* $(\mathbf{S}_C, \mathbf{S}_V, \mathbf{S}_P)$ which include the solution domain, boundary and initial conditions and possibly other parameters, and then the basic *model parameters* $\mathbf{m}$ which include coefficients, moduli, etc. which parametrize the various models within the set characterized by the theoretical framework. Thus, the calibration process is performed with a simple set of scenario parameters $\mathbf{S}_C$ defining for

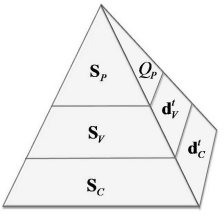

Fig. 1. The prediction pyramid of complexity.

instance a simple domain characteristic of laboratory tests, where an initial (prior) set of parameters $\mathbf{m}_0$ are re-adjusted (calibrated) through inverse analysis that employs observational data $\mathbf{d}$ (or $\mathbf{d}_C$ for calibration). The validation process is conducted using scenario $\mathbf{S}_V$ which defines a more complex case in which a new set of experiments related to the QoI's are performed involving observational data $\mathbf{d}_V$, and finally, the calibrated and not-invalidated model is used to make the prediction QoI using the full prediction scenario parameters $\mathbf{S}_P$. There may be several validation scenarios each designed to study the validity of different features of the model.

Returning to the list of processes essential to meaningful computer predictions, we add the *verification* process, the process of determining if the mathematical models are faithfully approximated by the discrete computational model. This process has two components: *code verification* and *solution verification*. Code verification involves a body of procedures designed to detect errors in coding, performance, and efficiency of computer programs developed to implement computational renderings of mathematical models of various physical phenomena. This involves the use of benchmark problems, manufactured solutions, convergence tests, and other procedures. Solution verification involves the derivation and implementation of *a posteriori* error estimates (e.g. Ref. 2). We will take up this subject in more detail in future work.

Finally, with a calibrated, non-invalidated, "verified" computational model, we can, in principle, calculate the QoI's for the full prediction model scenario $\mathbf{S}_P$. Unfortunately, the actual process of producing a meaningful prediction that is based on all of the knowledge we have is much more complex. Every step in this process encounters uncertainties, the model parameters $\mathbf{m}$, the observational data $\mathbf{d}$, the choice of a theoretical model, and the design of the validation process itself. The problem of overriding importance is to characterize in a meaningful way all of these uncertainties, to trace their propagation through the various solution processes, and to ultimately determine and quantify the uncertainty in the target QoI's. This complicated and daunting process is the modern problem of computational prediction. It is called *uncertainty quantification*.

The abstract mathematical model. The full mathematical model of physical events of interest along with constraints, boundary and initial conditions, and constitutive equations, can be expressed as the abstract problem of finding a function $\mathbf{u}$ in a space $\mathcal{U}$ of trial functions, such that

$$A(\mathbf{m}, \mathbf{S}, \mathbf{u}(\mathbf{m}, \mathbf{S})) = 0, \tag{6.1}$$

where $\mathbf{m}$ and $\mathbf{S}$ denote the collections of model and scenario parameters, respectively. We shall refer to $A(\cdot, \cdot, \cdot)$ as the *forward problem*.

Statistical Inverse Theory. Every step in both calibration and validation encounters uncertainties in the model parameters $\mathbf{m}$, the scenario parameters $\mathbf{S}$, the observational data $\mathbf{d}$, the choice of a theoretical model, and the design of the validation process itself. The problem of overriding importance is to characterize in a meaningful way all of these uncertainties, to trace their propagation through the various

solution processes, and to ultimately determine and quantify the uncertainty in the target QoI's. In the case of tumor growth models, examples of QoI's are values such as tumor volume or tumor shape, characterized by the ratio of tumor perimeter to volume. We shall employ Bayesian approaches to calibration and validation, based on contemporary treatments of statistical inverse analysis such as the one described in the books of Tarantola,[69] Kaipio and Somersalo,[49] Calvetti and Somersalo,[25] Tan and Colin,[68] and by Cacuci.[23] The main premise of this theory is that of subjective probability; the model parameters $\mathbf{m}$, the observational calibration data $\mathbf{d}_c$, the observational validation data $\mathbf{d}_v$, the theoretical model, and the QoI's are not deterministic; they are random variables characterized by probability density functions (pdf's), $\rho_M(\mathbf{m})$, $\rho_D(\mathbf{d}_c)$, $\rho_V(\mathbf{d}_v)$, $\theta(\mathbf{d}|\mathbf{m})$. (We assume here for simplicity that the scenario parameters are deterministic, but this is not a necessary aspect of the general approach.) The model is thus transformed into a stochastic model. We express this by rewriting (6.1) in the form

$$A(\rho_M(\mathbf{m}), \mathbf{S}, \mathbf{u}(\rho_M(\mathbf{m}), \mathbf{S})) = 0. \tag{6.2}$$

Calibration. The process of calibration hinges on the definition of a set of simple calibration scenarios $\mathbf{S}_c$ and on obtaining calibration data from this scenario $\mathbf{d}_c$. Following the arguments in Ref. 69, the solution to the calibration problem is the updated pdf $\sigma_M(\mathbf{m})$ defined as

$$\sigma_M(\mathbf{m}) = k\rho_M(\mathbf{m})L_D(\mathbf{m}), \quad L_D(\mathbf{m}) = \int_{\mathcal{D}} \frac{\rho_D(\mathbf{d}_c)\theta(\mathbf{d}_c|\mathbf{m})}{\mu_D(\mathbf{d}_c)}\, d\mathbf{d}_c. \tag{6.3}$$

Here k is a normalization constant, $L_D(\mathbf{m})$ is the likelihood function which involves integration of the data manifold $\mathcal{D}$ and $\mu_D(\mathbf{d}_c)$ is the homogeneous pdf associated with $\mathcal{D}$. Evaluation of $\theta(\mathbf{d}_c|\mathbf{m})$ requires solving the forward problem (6.1) for comparison between model output and observed data.

Validation. The process of validation, according to Ref. 10, requires more general data, $\mathbf{d}_v$, from a different scenario $\mathbf{S}_v$ for comparisons with the calibrated model predictions. To begin, another pdf is formed analogously to (6.3), i.e.

$$\sigma_V(\mathbf{m}) = k\sigma_M(\mathbf{m})L_V(\mathbf{m}), \quad L_V(\mathbf{m}) = \int_{\mathcal{V}} \frac{\rho_V(\mathbf{d}_v)\theta(\mathbf{d}_v|\mathbf{m})}{\mu_V(\mathbf{d}_v)}\, d\mathbf{d}_v. \tag{6.4}$$

Note that integration is now being done over the validation data manifold with the corresponding homogeneous pdf $\mu_V(\mathbf{d}_v)$. The second step of the validation process consists in solving the stochastic model using both pdf's $\sigma_M(\mathbf{m})$ and $\sigma_V(\mathbf{m})$ and for a new scenario $\mathbf{S}_P$. These two solutions, $\mathbf{u}(\sigma_M(\mathbf{m}), \mathbf{S}_P)$ and $\mathbf{u}(\sigma_V(\mathbf{m}), \mathbf{S}_P)$ are then used to compute the pdf's of the corresponding quantity of interest, $q_C(\mathbf{m})$ and $q_V(\mathbf{m})$. They are then compared under a predefined metric, $D(\cdot, \cdot)$; if the distance is less than a subjective tolerance γ_V, we say the model is "not invalidated". Otherwise the model is invalid and either the model needs alteration or more calibration data is required. This paradigm is illustrated in Fig. 2.

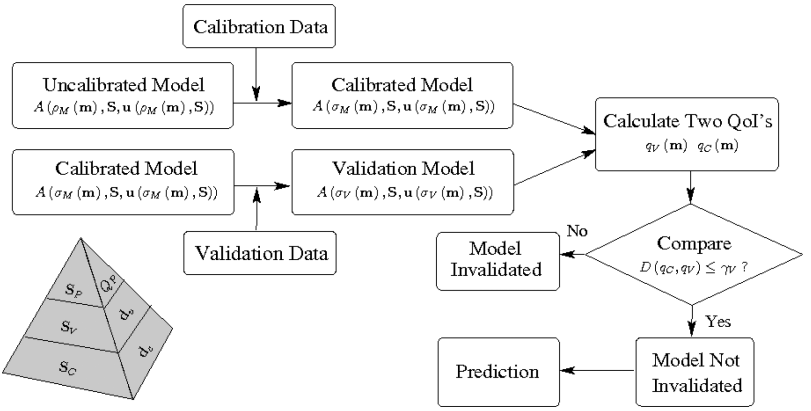

Fig. 2. Validation flowchart under a Bayesian approach. The inset illustrates the prediction pyramid of complexity. Layers of the pyramid represent scenarios increasing in complexity from calibration to validation to prediction. Required for the first two scenarios are data, $\mathbf{d}_c$ and $\mathbf{d}_v$, for comparison against output data expected from model predictions.

7. An Outline of a Bayesian Approach to Predictive Models of Tumor Growth

We shall now outline an example of *statistical calibration* and *validation* processes based on Bayesian methodologies laid down in the preceding section. The example employs a model from the general class of models developed in Sec. 5, and the processes lead, in principle, to the *quantification of uncertainty* in key quantities of interest. Key features of such approaches which should be emphasized are listed as follows:

- the Bayesian framework described earlier, forces one to identify what is known about the problem under consideration: the parameters and their uncertainty, the mathematical theory and how it maps parameters into observables, and to specify the observables themselves and their uncertainties;
- our approach also hinges on the identification of QoI's and, ultimately, will involve the sensitivity of specific QoI's to changes in parameters or to modifications in the theory;
- statistical calibration at various levels in the prediction pyramid, and ultimately statistical validation, should lead to *posterior* pdf's which improve the predictability of the model by combining what is known about the theory and, *a priori*, the model parameters and the observables. If not, more suitable data may be needed, or the model may need to be modified, extended or abandoned and replaced by a more sophisticated model. This process should be viewed as homogenizing, in a tumor specific way, the behaviors of what is happening at the lower scales. If model modification is needed, additional models of the lower scales may conceivably be incorporated to capture the parameters in a more comprehensive manner.

As a test case and a simple example, we consider a class of models similar to those described in Sec. 5.1 and treat the medium as a mixture of three inviscid incompressible fluids with volume fraction φ_α, $\alpha = 1, 2, 3$. These evolve along with a single nutrient characterized by the concentration m. We regard $\varphi_1 \equiv \varphi_T = \varphi_T(\mathbf{x}, t)$ as the volume fraction of tumor cells; φ_2 and φ_3 will denote volume fractions of healthy tissue cells and extracellular fluid respectively ($\varphi_3 = 1 - \varphi_1 - \varphi_2$). As is often done in contemporary literature, we ignore convection in the mass balance equations and take $\rho_1 = \rho_2 = \rho_3 = \rho$. This last assumption is justified by arguing that all cells and extracellular fluid is primarily composed of water. For simplicity, we take the Helmholtz free energy for each species to be of the form:

$$\Psi_\alpha = \frac{c}{4}\varphi_\alpha^2(1-\varphi_\alpha)^2 + am\varphi_\alpha + \frac{\varepsilon}{2}|\nabla\varphi_\alpha|^2 \tag{7.1}$$

so that the chemical potential is

$$\mu_\alpha = f(\varphi_\alpha) + am - \varepsilon\Delta\varphi_\alpha, \quad \alpha = 1, 2, 3, \tag{7.2}$$

where

$$f(\varphi_\alpha) = \frac{c}{2}\varphi_\alpha(1-2\varphi_\alpha)(1-\varphi_\alpha). \tag{7.3}$$

Here c is a known absolute constant and ε is a real regularization or penalty parameter not viewed as a material parameter. The parameter a is a taxis coefficient associated with the interaction of cells with nutrients.

Considering first the deterministic case in correspondence with (6.1), we have the following model:

For the prediction scenario $\mathbf{S}_P = (\Omega, \boldsymbol{\varphi}^0, \hat{\boldsymbol{\varphi}}, m_0, \hat{m})$ determine

$$\mathbf{u}(\mathbf{m}, \mathbf{S}_P) = (\varphi_T(\mathbf{m}, \mathbf{x}, t), \varphi_2(\mathbf{m}, \mathbf{x}, t),\ \varphi_3(\mathbf{m}, \mathbf{x}, t),\ m(\mathbf{m}, \mathbf{x}, t)) \tag{7.4}$$

$(\mathbf{x}, t) \in \Omega \times [0, T]$ such that

$$\mathbf{A}(\mathbf{m}, \mathbf{S}_P, \mathbf{u}(\mathbf{m}, \mathbf{S}_P)) = \mathbf{0} \tag{7.5}$$

In writing Eq. (7.5), it is implied that the following system must be satisfied:

$$\left.\begin{aligned}
&\rho\frac{\partial\varphi_T}{\partial t} = \nabla\cdot M\nabla\mu_T + \lambda_T\varphi_T - \lambda_P\varphi_T,\\
&\rho\frac{\partial\varphi_2}{\partial t} = \nabla\cdot M\nabla\mu_2 + \lambda_{T2}\varphi_2 - \lambda_{P2}\varphi_2,\\
&\frac{\partial m}{\partial t} = \nabla\cdot D\nabla m - \sigma m(\varphi_T + \varphi_2),\\
&\varphi_\alpha(\mathbf{m}, \mathbf{x}, 0) = \varphi_\alpha^0, \quad \alpha = 1(= T), 2, 3,\ \mathbf{x} \in \Omega,\\
&m(\mathbf{m}, \mathbf{x}, 0) = m_0(\mathbf{x}),\ \mathbf{x} \in \Omega,\\
&\varphi_\alpha(\mathbf{m}, \mathbf{x}, t)|_{\partial\Omega} = \hat{\varphi}_\alpha(\mathbf{x}),\ \mathbf{x} \in \partial\Omega, t \in [0, T],\ \alpha = 1, 2,\\
&m(\mathbf{m}, \mathbf{x}, t)|_{\partial\Omega} = \hat{m}(\mathbf{x}),\ \mathbf{x} \in \partial\Omega,\ t \in [0, T],\\
&\varphi_3 = 1 - \varphi_1 - \varphi_2.
\end{aligned}\right\} \tag{7.6}$$

Here the initial condition data and boundary data $(\boldsymbol{\varphi}^0 = (\varphi_1^0, \varphi_2^0, \varphi_3^0)$, $\hat{\boldsymbol{\varphi}} = (\hat{\varphi}_1, \hat{\varphi}_2, \hat{\varphi}_3), m_0, \hat{m})$ are assumed to be known exactly, a convenient simplification but not a necessary factor in the implementation, as we discuss below.

The region Ω is an open, bounded, connected domain in $\mathbb{R}^n$, generally represented by a computer-generated rendition of an image (e.g. an MRI image) of a region of a tissue, such as the computer-generated image shown in Fig. 3. (Image taken from Ref. 42.) Thus, the domain Ω itself may have geometrical uncertainties, and if these are judged important, the geometry of Ω must be added to the list of parameters to be calibrated. In the case of an invasive tumor, this will very likely be the case. Concerning the initial and boundary data, these may also be initially unknown and could also be determined, in principal, through statistical inverse analysis.

In this case the model parameters are listed as follows:

$$(\rho, \lambda_T, \lambda_P, \lambda_{T2}, \lambda_{P2}, M, a, D, \sigma). \tag{7.7}$$

We remark that the parameters $\lambda_T, \lambda_P, \lambda_{T2}$ and λ_{P2} can be considered as homogenizations of events at the molecular and cellular scales in connection with the first five hallmarks of cancer, while M is related to invasion. Further, D and a can be thought of as being loosely related to angiogenesis. The condition (recall $(2.27)_1$)

$$\sum_{\alpha=1}^{3}(\Gamma_\alpha - \nabla \cdot \mathbf{j}_\alpha) = 0 \tag{7.8}$$

in this case results in the constraint on the parameters $a, \lambda_T, \lambda_P, \lambda_{1\alpha}, \lambda_{2\alpha}$ and M:

$$\begin{aligned} 0 = {} & \lambda_T\varphi_T - \lambda_P\varphi_T + \sum_{\alpha=2}^{3}(\lambda_{T\alpha}\varphi_\alpha - \lambda_{P\alpha}\varphi_\alpha) \\ & + M\sum_{\alpha=1}^{3}\Delta(f(\varphi_\alpha) + am - \epsilon\Delta\varphi_\alpha). \end{aligned} \tag{7.9}$$

We note as this constraint involves λ_{T3} and λ_{P3} that these parameters must also be included in the count of the number of parameters to be solved for despite the fact that they do not appear in the governing equations. Thus, there are 11 parameters to calibrate.

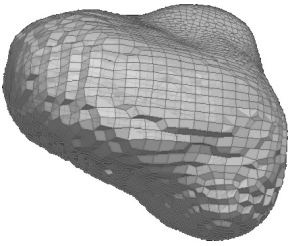

Fig. 3. Computer-generated domain obtained by generating a finite-element mesh based on an MRI image of a canine prostate.

As a quantity of interest, we shall take the change in volume of the tumor constituent, φ_T, over a time interval $[0, T]$:

$$Q(\mathbf{u}(\mathbf{m}, \mathbf{S}_P)) = \int_\Omega (\varphi_T(\mathbf{m}, \mathbf{x}, T) - \varphi_T(\mathbf{m}, \mathbf{x}, 0))\, d\mathbf{x}. \tag{7.10}$$

The sensitivities of this QoI to changes in parameters can be defined as the vector

$$\mathcal{S} = \frac{\partial Q(\mathbf{u}(\mathbf{m}, \mathbf{S}_P))}{\partial \mathbf{m}}. \tag{7.11}$$

In general, we attempt to avoid choices of QoI's which are very sensitive to changes in $\mathbf{m}$.

Since the model parameters manifold may not, in general, be a linear space, we may use instead of the normalized parameters (see Ref. 69),

$$\begin{gathered} \mathbf{m} = (m_1, m_2, \ldots, m_{11}), \\ m_1 = \log \rho/\rho_0, \quad m_2 = \log \lambda_T/\lambda_{T0}, \ldots, m_{11} = \log \sigma/\log \sigma_0, \end{gathered} \tag{7.12}$$

where $(\rho_0, \lambda_{T0}, \ldots, \sigma_0)$ are arbitrary finite positive reference values.

Currently, choosing the values of these parameters resembles more of an art than an exact science. As is often the case, even if ideal experiments are performed to determine model parameters, the method of obtaining the data and then projecting it into the parameter value is by no means exact. Error is inherent in each step. One major source of error arises in the assumption frequently invoked that results from *in vitro* experiments, where data is usually generated, somehow reflect *in vivo* behavior. Thus, cell doubling times observed in *in vitro* experiments for mitosis rates could be a gross over (or under) estimate. Further, cell staining is not always clear, i.e. the stains could be "blurry", and the projection of cell counts from a few samples of cell cultures to the parameter value is not a well-defined operation. A predictive tool must accurately account for such errors.

We choose to handle this issue by characterizing the model parameters $\mathbf{m}$ in (7.7) not as deterministic constants, but as random variables where the probability density function reflects the current knowledge known about the parameter, or alternatively, the amount of uncertainty in the parameter. We thus regard the parameter manifold $\mathcal{M}$ as a sample space in a probability space $(\mathcal{M}, \mathcal{U}_M, \mathbb{P})$, where $\mathcal{U}_M$ is a σ-algebra on $\mathcal{M}$ and $\mathbb{P}$ is a probability measure. We assume that there exists an absolutely continuous Lebesgue measure $\mu_M(\mathbb{B}) = \mathbb{P}(R^{-1}(\mathbb{B}))$, $\mathbb{B}$ being a member of the σ-algebra of Borel sets in $\mathbb{R}^d$, R being a random vector, and a probability density function $\rho_M(\mathbf{m})$ such that $d\mathbb{P} = \rho_M(\mathbf{m})d\mathbf{m}$. Our first goal is to define the prior pdf, $\rho_M(\mathbf{m})$. Owing to (7.9), the components of $\mathbf{m}$ are not necessarily independent uncorrelated random variables, and in some instances, joint probability densities must be considered. For simplicity, however, we assume *a prior* pdf such as

$$\rho_M(\mathbf{m}) = \rho_1(m_1)\rho_2(m_2)\rho_3(m_3)\rho_{45}(m_4, m_5)\rho_{67}(m_6, m_7)\cdots\rho_{11}(m_{11}). \tag{7.13}$$

If these parameters are correlated in some degree, this fact should become apparent in the calibration processes.

Calibration. The calibration process will, in general, be performed in two or more sequences of component experiments representing two or more layers at the base of the prediction pyramid. In the first level, component tests provide component observational data and these are used in the Bayesian theorem to generate *posterior* pdfs. For example, if a handbook value or a rough estimate of the taxis coefficient a is known and if bounds $a_{\min} \leq a \leq a_{\max}$ are known, a uniform pdf $\rho_9(m_9) = \rho_9(a)$ can be inferred. A simple experiment, perhaps an *in vitro* lab experiment, can provide observation data $\rho^1_{D(9)}(d)$ and these can be introduced in the Bayesian formula to generate *a posterior* pdf, $\sigma^1_9(m_9)$ for that component, a.

At the second level of the pyramid, coupled calibration tests each involving two or more parameters can be devised. The *posterior* pdfs generated at the first-level of calibration are used to construct joint *prior* pdfs for the second tier, e.g.

$$\rho^2_{1,2}(m_1, m_2) = \sigma^1_1(m_1)\sigma^1_2(m_2). \tag{7.14}$$

The various components making up the *prior* $\rho_M(\mathbf{m})$ can be obtained in many ways. As noted, if finite upper and lower bounds are known, a uniform pdf can be assumed. Alternatively, *in vitro* tests on cell samples can yield estimates of a mean and variance, and if appropriate, can be cast into a Gaussian or Beta pdf formulation. It is worthwhile to note the importance of calibration data from *in vitro* experiments. Although frequently discounted as irrelevant to *in vivo* phenomena, *in vitro* laboratory data can supply vital knowledge on *priors* when no other information is available. This is beneficial since the more information a *prior* contains, the better guidance one can obtain through observational data. These parameters will be ultimately calibrated using *in vivo* data and if the resulting model is invalid, the shortcomings in the model or the quality of the data may then be addressed.

Once the *prior* $\rho_M(\mathbf{m})$ is available, we compute the calibrated *posterior* $\sigma_M(\mathbf{m})$ using the Bayesian construction

$$\sigma_M(\mathbf{m}) = k\rho_M(\mathbf{m}) \int_{\mathcal{D}} \frac{\theta(\mathbf{d}|\mathbf{m})\rho_D(\mathbf{d})}{\mu_D(\mathbf{d})}\, d\mathbf{d}, \tag{7.15}$$

where k is a normalization constant, $\rho_D(\mathbf{d})$ is the *prior* pdf describing uncertainties in the observational data, $\mu_D(\mathbf{d})$ is the homogeneous pdf associated with the data manifold $\mathcal{D}$ and $\theta(\mathbf{d}|\mathbf{m})$ is the conditional likelihood probability determined by the theoretical model, i.e. the forward problem (7.6). In other words, problem (7.6) maps given samples of parameters $\mathbf{m}$ into theoretical values of the observables with a distribution $\theta(\mathbf{d}|\mathbf{m})$.

It must be realized that (7.15) characterizes a formal definition of $\sigma_M(\mathbf{m})$. However, it is often impractical to analytically evaluate the expression on the right-hand side. Thus, to determine the *posterior* pdf, sampling algorithms are often employed, which generate a finite number of pointwise values of σ_M which can then be fully characterized via an interpolation method. We note that σ_M is defined on an N-dimensional manifold ($N = 11$ in this example) and sufficient sampling of the

space becomes very expensive as N gets large. This problem is often referred to as the "curse of dimensionality". The new ICES software package QUESO[37] enables the implementation of the Markov-Chain Monte Carlo method or the Metropolis–Hastings scheme to aid in this effort.

Once $\sigma_M(\mathbf{m})$ is available, we return to the stochastic forward problem for the prediction scenario:

$$A(\sigma_M(\mathbf{m}), \mathbf{S}_P, \mathbf{u}(\sigma_M(\mathbf{m}), \mathbf{S}_P)) = 0. \tag{7.16}$$

This represents a large stochastic system with random coefficients with solution $\mathbf{u}$ a random variable. Several methods can be considered for the numerical solution of (7.16), the most common being the classical Monte Carlo method in which each sample $\mathbf{m} \in \mathcal{M}$ is mapped into a forward solution $\mathbf{u}(\mathbf{m})$ of (7.6). The Monte Carlo method, while very robust, can be extremely slow. In cases in which $\mathbf{u}(\sigma_M(\mathbf{m}))$ is smooth with respect to the random variable $\mathbf{m}$, other methods such as polynomial chaos,[44] stochastic collocation,[9,79] stochastic Galerkin[34] or other methods (see Ref. 78) can be used. In any case, the solution of (7.16) for realistic models of tumor growth can be a daunting task, pressing (or exceeding) the limits of the target computer systems available.

Validation. The validation process is performed on a scenario $\mathbf{S}_V$ that possesses as many features of the final prediction scenario as feasible, but generally (indeed, by definition) involves some intermediate level of sophistication or time scale that cannot realistically be attained in the final prediction scenario. Indeed, if one can do experiments within the prediction scenario $\mathbf{S}_P$ these are disqualified as predictions and become validation experiments. The calibration *posterior* pdf $\sigma_M(\mathbf{m})$ becomes the *prior* for the validation experiments, with validation observations $\mathbf{d}_V$ associated with *prior* pdfs $\rho_V(v)$. The Bayesian inverse analysis produces the validation *posterior*, $\sigma_V(\mathbf{m})$:

$$\sigma_V(\mathbf{m}) = \hat{k} \int_{\mathcal{V}} \frac{\theta(\mathbf{v}|\mathbf{m})\rho_V(\mathbf{v})}{\mu_V(\mathbf{v})}\, d\mathbf{v}, \tag{7.17}$$

which is again evaluated using statistical sampling methods. The forward validation problem is then

$$A(\sigma_V(\mathbf{m}), \mathbf{S}_P, \mathbf{u}(\sigma_V(\mathbf{m}), \mathbf{S}_P)) = 0 \tag{7.18}$$

which is a stochastic system of partial differential equations and which we assume can be solved numerically for the random field $\mathbf{u}(\sigma_V(\mathbf{m}), \mathbf{S}_P)$.

Next comes the fundamental step of *model validation* (or non-invalidation, as described earlier). The QoIs computed using the calibrated forward model and the validation *posterior* given in (7.17), are the following random variables

$$\begin{aligned} Q^c(\mathbf{u}(\sigma_M(\mathbf{m}), \mathbf{S}_P))(\mathbf{m}) &= \int_\Omega q_c(\mathbf{m}, \mathbf{x})\, d\mathbf{x} \\ Q^v(\mathbf{u}(\sigma_V(\mathbf{m}), \mathbf{S}_P))(\mathbf{m}) &= \int_\Omega q_v(\mathbf{m}, \mathbf{x})\, d\mathbf{x}, \end{aligned} \tag{7.19}$$

where

$$q_i(\mathbf{m}, \mathbf{x}) = \phi_T(\mathbf{m}, \mathbf{x}, T) - \phi_T(\mathbf{m}, \mathbf{x}, 0), \quad i = c, v. \tag{7.20}$$

The random variable Q^c is associated with the pdf $\sigma_M(\mathbf{m})$ and Q^v is associated with $\sigma_V(\mathbf{m})$. At this point a metric must be defined to compare the two QoIs $Q^c(\mathbf{u}(\sigma_M(\mathbf{m}), \mathbf{S}_P))(\mathbf{m})$ and $Q^v(\mathbf{u}(\sigma_V(\mathbf{m}), \mathbf{S}_P))(\mathbf{m})$ along with a validation tolerance. As both of these quantities are random variables, one might consider a metric comparing their cumulative distribution functions, $F_Q^c(\mathbf{m})$ and $F_Q^v(\mathbf{m})$, such as

$$\max_{y \in [0,1]} |(F_Q^c)^{-1}(y) - (F_Q^v)^{-1}(y)|. \tag{7.21}$$

This metric is illustrated in Fig. 4. Whichever metric is chosen, if the distance between the two QoI's is less than the defined tolerance, the model is accepted and declared "valid" (actually, not invalid). If the tolerance is not met, the model is invalid and must be rejected.

We note that in the case a model must be rejected, there are two possible scenarios. The first, and probably the simplest, is that more data is required for proper calibration. The calculation of sensitivities, as in (7.11), can suggest which parameters have the greatest influence on values of the particular QoI's and provide insight into what further data would yield the greatest information. The second scenario requires that the model itself must be modified, e.g. adding more terms or changing the assumptions about the physics. Another possibility would be that models of events at smaller scales are needed and should be coupled to the original

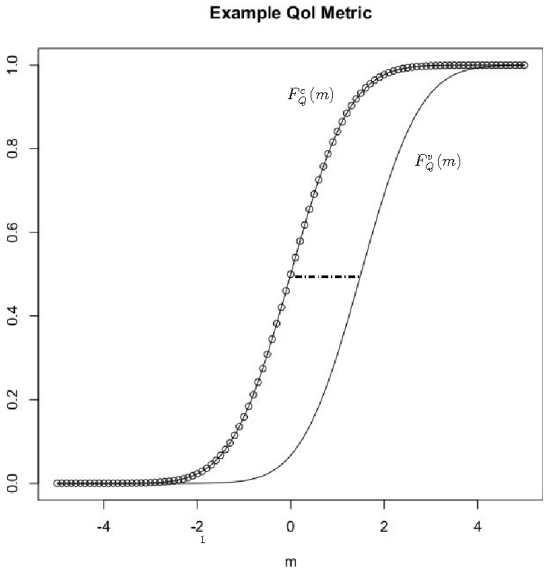

Fig. 4. Illustration of possible metric to compare two cumulative distribution functions. The dashed line indicates the metric distance between the two pdfs.

model in such a way as to characterize the parameters in a more comprehensive manner. For examples of models at smaller scales see the review paper by Bellomo and Delitala.[13]

Uncertainty quantification. Given the QoI in (7.10) for a validated model, we quantify the uncertainty in the prediction by computing its mean and centered moments:

$$\mathbb{E}[Q] = \int_{\mathcal{M}} Q(\mathbf{m})\sigma_M(\mathbf{m})\, d\mathbf{m}, \tag{7.22}$$

$$\mu_k = \mathbb{E}[(Q - \mathbb{E}[Q])^k] = \int_{\mathcal{M}} (Q(\mathbf{m}) - \mathbb{E}[Q])^k \sigma_M(\mathbf{m})\, d\mathbf{m}. \tag{7.23}$$

In particular, the mean $\mathbb{E}[Q]$ and the variance

$$\mathrm{Var}(Q) = \mathbb{E}[(Q - \mathbb{E}[Q])^2], \tag{7.24}$$

are in general the first properties of the QoI's of interest. *These numbers quantify the uncertainty in the quantity of interest.*

8. Concluding Remarks

The continuum mixture models developed in this work are not to be held in conflict with those obtained through statistical mechanics arguments using cellular models or with those derived from Boltzmann type models of non-equilibrium thermodynamics. Indeed, these types of models can be called upon to deliver, through ensemble averages or various homogenization methods, information on forms of the constitutive equations for the chemical potential, free energies or even parameters of the model. The inevitable question is which models deliver predictions of sufficient credibility to be the basis of important decisions. But this is precisely the general issue addressed by the Bayesian framework we laid down in this paper.

On a broader plain, one could ask what level of sophistication of the model is needed to deliver results of acceptable accuracy. This may be a subject that can be addressed using notions of adaptive modeling, discussed in Refs. 58 and 59. The interplay of these ideas with the methods of sensitivity analysis and statistical calibration and validation could move the field still further toward predictive models of tumor growth.

We have developed in this work two components that we argue can form a basis for predictive modeling of tumor growth. First, we established a general mixture theory for a complex mass of N constituents, M of which are solids and $N - M$ are fluids. We then specialized these so as to describe the response of a general mixture to such complex phenomena as deformation, growth or death, surface effects, and non-isothermal behavior. This is based on phase-field or diffuse-interface models of a continuum media. We then outlined a process of statistical calibration and validation which could lead to concrete methods of model calibration and validation. Finally, we demonstrated how uncertainties in specific quantities of interest, such as a change in

the volume of tumor cells, can be evaluated. We hope to describe extensions and implementation of these theories and methodologies in future work.

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