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MATHEMATICAL ANALYSIS OF HYDRODYNAMICS AND TISSUE DEFORMATION INSIDE AN ISOLATED SOLID TUMOR

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Abstract. In this article, we present a biphasic mixture theory based mathematical model for the hydrodynamics of interstitial fluid motion and mechanical behavior of the solid phase inside a solid tumor. The tumor tissue considered here is an isolated deformable biological medium. The solid phase of the tumor is constituted by vasculature, tumor cells, and extracellular matrix, which are wet by a physiological extracellular fluid. Since the tumor is deformable in nature, the mass and momentum equations for both the phases are presented. The momentum equations are coupled due to the interaction (or drag) force term. These governing equations reduce to a one-way coupled system under the assumption of infinitesimal deformation of the solid phase. The well-posedness of this model is shown in the weak sense by using the inf-sup (Babuska–Brezzi) condition and Lax–Milgram theorem in 2D and 3D. Further, we discuss a one-dimensional spherical symmetry model and present some results on the stress fields and energy of the system based on L^2 and Sobolev norms. We discuss the so-called phenomena of "necrosis" inside a solid tumor using the energy of the system.

1. Introduction

Tumors (or biological tissues) are a mixture of several cell populations. These cells are attached to the extracellular matrix (ECM) which is wet by an extracellular fluid (see Fig. 1) [29]. In general, the domain classification of such a model consists of five constituents: two fluid and three solid. Intravascular (mainly blood plasma) and interstitial fluids are the two fluid constituents. Depending on the type of cell, the three constituents are (i) normal host cells (ii) viable tumor cells which can proliferate (iii) dead or necrotic cells [30]. Typically, intravascular and interstitial fluids form principal fluid phases. The three types of cell and ECM components of tumor tissue are treated as a single solid phase [13, 25]. The extracellular matrix acts as a scaffolding system which gives a structure and rigidity to the cells. In this work, we adopt a biphasic mixture theory [9] to model a solid tumor as a

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macromolecular mixture of one solid and one fluid phase. In earlier mathematical

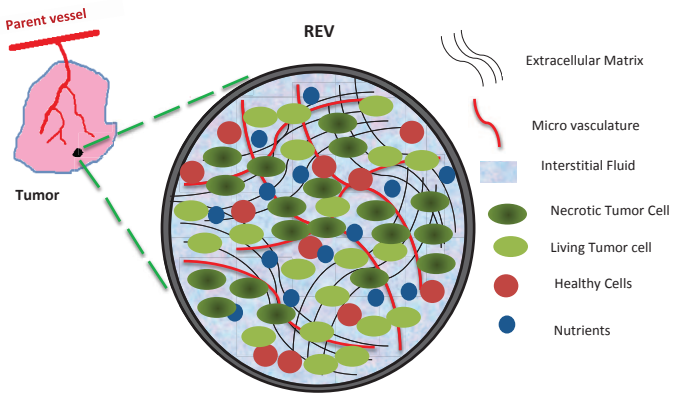

FIGURE 1. Anatomy of a tumor within a representative elementary volume (REV)

models of avascular tumor growth [2], it is assumed that a tumor is made of a single type of cells having a constant density [19]. Consequently, various experimental and theoretical evidence has shown that the earlier description was not sufficient to study the tumor dynamics. Hence, the multiphase models came into the existence [1,3,5,6,9,10,18]. In this description, one can consider the density variations within the components to evaluate the evolution of stresses and to take into consideration mechanical interactions among the constituents [26]. Ambrosi et al. [1] presented an alternative way of closing mass and momentum equations. They have provided a mechanical basis using the Darcy equation for porous media which relates the velocities of cells to their corresponding pressures. Byrne et al. [9] gave a mathematical model of avascular tumor growth using a mixture theory. The main feature is the dependency of the proliferation rate upon cellular stress, rather than on the nutrient concentration alone. Their model is capable of determining stress distribution inside the solid tumor. Preziosi and Tosin [26] have proposed a multiphase model for tumor growth, which involves multiple components like tumor cells, host cells, extracellular matrix and extracellular fluid inside a tumor. The advection term of the chemical transport reaction equation involves composite velocity which is the volume averaged velocity of all the constituents present in the mixture. Kim et al. [23] have discussed a three-dimensional continuum model of tumor growth treating the tumor as a hypoelastic material. Growth has been estimated using the nutrient concentration obtained from the diffusion-advection equation and the stress has been determined from the constitutive equation for a hypoelastic material. Recently, Dey and Raja Sekhar [13] have presented a detailed description of a mixture theory model that represents the hydrodynamics and nutrients transport inside solid tumors. This study is a prerequisite to understanding solid tumor growth. The solid phase velocity is useful in understanding the mechanical behavior of the cellular phase towards the extracellular fluid. Further, this study helps us to

understand the convective solute transport based on the biphasic mixture theory. A detailed literature survey shows that the concept of biphasic mixture theory is useful in describing the mechanics of interstitial fluid flow, solute transport and growth inside a solid tumor. While the above studies are more focused on modeling aspects and obtaining a corresponding solution analytically or numerically, there does exist some limited literature dealing with more mathematical treatment of existence and uniqueness results. For example, Showalter [31] considered a homogeneous and isotropic elastic medium to form a system that consists of the equilibrium equation for solid momentum balance and the diffusion equation for Darcy flow. This system describes the Biot consolidation model in poroelasticity as well as a coupled quasi-static problem in thermoelasticity. The existence, uniqueness, and regularity theory for this system has been studied there. Further, Cao et al. [12] have considered the same model as in [31] with the dilation-dependent permeability. The modified Rothe's method has been used to establish the existence of a weak solution. On the other hand, the convergence of the finite element approximation has been proved and verified through numerical experiments. In another study, Cao et al. [11] have considered a nonlinear steady flow model which has applications in a deformable biological medium, using the theory of poroelasticity that consists of an elasticity equation for the displacement of the solid phase and Darcy's equation for the interstitial fluid phase pressure. Their model becomes nonlinear due to the assumption of dilation-dependent interstitial permeability of the solid matrix. Existence and uniqueness of a weak solution is established. Convergence of the finite element approximation is proved and verified through numerical experiments. Giverso et al. [37] proposed a simple way of describing a tumor as a linear elastic material from a reference configuration that is continuously evolving in time due to growth and remodeling. They assumed that the tumor mass is a very ductile material, so that it can only sustain moderate stresses while the deformation induced by growth, that can actually be quite big, mainly induces a plastic reorganization of malignant cells. Further, Mascheroni et al. [38] presented a biphasic model for tumor growth based on the mechanics of fluid-saturated porous media. They assumed that the porous medium is identified with the tumor cells and the extracellular matrix, and represents the system's solid phase, whereas the interstitial fluid constitutes the liquid phase. Moreover, they analyzed the dependence of tumor development on the mechanical environment, with a particular focus on cell reorganization and its role in stress relaxation. Apart from that, there also exists quite an extensive literature on the existence of solutions in non-linear elasticity, see e.g., [34–36]. A. Tosin [32] considered multiphase models of tumor growth in interaction with a surrounding tissue, also taking into account the interplay with diffusible nutrients feeding the cells. He has discussed some qualitative properties such as a priori non-negativity, boundedness, and uniqueness of the solutions. Existence of the solution is studied in the one-dimensional time-independent case. Recently, Maurizio Verri et al. [33] have considered a one-dimensional poro-visco-elastic model for which they derive explicit solutions in the cases where the external applied load is characterized by a step pulse or a trapezoidal pulse in time. Also, the well-posedness of the one-dimensional model is studied in the presence or absence of viscoelasticity. They

have shown, by means of mathematical analysis, the role of structural viscoelasticity in the biomechanical response of deformable porous media with incompressible constituents to sudden changes in external applied loads. In most of the earlier literature, the hydrodynamics and mechanics of growth process are simulated for a radially symmetric spherical domain without understanding the well-posedness of the system in a higher dimension. In this direction, we have found limited literature on the existence and uniqueness of the hydrodynamic model based on the theory of poroelasticity corresponding to deformable biological tissues. Our attempt is to show the well-posedness of poroelastodynamics inside an isolated non-growing solid tumor based on the mixture theory model in the weak sense. This study gives the existence of a unique weak solution of the model using the Lax–Milgram theorem and inf-sup condition. Further, we comment on the stability estimates of the solution. Explicit behavior of stress fields inside the tumor is discussed corresponding to the one-dimensional spherical symmetry model. A detailed analysis of the stress field is presented.

2. Mathematical formulation

The present model considers an isolated tumor which behaves as a homogeneous deformable porous medium. Fig. 1 represents a solid tumor attached to a parent vessel on a macroscopic scale. A representative elementary volume (REV) that consists of various cell population (necrotic tumor cells, living tumor cells, healthy cells), microvasculature, ECM (to which cells are attached), interstitial fluid etc. are shown as part of Fig. 1. The deformable solid phase of the tumor is assumed to be constituted by an ensemble of interstitial, vascular regions and cell population and the fluid phase is constituted by extracellular fluid in which tumor cells can survive. Fluid in the extracellular matrix is viscous and contains various nutrients, drug molecules, electrolytes and plasma proteins. The movement of the extracellular fluid within the interstitial space causes solid phase deformation. Suppose $\Omega \subset \mathbb{R}^d$, $d = 2,\ 3$, denotes a bounded, Lipschitz domain in which a tumor is occupied. Let $\mathbf{V}_f$ and $\mathbf{V}_s$ denote the extracellular fluid velocity and velocity of the solid phase respectively. The apparent densities of the fluid and solid phases are denoted by $\tilde{\rho}_f$ and $\tilde{\rho}_s$ respectively, and ϕ_f and ϕ_s are the respective volume fractions. The following are the mass conservation equations for each phase in a generic form. Thus, for $x \in \Omega$ [1, 9, 13], we have

$$\frac{\partial(\tilde{\rho}_f\phi_f)}{\partial t} + \nabla \cdot [(\tilde{\rho}_f\phi_f)\mathbf{V}_f] = \tilde{\rho}_f S_f(x,t), \tag{2.1}$$

$$\frac{\partial(\tilde{\rho}_s\phi_s)}{\partial t} + \nabla \cdot [(\tilde{\rho}_s\phi_s)\mathbf{V}_s] = \tilde{\rho}_s S_s(x,t), \tag{2.2}$$

where $S_f(x,t)$ and $S_s(x,t)$ represent the fluid phase and solid phase generation (mainly the growth of cell population) respectively. For the saturated mixture $\phi_f + \phi_s = 1$ we have the following combined form of (2.1)–(2.2) as (when the apparent densities of the fluid and solid phase are equal and constant i.e., $\tilde{\rho}_f = \tilde{\rho}_s$), we have

$$\nabla \cdot (\phi_f\mathbf{V}_f + \phi_s\mathbf{V}_s) = S_f(x,t) + S_s(x,t). \tag{2.3}$$

When the mixture is closed, equation (2.3) reduces to

$$\nabla \cdot (\phi_f \mathbf{V}_f + \phi_s \mathbf{V}_s) = 0. \tag{2.4}$$

Note that the time scale of the tumor cell growth process is significantly larger compared to the perfusion process and the interstitial nutrients transport. Further, this cell growth process dominates other growth factors inside the interstitial space. Therefore, during perfusion and interstitial transport, typically no new cell generation is detected [4, 25]. Based on these assumptions Eq. (2.3) becomes

$$\nabla \cdot (\phi_f \mathbf{V}_f + \phi_s \mathbf{V}_s) = S_f(x,t). \tag{2.5}$$

Typically, the fluid source $S_f(x,t)$ is assumed to be driven by the average transmural pressure and is given by [13, 25],

$$S_f(x,t) = S_V(x,t) - S_L(x,t) = \frac{L_p A(P_{ev} - P)}{V} - \frac{L_{p_L} A_L (P - P_L)}{V}, \quad x \in \Omega, \tag{2.6}$$

where S_V and S_L represent the volumetric flow rate across the capillary and lymphatic drainage rate per unit tissue volume respectively. Further, L_p and L_{p_L} are the average hydraulic conductivity coefficients of capillary and lymphatic walls respectively; A/V and A_L/V respectively denote the capillary and lymphatic surface area per unit tissue volume in the tumor tissue (i.e. vascular and lymphatic surface densities); $P_{ev} = P_V - \sigma_f(P_V^{os} - P_{int}^{os})$ is regarded as the effective vascular pressure; P_V and P_L are the average vascular and lymphatic pressures, respectively and P is the average interstitial fluid pressure (IFP). P_V^{os} and P_{int}^{os} are respectively, the osmotic pressure of plasma within the capillary and the osmotic pressure of the interstitial fluid. σ_f is the average osmotic reflection coefficient, whose value lies in (0, 1] depending on the solute and structure of the micro-vessel. The vessel wall becomes impermeable to the solute when $\sigma_f = 1$. With the help of (2.6) the mass conservation equation (2.5) becomes

$$\nabla \cdot (\phi_f \mathbf{V}_f + \phi_s \mathbf{V}_s) = -\frac{L_p A}{V}(1 + L_r A_r)(P - P_F), \tag{2.7}$$

where $L_r A_r = L_{pL} A_L / L_p A$ and $P_F = (L_p A P_{ev} + L_{pL} A_L P_L)/(L_p A + L_{pL} A_L)$. $L_r A_r$ denotes the ratio of the strength of the distributed solute source through the vasculature and sink through the lymph vessels and P_F is the weighted vascular pressure.

A momentum balance equation for each of the constituent phases (solid and fluid) in the binary mixture of the cellular phase (solid) and extracellular fluid is given by [1, 9, 13],

$$\rho_j \Big(\frac{\partial \mathbf{V}_j}{\partial t} + (\mathbf{V}_j \cdot \nabla)\mathbf{V}_j \Big) = \nabla \cdot \mathbf{T}_j + \mathbf{\Pi}_j + \mathbf{b}_j \quad \text{for} \quad j \in \{f, s\}, \tag{2.8}$$

where $\rho_j = \phi_j \tilde{\rho}_j$ is the true mass density of the j^{th} phase of the mixture. $\mathbf{T}_j$ is the stress tensor for the j^{th} phase of the mixture. $\mathbf{\Pi}_j$ is the resultant of the forces acting on the j^{th} phase of mixture due to the interactions with the other phase. $\mathbf{b}_j$ is the body force of the j^{th} phase of mixture. Constitutive relations for the

corresponding stress tensors for each phase are [1, 9, 13],

$$\mathbf{T}_f = -\phi_f P\mathbf{I} + \lambda_f(\nabla\cdot\mathbf{V}_f)\mathbf{I} + \mu_f(\nabla\mathbf{V}_f + (\nabla\mathbf{V}_f)^T), \tag{2.9}$$

$$\mathbf{T}_s = -\phi_s P\mathbf{I} + \chi(\phi_s)(\nabla\cdot\mathbf{U}_s)\mathbf{I} + \mu_s(\phi_s)(\nabla\mathbf{U}_s + (\nabla\mathbf{U}_s)^T). \tag{2.10}$$

Here

- P is hydrodynamic pressure,
- λ_f, μ_f are first and second coefficients of viscosity corresponding to interstitial fluid,
- $\mathbf{U}_s$ is displacement vector,
- $\mathbf{V}_s = \partial\mathbf{U}_s/\partial t$ is velocity vector of the solid phase,
- χ, μ_s are elastic parameters corresponding to the solid phase,
- $\chi = \nu_p\mathcal{Y}/(1+\nu_p)(1-2\nu_p)$ and $\mu_s = \mathcal{Y}/2(1+\nu_p)$, $\mathcal{Y}$ and ν_p are Young's modulus and Poisson ratio respectively.

Preziosi and Farina [27], Byrne and Preziosi [9], Ambrosi and Preziosi [1] and Dey and Raja Sekhar [13] have reported the generic form of the interaction forces $\mathbf{\Pi}_j$ as a function of pressure, volume fractions, source terms, and relative velocity. These satisfy the following relation

$$\mathbf{\Pi}_f + \mathbf{\Pi}_s + \tilde{S}_s\mathbf{V}_s + \tilde{S}_f\mathbf{V}_f = 0. \tag{2.11}$$

For both closed and non-closed mixture, from the above relation, the interaction forces ($\mathbf{\Pi}_j$) can be reduced to the following form [1, 9, 13, 27]

$$\mathbf{\Pi}_s = P\nabla\phi_s + \frac{1}{K}\Big(1 - \frac{\tilde{S}_f K}{2}\Big)(\mathbf{V}_f - \mathbf{V}_s), \tag{2.12a}$$

and

$$\mathbf{\Pi}_f = P\nabla\phi_f + \frac{1}{K}\Big(1 + \frac{\tilde{S}_f K}{2}\Big)(\mathbf{V}_s - \mathbf{V}_f). \tag{2.12b}$$

The structure as in (2.12a) and (2.12b) is more general and is very challenging to handle. However, literature indicates that the product $\tilde{S}_f K$ which is called the biological number has no contribution towards the momentum transfer across the constituent phases [1, 9, 13, 27]. Correspondingly, the above form of $\mathbf{\Pi}_s$ and $\mathbf{\Pi}_f$ reduces to

$$-\mathbf{\Pi}_s = \mathbf{\Pi}_f = \tfrac{1}{K}(\mathbf{V}_s - \mathbf{V}_f) + (\nabla\phi_f)P. \tag{2.13}$$

where K represents hydraulic conductivity of tumor tissue. The term $(1/K)$ is known as the drag coefficient. The hydraulic conductivity (K) of tumor tissue is given by $K = k/\mu_f$, where k is a permeability prefactor, and μ_f is the viscosity of the interstitial fluid. The equation (2.13) shows that the interaction forces satisfy Newton's third law.

It may be noted that the permeability of a porous medium can be characterized as isotropic or anisotropic depending on whether the same depends on the direction or not. When it depends on the direction, the permeability is no longer a scalar and it becomes a tensor according to dimension. On the other hand, if the permeability is a function of space, it is called heterogeneous, otherwise homogeneous. Most of the biological applications involving tissue may demand

anisotropic/heterogeneous permeability. For example, some of the biological tissues and cells display anisotropic permeability [46]. In particular, articular cartilage typically shows anisotropic nature [47, 49]. Further, the variations in the porosity sometimes may induce nonlinear permeability [48]. Such a general nature of permeability may lead to some mathematical challenges like invertibility etc. and we avoid those issues in this study. Hence, we assume that the permeability is isotropic so that it is a scalar constant.

2.1. Assumptions on the present model. The above formulation as in (2.1)–(2.13) is very generic and appears very difficult to handle straight away. Hence, we propose to follow a step-by-step simplification. To this extent, we consider a simplified model based on the following assumptions:

- The nutrient perfusion and transport rate is much faster than tumor cell growth. We consider the tumor as a static perfused biological domain. Thus during the generation of nutrients inside the interstitial space, tumor cells cannot divide to produce new cells. In the absence of cell generation term (i.e., ϕ_s), ϕ_s becomes constant (for details one can refer to Dey and Raja Sekhar [13]).
- Due to the absence of growth of the cell phase, the deformation inside the solid phase does depend on the interstitial drag. The resistance from the cellular phase becomes negligible due to the absence of growth. Hence, one can ignore cell velocity ($\partial \mathbf{U}_s/\partial t = \mathbf{V}_s \simeq 0$). The corresponding deformation is regarded as the infinitesimal deformation of the solid phase [39]. Due to this assumption, the momentum equation for the fluid phase does not contain any solid velocity term and the corresponding situation is called one-way coupling between the interstitial fluid velocity and solid displacement [13]. However, one can relax this assumption by taking the time variation of cellular displacement due to interstitial drag into account [40].
- The motion of interstitial fluid flow and solid phase deformation are slow (i.e. we can neglect inertial terms compared to viscous stress terms).

Under these assumptions, by substituting constitutive relations (2.9), (2.10) and (2.13) in the momentum equation (2.8), we get the following system of equations along with the mass conservation equation,

$$-\nabla \cdot (2\mu_f D(\mathbf{V}_f) + \lambda_f(\nabla \cdot \mathbf{V}_f)\mathbf{I} - \phi_f P\mathbf{I}) + \frac{1}{K}\mathbf{V}_f = \mathbf{b}_f \quad \text{in} \quad \Omega, \tag{2.14}$$

$$-\nabla \cdot (2\mu_s D(\mathbf{U}_s) + \chi(\nabla \cdot \mathbf{U}_s)\mathbf{I} - \phi_s P\mathbf{I}) - \frac{1}{K}\mathbf{V}_f = \mathbf{b}_s \quad \text{in} \quad \Omega, \tag{2.15}$$

$$\nabla \cdot (\phi_f \mathbf{V}_f) = S_f \quad \text{in} \quad \Omega, \tag{2.16}$$

where $D(\cdot)$ denotes the deviatoric matrix which is defined as

$$D(\mathbf{u}) = \tfrac{1}{2}(\nabla \mathbf{u} + (\nabla \mathbf{u})^t),$$

$(\nabla \mathbf{u})^t$ denotes the transpose of the matrix $\nabla \mathbf{u}$. In order to close the above system of equations, we need to support it with suitable boundary conditions. The model at hand is in-vitro analogous, which is typically handled while maintaining suitable ambient pressure or stress conditions during experiments. Most of the studies involving in-vitro model have considered pressure conditions [4,9,13,25]. However,

it may be noted that pressure, being the pore pressure, relates directly to the fluid phase of the tissue. On the other hand, the ambient solid phase stress condition relates to the tissue deformation. Hence, the stress boundary condition is expected to show a significant impact on the mechanical behavior of the tissue. Accordingly, we propose the following ambient conditions.

2.2. Boundary conditions.

$$\mathbf{T}_s \cdot \mathbf{n} = 0 \quad \text{in} \quad \partial\Omega, \qquad (\mathbf{T}_f - \mathbf{T}_\infty) \cdot \mathbf{n} = 0 \quad \text{on} \quad \partial\Omega, \tag{2.17}$$

where $\mathbf{n}$ denotes the outward normal unit vector to the boundary $\partial\Omega$. We relate ambient stress $\mathbf{T}_\infty$ as $-P_\infty \mathbf{I}$ (P_∞ is the ambient pressure). Since the in-vitro environment deals with tumors in isolation with fixed ambient conditions, the overall normal stress is made equal to the atmospheric pressure.

3. Non-dimensional Equations

Using the following transformations

$$\hat{\mathbf{x}} = \frac{\mathbf{x}}{R}, \quad \nabla' = R\nabla, \quad \hat{P} = \frac{P}{P_F}, \quad \hat{\mathbf{V}}_f = \frac{\mathbf{V}_f}{\frac{RP_F}{\mu_f}}, \quad \hat{\mathbf{U}}_s = \frac{\mathbf{U}_s}{\frac{R^3 P_F}{\mu_f \nu}},$$

we get the following dimensionless form of the governing equations (2.14)–(2.17)

$$-\nabla \cdot \Big(2D(\mathbf{V}_f) + \frac{\lambda_f}{\mu_f}(\nabla \cdot \mathbf{V}_f)\mathbf{I} - \phi_f P \mathbf{I}\Big) + \frac{1}{\mathrm{Da}}\mathbf{V}_f = \mathbf{b}_f \quad \text{in} \quad \Omega, \tag{3.1}$$

$$-\nabla \cdot \Big(\frac{\varrho_t}{(1+\nu_p)} D(\mathbf{U}_s) + \frac{\nu_p \varrho_t}{(1+\nu_p)(1-2\nu_p)}(\nabla \cdot \mathbf{U}_s)\mathbf{I} - \phi_s P \mathbf{I}\Big) - \frac{1}{\mathrm{Da}}\mathbf{V}_f = \mathbf{b}_s \quad \text{in } \Omega, \tag{3.2}$$

$$\nabla \cdot (\phi_f \mathbf{V}_f) = -\alpha_t^2 (1 + L_r A_r)(P - 1) \quad \text{in} \quad \Omega, \tag{3.3}$$

where $\mathbf{b}_f$, and $\mathbf{b}_s$ are modified non-dimensional body force terms, α_t is the strength of the solute source, $L_r A_r$ is the ratio of the hydraulic conductivities of blood and lymph vessels and Da is the Darcy number (Permeability parameter). Expressions for these non-dimensional parameters are defined in section 5.

Boundary conditions become:

$$\Big(2D(\mathbf{V}_f) + \frac{\lambda_f}{\mu_f}(\nabla \cdot \mathbf{V}_f)\mathbf{I} - \phi_f P \mathbf{I}\Big) \cdot \mathbf{n} = \mathbf{T}_\infty \cdot \mathbf{n} \quad \text{on} \quad \partial\Omega, \tag{3.4}$$

$$\Big(\frac{\varrho_t}{(1+\nu_p)} D(\mathbf{U}_s) + \frac{\nu_p \varrho_t}{(1+\nu_p)(1-2\nu_p)}(\nabla \cdot \mathbf{U}_s)\mathbf{I} - \phi_s P \mathbf{I}\Big) \cdot \mathbf{n} = 0 \quad \text{on} \quad \partial\Omega. \tag{3.5}$$

For the sake of computational convenience, we assume $\lambda = \frac{\lambda_f}{\mu_f}$, $\alpha_1 = \frac{\varrho_t}{2(1+\nu_p)}$, $\alpha_2 = \frac{\nu_p \varrho_t}{(1+\nu_p)(1-2\nu_p)}$, and $a_0 = \alpha_t^2(1 + L_r A_r)$.

4. Well-posedness

In this section, we establish the well-posedness of the system of equations (3.1)-(3.5). Well-posedness of a partial differential equation or a system of partial differential equations consists of a three-step verification in the sense of J. Hadamard [7,20], namely (i) there should exist at least one solution, (ii) the existing solution is unique, and (iii) the solution depends continuously on the given data (or stability),

i.e. a small error in the data entails a small error in the solution. The existence of a solution means that the given model is coherent and uniqueness and stability increase the possibility of providing accurate numerical approximations [28].

In the system of Eqs. (3.1)–(3.3), $\mathbf{V}_f$, P, and $\mathbf{U}_s$ are the unknown functions. Parameters μ_i, ϕ_i, λ_f, K, χ are the known constants, and functions $\mathbf{b}_i \in L^2(\Omega)^d$ where $i = s,\ f$, $\mathbf{T}_\infty \cdot \mathbf{n} \in L^2(\partial\Omega)^d$ are the known functions. $c_0 > 0$, c_p are some real constants which appear in Korn's and Poincare's inequalities, respectively[1].

4.1. Weak formulation. We choose the test functions $\mathbf{W} \in \mathbf{X}$, $\mathbf{Z} \in \mathbf{X}$, $q \in M$ and then multiply correspondingly, with each of the equations (3.1)–(3.3). We perform integration by parts while using the boundary conditions to obtain the following weak formulation:

Find $(\mathbf{V}_f, \mathbf{U}_s, P) \in \mathbf{X} \times \mathbf{X} \times M$ such that

$$(Q_{wsf}) \begin{cases} 2(D(\mathbf{V}_f) : D(\mathbf{W}))_\Omega + \lambda(\nabla \cdot \mathbf{V}_f, \nabla \cdot \mathbf{W})_\Omega \\ -\phi_f(P, \nabla \cdot \mathbf{W})_\Omega + \frac{1}{\mathrm{Da}}(\mathbf{V}_f, \mathbf{W})_\Omega = (\mathbf{b}_f, \mathbf{W})_\Omega + (\mathbf{T}_\infty \cdot \mathbf{n}, \mathbf{W})_{\partial\Omega} \\ 2\alpha_1(D(\mathbf{U}_s) : D(\mathbf{Z}))_\Omega + \alpha_2(\nabla \cdot \mathbf{U}_s, \nabla \cdot \mathbf{Z})_\Omega \\ -\phi_s(P, \nabla \cdot \mathbf{Z})_\Omega - \frac{1}{\mathrm{Da}}(\mathbf{V}_f, \mathbf{Z})_\Omega = (\mathbf{b}_s, \mathbf{Z})_\Omega \\ \phi_f(\nabla \cdot \mathbf{V}_f, q)_\Omega = (S_f, q)_\Omega \end{cases}$$

holds for all $(\mathbf{W}, \mathbf{Z}, q) \in \mathbf{X} \times \mathbf{X} \times M$. One may observe that the above system (Q_{wsf}) is a one-way coupled system in variables $\mathbf{V}_f$ and $\mathbf{U}_s$, i.e. the fluid momentum equation is free from the solid phase velocity. However, the solid momentum equation is coupled to the fluid phase velocity. It should be noted that the interstitial fluid pressure couples the fluid and solid momentum equations. Thus, we can split the weak formulation (Q_{wsf}) into two subparts.

(A) Find $(\mathbf{V}_f, P) \in \mathbf{X} \times M$

$$(Q_{wf}) \begin{cases} 2(D(\mathbf{V}_f) : D(\mathbf{W}))_\Omega + \lambda(\nabla \cdot \mathbf{V}_f, \nabla \cdot \mathbf{W})_\Omega + \frac{1}{\mathrm{Da}}(\mathbf{V}_f, \mathbf{W})_\Omega \\ -\phi_f(P, \nabla \cdot \mathbf{W})_\Omega = (\mathbf{b}_f, \mathbf{W})_\Omega + (\mathbf{T}_\infty \cdot \mathbf{n}, \mathbf{W})_{\partial\Omega} \\ \phi_f(\nabla \cdot \mathbf{V}_f, q)_\Omega = (S_f, q)_\Omega \end{cases}$$

holds for all $(\mathbf{W}, q) \in \mathbf{X} \times M$, and

(B) For a given $\mathbf{V}_f \in \mathbf{X}$ and $P \in M$, find $\mathbf{U}_s \in \mathbf{X}$ such that

$$(Q_{ws}) \begin{cases} 2\alpha_1(D(\mathbf{U}_s) : D(\mathbf{Z}))_\Omega + \alpha_2(\nabla \cdot \mathbf{U}_s, \nabla \cdot \mathbf{Z})_\Omega \\ = \phi_s(P, \nabla \cdot \mathbf{Z})_\Omega + \frac{1}{\mathrm{Da}}(\mathbf{V}_f, \mathbf{Z})_\Omega + (\mathbf{b}_s, \mathbf{Z})_\Omega \end{cases}$$

holds for all $\mathbf{Z} \in \mathbf{X}$.

4.2. Abstract formulation corresponding to the weak formulation. One may note that the fluid source term appears/disappears depending on whether the mixture is not closed/closed with respect to the mass. When the mixture is not closed, the source term S_f is of the form $S_f = -a_0 P + a_0$ where $a_0 = \alpha_t^2(1 + L_r A_r)$.

[1]For function spaces and other preliminary results we refer to the Appendix section 8.

We consider both the possibilities while writing the abstract formulation. In order to write the abstract formulation, we introduce the following bilinear forms

$$a(\cdot\,,\cdot)\colon \mathbf{X}\times\mathbf{X}\to\mathbb{R},\quad b(\cdot\,,\cdot)\colon \mathbf{X}\times M\to\mathbb{R},\quad \text{and}\quad c(\cdot\,,\cdot)\colon M\times M\to\mathbb{R},$$

defined by

$$a(\mathbf{V}_f,\mathbf{W}) = 2(D(\mathbf{V}_f) : D(\mathbf{W}))_\Omega + \lambda(\nabla\cdot\mathbf{V}_f,\nabla\cdot\mathbf{W})_\Omega + \frac{1}{\mathrm{Da}}(\mathbf{V}_f,\mathbf{W})_\Omega, \tag{4.1}$$

$$b(\mathbf{W},P) = -\phi_f(P,\nabla\cdot\mathbf{W})_\Omega,\quad \text{and}\quad c(P,q) = a_0(P,q)_\Omega. \tag{4.2}$$

The linear forms

$$\mathbf{F}\colon \mathbf{X}\to\mathbb{R},\quad \text{and}\quad G\colon M\to\mathbb{R}$$

are defined by

$$\langle\mathbf{F},\mathbf{W}\rangle = (\mathbf{b}_f,\mathbf{W})_\Omega + (\mathbf{T}_\infty\cdot\mathbf{n},\mathbf{W})_{\partial\Omega},\quad \text{and}\quad \langle G,q\rangle = -(a_0,q)_\Omega. \tag{4.3}$$

With respect to these bilinear and linear forms, we get the following abstract formulation corresponding to the weak formulation (Q_{wf}) in case of a non-closed mixture:

Find $(\mathbf{V}_f,P)\in\mathbf{X}\times M$ such that

$$(Q_{af})\begin{cases} a(\mathbf{V}_f,\mathbf{W}) + b(\mathbf{W},P) = \langle\mathbf{F},\mathbf{W}\rangle \\ b(\mathbf{V}_f,q) - c(P,q) = \langle G,q\rangle \end{cases}$$

holds for all $(\mathbf{W},q)\in\mathbf{X}\times M$.

Further, in case of a closed mixture, the weak formulation (Q_{af}) reduces to the following abstract formulation:

Find $(\mathbf{V}_f,P)\in\mathbf{X}\times M$ such that

$$(Q'_{af})\begin{cases} a(\mathbf{V}_f,\mathbf{W}) + b(\mathbf{W},P) = \langle\mathbf{F},\mathbf{W}\rangle \\ b(\mathbf{V}_f,q) = 0 \end{cases}$$

holds for all $(\mathbf{W},q)\in\mathbf{X}\times M$.

Finally, we have the following abstract formulation corresponding to the weak formulation (Q_{ws}):

Define a bilinear form $B_s(\cdot\,,\cdot)\colon \mathbf{X}\times\mathbf{X}\to\mathbb{R}$ by

$$B_s(\mathbf{U}_s,\mathbf{Z}) = 2\alpha_1(D(\mathbf{U}_s) : D(\mathbf{Z}))_\Omega + \alpha_2(\nabla\cdot\mathbf{U}_s,\nabla\cdot\mathbf{Z})_\Omega, \tag{4.4}$$

and a linear form $L\colon \mathbf{X}\to\mathbb{R}$ by

$$L(\mathbf{Z}) = \phi_s(P,\nabla\cdot\mathbf{Z})_\Omega + \frac{1}{\mathrm{Da}}(\mathbf{V}_f,\mathbf{Z})_\Omega + (\mathbf{b}_s,\mathbf{Z})_\Omega. \tag{4.5}$$

The abstract formulation becomes:

For a given $\mathbf{V}_f\in\mathbf{X}$ and $P\in M$, find $\mathbf{U}_s\in\mathbf{X}$ such that

$$(Q'_{as})\big\{B_s(\mathbf{U}_s,\mathbf{Z}) = L(\mathbf{Z}),\quad \forall\mathbf{Z}\in\mathbf{X}.$$

One may note that the problem (Q_{ws}) involves the derivative terms of the displacement function $\mathbf{U}_s$, and the velocity function $\mathbf{V}_f$. Hence, it is clear that the corresponding solution will never be unique with respect to $\mathbf{U}_s$. This difficulty

can be resolved by seeking $\mathbf{U}_s$ in the quotient space $H^1(\Omega)^d/\mathbb{R}^d$ equipped with the quotient norm

$$\|\dot{\mathbf{V}}\|_{H^1(\Omega)^d/\mathbb{R}^d} = \inf_{\mathbf{V}\in\dot{\mathbf{V}}} \|\mathbf{V}\|_{H^1(\Omega)^d}, \tag{4.6}$$

where for any element $\mathbf{V} \in H^1(\Omega)^d$, $\dot{\mathbf{V}}$ denotes an equivalence class in $H^1(\Omega)^d/\mathbb{R}^d$. The following theorem says that the quotient norm $\|\dot{\mathbf{V}}\|_{H^1(\Omega)^d/\mathbb{R}^d}$ in the space $H^1(\Omega)^d/\mathbb{R}^d$ is equivalent to the seminorm $\|\nabla\mathbf{V}\|_{L^2(\Omega)^d}$ in the space $H^1(\Omega)^d$. We refer to [24] for the proof.

THEOREM 4.1. [17] *Let Ω be a bounded, connected and Lipschitz-continuous open subset of $\mathbb{R}^d$. The space $H^1(\Omega)^d/\mathbb{R}^d$ is a Hilbert space for the quotient norm (4.6). Moreover, in this space the functional $\dot{\mathbf{V}} \mapsto \|\nabla\mathbf{V}\|_{L^2(\Omega)^d}$ is a norm equivalent to (4.6).*

Hence, in order to get a unique solution, we define $\mathcal{H} = H^1(\Omega)^d/\mathbb{R}^d$. The abstract weak formulation (Q'_{as}) in the space $\mathcal{H}$ becomes:

For a given $\mathbf{V}_f \in \mathbf{X}$ and $P \in M$, find $\dot{\mathbf{U}}_s \in \mathcal{H}$ such that

$$(Q_{as}) \Big\{ B_s(\dot{\mathbf{U}}_s, \dot{\mathbf{Z}}) = L(\dot{\mathbf{Z}}), \quad \forall \dot{\mathbf{Z}} \in \mathcal{H},$$

where

$$B_s(\dot{\mathbf{U}}_s, \dot{\mathbf{Z}}) = 2\alpha_1(D(\mathbf{U}_s) : D(\mathbf{Z}))_\Omega + \alpha_2(\nabla\cdot\mathbf{U}_s, \nabla\cdot\mathbf{Z})_\Omega, \quad \forall\, \mathbf{U}_s \in \dot{\mathbf{U}}_s,\ \mathbf{Z} \in \dot{\mathbf{Z}} \tag{4.7}$$

and

$$L(\dot{\mathbf{Z}}) = \phi_s(P, \nabla\cdot\mathbf{Z})_\Omega + \frac{1}{\mathrm{Da}}(\mathbf{V}_f, \mathbf{Z})_\Omega + (\mathbf{b}_s, \mathbf{Z})_\Omega, \quad \forall\, \mathbf{Z} \in \dot{\mathbf{Z}} \tag{4.8}$$

4.3. Existence and uniqueness. In this section we show the existence and uniqueness of the weak solution for the abstract problems (Q_{af}), (Q'_{af}) and (Q_{as}). For this purpose we would like to turn to some standard theorems available in the literature for help. Let us rewrite these abstract formulations as

(I) Find $(\mathbf{V}_f, P) \in \mathbf{X} \times M$ such that

$$(Q_{af}) \begin{cases} a(\mathbf{V}_f, \mathbf{W}) + b(\mathbf{W}, P) = \langle \mathbf{F}, \mathbf{W} \rangle \\ b(\mathbf{V}_f, q) - c(P, q) = \langle G, q \rangle \end{cases}$$

holds for all $(\mathbf{W}, q) \in \mathbf{X} \times M$.

(II) Find $(\mathbf{V}_f, P) \in \mathbf{X} \times M$ such that

$$(Q'_{af}) \begin{cases} a(\mathbf{V}_f, \mathbf{W}) + b(\mathbf{W}, P) = \langle \mathbf{F}, \mathbf{W} \rangle \\ b(\mathbf{V}_f, q) = 0 \end{cases}$$

holds for all $(\mathbf{W}, q) \in \mathbf{X} \times M$.

(III) For a given $\mathbf{V}_f \in \mathbf{X}$ and $P \in M$, find $\dot{\mathbf{U}}_s \in \mathcal{H}$ such that

$$(Q_{as}) \Big\{ B_s(\dot{\mathbf{U}}_s, \dot{\mathbf{Z}}) = L(\dot{\mathbf{Z}}), \quad \forall\, \dot{\mathbf{Z}} \in \mathcal{H}.$$

Correspondingly, we present the proof as follows:

$(\mathrm{I})_\mathrm{s}$ Problem (Q_{af}) satisfies all the assumptions of Proposition 1.4 (see [8] p. 45). Indeed, we have

$$|a(\mathbf{V}_f, \mathbf{W})| \leqslant \beta \|\mathbf{V}_f\|_{\mathbf{X}} \|\mathbf{W}\|_{\mathbf{X}} \tag{4.9}$$

$$|b(\mathbf{W}, P)| \leqslant \phi_f \|P\|_M \|\mathbf{W}\|_{\mathbf{X}} \tag{4.10}$$

$$|c(P, q)| \leqslant a_0 \|P\|_M \|q\|_M \tag{4.11}$$

where $\beta = \max\{2 + |\lambda|, 1/\mathrm{Da}\}$. These estimates establish the boundedness (continuity) of the bilinear forms $a(\cdot\,,\cdot)$, $b(\cdot\,,\cdot)$, and $c(\cdot\,,\cdot)$.

Further, in order to show the coercivity of $a(\cdot\,,\cdot)$, and $c(\cdot\,,\cdot)$, choose $\mathbf{W} = \mathbf{V}_f$ in the definition of $a(\cdot\,,\cdot)$, to get

$$\begin{aligned} a(\mathbf{V}_f, \mathbf{V}_f) &= 2(D(\mathbf{V}_f) : D(\mathbf{V}_f))_\Omega + \lambda(\nabla \cdot \mathbf{V}_f, \nabla \cdot \mathbf{V}_f)_\Omega + \frac{1}{\mathrm{Da}}(\mathbf{V}_f, \mathbf{V}_f)_\Omega \\ &\geqslant 2\|D(\mathbf{V}_f)\|^2_{M^{d^2}} + \frac{1}{\mathrm{Da}}\|\mathbf{V}_f\|^2_{M^d} \\ &\geqslant \alpha \|\mathbf{V}_f\|^2_{\mathbf{X}}, \qquad \text{(by Korn's inequality)}, \end{aligned} \tag{4.12}$$

where $\alpha = \min\left\{2, \frac{1}{\mathrm{Da}}\right\}/c_0$. Next, choose $q = P$ in the definition of $c(\cdot\,,\cdot)$, to get

$$c(P, P) = a_0 \|P\|^2_M. \tag{4.13}$$

Further, we have the following bounds for F and G

$$\|\mathbf{F}\|_{\mathbf{X}'} \leqslant \|\mathbf{b}_f\|_{M^d} + t_r \|\mathbf{T}_\infty \cdot \mathbf{n}\|_{L^2(\partial\Omega)^d}, \tag{4.14}$$

$$\|G\|_{M'} \leqslant \|a_0\|_M, \tag{4.15}$$

which shows that $F \in \mathbf{X}'$ and $G \in M'$, where t_r is a constant that appears due to the use of *the trace theorem*. Hence, according to Proposition 1.4 (see [8], p. 45), there exists a unique pair $(\mathbf{V}_f, P)$ which will satisfy (Q_{af}). Moreover, the following stability bound holds

$$\frac{\alpha}{2}\|\mathbf{V}_f\|^2_{\mathbf{X}} + \frac{a_0}{2}\|P\|^2_M \leqslant \frac{1}{2\alpha}\left(\|\mathbf{b}_f\|_{M^d} + t_r\|\mathbf{T}_\infty \cdot \mathbf{n}\|_{L^2(\partial\Omega)^d}\right)^2 + \frac{1}{2a_0}\|a_0\|^2_M. \tag{4.16}$$

Remark 4.1. It is required to note that $\lambda = \frac{\lambda_f}{\mu_f}$ (which is the ratio of the two viscosity coefficients) needs some attention while showing coercivity. The literature [41–45] suggests that researchers have debated on the sign (or value) of $\frac{\lambda_f}{\mu_f}$. If $\lambda \geqslant 0$, then the coercivity of $a(\cdot\,,\cdot)$, as shown by us in (4.12), holds good. But when $\lambda < 0$ (i.e., typical Stoke's hypothesis), we lose the coercivity of $a(\cdot\,,\cdot)$ in the present case. In such a situation, i.e. when $\lambda < 0$, we can recover coercivity of $a(\cdot\,,\cdot)$ easily by redefining the boundary condition corresponding to the fluid phase. One can assume a mixed boundary condition or a Dirichlet boundary condition on the fluid phase velocity. In either of the cases, the coercivity can be shown by using Korn's inequality.

$(II)_s$ To show the existence of a unique solution for the abstract problem (Q'_{af}) we shall verify the assumptions of Corollary 4.1 (see [17], p. 61).

Claim:

(i) $a(\cdot\,,\cdot)$ is bounded and $\mathbf{Y}$-coercive, where $\mathbf{Y} = \{\mathbf{V} \in \mathbf{X} : b(\mathbf{V}, q) = 0 \ \forall q \in M\}$.
(ii) $b(\cdot\,,\cdot)$ is bounded and satisfies the inf-sup condition.
(iii) The linear operator $\mathbf{F}$ belongs to $\mathbf{X}'$.

The boundedness of $a(\cdot\,,\cdot)$ and $b(\cdot\,,\cdot)$ holds by virtue of the estimates (4.9) and (4.10) respectively. Equation (4.14) shows that $\mathbf{F}$ belongs to $\mathbf{X}'$. In order to show the coercivity of $a(\cdot\,,\cdot)$ on the subspace $\mathbf{Y}$ of $\mathbf{X}$, we choose $\mathbf{W} = \mathbf{V}_f$ in the definition of $a(\cdot\,,\cdot)$, to get

$$
\begin{aligned}
(4.17) \qquad a(\mathbf{V}_f, \mathbf{V}_f) &= 2(D(\mathbf{V}_f) : D(\mathbf{V}_f))_\Omega + \frac{1}{\mathrm{Da}}(\mathbf{V}_f, \mathbf{V}_f)_\Omega \\
&= 2\|D(\mathbf{V}_f)\|^2_{M^{d^2}} + \frac{1}{\mathrm{Da}}\|\mathbf{V}_f\|^2_{M^d} \\
&\geqslant \alpha\|\mathbf{V}_f\|^2_{\mathbf{X}}, \qquad \text{(by Korn's inequality)},
\end{aligned}
$$

where $\alpha = \min\left\{2, \frac{1}{\mathrm{Da}}\right\}/c_0$. Further, the inf-sup condition says that

$$
(4.18) \qquad \sup_{\mathbf{V}_f \in \mathbf{X}, \mathbf{V}_f \neq 0} \frac{(q, \nabla \cdot \mathbf{V}_f)}{\|\mathbf{V}_f\|_{\mathbf{X}}} \geqslant \gamma \|q\|_M, \quad \forall q \in M
$$

for some positive constant γ. To prove (4.18), we have for any $q \in M$

$$
(4.19) \qquad \sup_{\mathbf{V}_f \in \mathbf{X}, \mathbf{V}_f \neq 0} \frac{(q, \nabla \cdot \mathbf{V}_f)}{\|\mathbf{V}_f\|_{\mathbf{X}}} \geqslant \frac{(q, \nabla \cdot \mathbf{W})}{\|\mathbf{W}\|_{\mathbf{X}}}, \quad \forall\, \mathbf{W} \in \mathbf{X},
$$

or in particular for any $\mathbf{W} \in H^1_0(\Omega)^d \subset \mathbf{X}$, and for any $q \in M$, we have

$$
(4.20) \qquad \sup_{\mathbf{V}_f \in \mathbf{X}, \mathbf{V}_f \neq 0} \frac{(q, \nabla \cdot \mathbf{V}_f)}{\|\mathbf{V}_f\|_{\mathbf{X}}} \geqslant \frac{(q, \nabla \cdot \mathbf{W})}{\|\mathbf{W}\|_{\mathbf{X}}}
$$

Now, as $q \in M$ there exists a unique function $\mathbf{W} \in (\mathbf{Y}_0)^\perp \subset H^1_0(\Omega)^d$ (by Corollary 8.1) such that

$$
(4.21) \qquad \nabla \cdot \mathbf{W} = q, \quad \|\mathbf{W}\|_{\mathbf{X}} \leqslant \delta \|q\|_M,
$$

where δ is a positive constant. Hence (4.20) and (4.21) give

$$
(4.22) \qquad \sup_{\mathbf{V}_f \in \mathbf{X}, \mathbf{V}_f \neq 0} \frac{(q, \nabla \cdot \mathbf{V}_f)}{\|\mathbf{V}_f\|_{\mathbf{X}}} \geqslant \frac{(q, \nabla \cdot \mathbf{W})}{\|\mathbf{W}\|_{\mathbf{X}}} = \frac{\|q\|^2_M}{\|\mathbf{W}\|_{\mathbf{X}}} \geqslant (1/\delta)\|q\|_M.
$$

Equation (4.22) implies that the inf − sup condition (4.18) holds for $\gamma = 1/\delta$. Hence, Corollary 4.1 (see [17], p. 61) implies that there exists a unique pair $(\mathbf{V}_f, P) \in \mathbf{X} \times M$ of functions which solve the problem (Q'_{af}), which means the problem (Q_{wf}) is well-posed in a weak sense. Also, the following bound holds

$$
(4.23) \qquad \|\mathbf{V}_f\|_{\mathbf{X}} + \|P\|_M \leqslant c_0(\|\mathbf{b}_f\|_{M^d} + \|\mathbf{T}_\infty \cdot \mathbf{n}\|_{L^2(\partial\Omega)^d}).
$$

$(III)_s$ Further, in order to show the well-posedness of the solid phase problem (Q_{as}), we use *the Lax–Milgram* theorem (see [14], p. 297). For a given pair $(\mathbf{V}_f, P) \in \mathbf{X} \times M$ (which exists from the above problems (Q_{af}) and (Q'_{af})) we have the following claims corresponding to the problem (Q_{as})

(i) $B_s(\cdot\,,\cdot)$ is bounded and coercive on $\mathcal{H}$,

(ii) $L(\cdot)$ belongs to the dual space $\mathcal{H}'$ of $\mathcal{H}$.

The following estimates prove the above claims:

$$|B_s(\dot{\mathbf{U}}_s, \dot{\mathbf{Z}})| \leqslant (2\alpha_1 + \alpha_2)\|\dot{\mathbf{U}}_s\|_{\mathcal{H}}\|\dot{\mathbf{Z}}\|_{\mathcal{H}} \tag{4.24}$$

and

$$B_s(\dot{\mathbf{U}}_s, \dot{\mathbf{U}}_s) = 2\alpha_1\|D(\mathbf{U}_s)\|^2_{M^{d^2}} + \alpha_2\|\nabla\cdot\mathbf{U}_s\|^2_M \geqslant \frac{2\alpha_1}{c_0}\|\dot{\mathbf{U}}_s\|^2_{\mathcal{H}}. \tag{4.25}$$

The estimates (4.24) and (4.25) show that $B_s(\cdot\,,\cdot)$ is bounded and coercive and we have

$$|L(\dot{\mathbf{Z}})| \leqslant (\phi_s\|P\|_M + \frac{c_p}{\mathrm{Da}}\|\mathbf{V}_f\|_{M^d} + c_p\|\mathbf{b}_s\|_{M^d})\|\dot{\mathbf{Z}}\|_{\mathcal{H}}. \tag{4.26}$$

We note, (4.26) indicates that $L(\cdot)$ belongs to $\mathcal{H}'$. According to the *Lax–Milgram* theorem there exists a unique solution $\dot{\mathbf{U}}_s \in \mathcal{H} = H^1(\Omega)^d/\mathbb{R}^d$ which satisfies (Q_{as}). Further, the following stability estimate holds,

$$\|\dot{\mathbf{U}}_s\|_{\mathcal{H}} \leqslant \frac{c_0}{2\alpha_1}\Big(\phi_s\|P\|_M + \frac{c_p}{\mathrm{Da}}\|\mathbf{V}_f\|_{M^d} + c_p\|\mathbf{b}_s\|_{M^d}\Big). \tag{4.27}$$

The above analysis shows that both the subproblems (Q_{ws}), and (Q_{wf}) are well-posed in a generalized sense, hence the system of equations (2.14)–(2.16) with boundary conditions (2.17) is well-posed in a weak sense.

Remark 4.2. In addition, we can consider more general data in Proposition. 1.4 (see [8], p. 45) and the Lax–Milgram Theorem (see [14], p. 297) by choosing reflexive Banach spaces instead of a Hilbert space (see [16, Theorem 3.6] and [15, Theorem 4.2]). Further, $\mathbf{T}_\infty\cdot\mathbf{n}$ can also be chosen in the space $H^{-1/2}(\partial\Omega)^d$ (the dual space of $H^{1/2}(\partial\Omega)^d$) instead of the space $L^2(\partial\Omega)^d$, and $\mathbf{b}_i$ for $i = f, s$ can also be chosen in the space [2] $(E^{-1}(\Omega))^d \subset (H^1(\Omega)^d)'$ instead of the space $L^2(\Omega)^d$.

5. One-dimensional spherical symmetry stress fields

Studying well-posedness of steady poroelastodynamics inside a solid tumor gives us a good understanding of the solution in the theoretical sense. The next task is to know the solution behavior in the physical sense that we can achieve by either doing numerical simulation or by solving our system of equations analytically. We seek an analytical solution of the spherical symmetry poroelastodynamic model corresponding to Eqs. (2.14)–(2.17) to understand the interstitial fluid motion and the infinitesimal solid phase deformation. In this context, we recall a recent study by Dey and Raja Sekhar [13], where one-dimensional poroelastodynamics inside an isolated tumor is presented. There they have assumed that such an isolated tumor is connected to the host tissue through a filling blood vessel and a drainage lymph vessel. This is as per existing clinical methods [21]. Dey and Raja Sekhar [13] have considered the continuity of pore pressure with the ambient pressure together with the stress-free condition at the tumor boundary. However, as indicated earlier, the deviations in the solid phase stress show influence on the corresponding tissue deformation. Hence, we have considered stress boundary conditions as in

[2] For details of the space $(E^{-1}(\Omega))^d$ one can see [22] p. 171–172.

Eq. (2.17). Since the one-dimensional model equation and the solution method do not deviate much from Dey and Raja Sekhar [13], we do not present the detailed solution procedure, rather we show a detailed analysis of the behavior of stress. It may be noted that such an analysis of the stress fields is not attempted in [13]. The non-dimensional governing equations (3.1)–(3.3) can be rewritten (when no body force is present in the model)

$$\phi_f \nabla P^{\text{in}} = \frac{1}{3}\nabla(\nabla \cdot \mathbf{V}_f^{\text{in}}) + \nabla^2 \mathbf{V}_f^{\text{in}} - \frac{1}{\text{Da}}\mathbf{V}_f^{\text{in}} \tag{5.1}$$

$$\phi_s \nabla P^{\text{in}} = \frac{\varrho_t}{2(1+\nu_p)(1-2\nu_p)}\nabla(\nabla \cdot \mathbf{U}_s^{\text{in}}) + \frac{\varrho_t}{2(1+\nu_p)}\nabla^2 \mathbf{U}_s^{\text{in}} + \frac{1}{\text{Da}}\mathbf{V}_f^{\text{in}} \tag{5.2}$$

$$\nabla \cdot (\phi_f \mathbf{V}_f^{\text{in}}) = S_f, \quad \text{where} \quad S_f = -\alpha_t^2(1 + L_r A_r)(P^{\text{in}} - 1) \tag{5.3}$$

Note that "*in*" represents the interstitial transport corresponding to the radial flow inside the solid tumor.

Multiplying by ϕ_f and taking the divergence into the equation (5.1), we obtain

$$\phi_f^2 \nabla^2 P^{\text{in}} = \frac{4}{3}\nabla^2(\nabla \cdot (\phi_f \mathbf{V}_f^{\text{in}})) - \frac{1}{\text{Da}}(\nabla \cdot (\phi_f \mathbf{V}_f^{\text{in}})) \tag{5.4}$$

Further, by the use of (5.3) in the above equation, we have

$$\phi_f^2 \nabla^2 (P^{\text{in}} - 1) = \frac{4}{3}\Big(\nabla^2 - \frac{3}{4\text{Da}}\Big) S_f \tag{5.5}$$

using $S_f = -\alpha_t^2(1+L_r A_r)(P^{\text{in}}-1)$, and some manipulation, we obtain the following steady Helmholtz equation for the IFP

$$(\nabla^2 - \gamma^2)(P^{\text{in}}(\mathbf{x}) - 1) = 0, \tag{5.6}$$

where

$$\gamma^2 = \frac{1}{\text{Da}\big(\frac{4}{3} + \frac{\phi_f^2}{\alpha_t^2(1+L_r A_r)}\big)}. \tag{5.7}$$

Following Dey and Raja Sekhar [13], we list the dimensionless parameters: α_t is the strength of the solute source, $L_r A_r$ is the ratio of the hydraulic conductivities of blood and lymph vessels and Da is the Darcy number (Permeability parameter). These can be expressed as

$$\alpha_t = \sqrt{L_p \mu_f (A/V)},$$
$$\text{Da} = k_{\text{in}}/R^2,$$
$$L_r A_r = L_{p_L} A_L / L_p A,$$

where L_p and L_{p_L} are the average hydraulic conductivities of capillary and lymphatic walls respectively, A/V and A_L/V respectively denote vascular and lymphatic surface densities, k_{in} is a permeability prefactor, μ_f is the dynamic viscosity of the interstitial fluid, and R is the radius of the spherical tumor. The extracellular fluid velocity (EFV) field satisfies

$$\nabla.[\phi_f \mathbf{V}_f^{\text{in}}(\mathbf{x})] = -\alpha_t^2(1 + L_r A_r)(P^{\text{in}}(\mathbf{x}) - 1). \tag{5.8}$$

Finally, the displacement field is found to satisfy

$$\nabla^2 P^{\text{in}}(\mathbf{x}) = \frac{4}{3}\nabla^2(\nabla.\mathbf{V}_f^{\text{in}}(\mathbf{x})) + \frac{\varrho_t(1-\nu_p)}{(1+\nu_p)(1-2\nu_p)}\nabla^2(\nabla.\mathbf{U}_s^{\text{in}}(\mathbf{x})), \tag{5.9}$$

where

- $\varrho_t = \mathcal{Y}R^2\rho_f/\mu_f^2$ is the dimensionless Young's modulus ($\mathcal{Y}$) associated with the solid phase, which represents the response of the solid phase (cellular phase + extracellular matrix) towards viscous drag due to interstitial fluid movement.
- ν_p is the Poisson ratio of the solid phase (cellular phase + extracellular matrix).

In the current study, we are rather interested in the spherical symmetry stress field for both the phases. Accordingly, we assume $P^{\text{in}}(\mathbf{x}) = P^{\text{in}}(r)$, $\mathbf{U}_s^{\text{in}}(\mathbf{x}) = U_s^{\text{in}}(r)\hat{\mathbf{e}}_r$, $\mathbf{V}_f^{\text{in}}(\mathbf{x}) = V_f^{\text{in}}(r)\hat{\mathbf{e}}_r$ etc. Thus, in the spherical symmetry form, Eqs. (5.6)–(5.9) are restated as

$$\left[\frac{1}{r^2}\frac{d}{dr}\left(r^2\frac{d}{dr}\right) - \gamma^2\right](P^{\text{in}}(r) - 1) = 0, \tag{5.10}$$

$$\frac{1}{r^2}\frac{d}{dr}(r^2\phi_f V_f^{\text{in}}) = -\alpha_t^2(1 + L_r A_r)(P^{\text{in}}(r) - 1), \tag{5.11}$$

$$\frac{1}{r^2}\frac{d}{dr}\left(r^2\frac{d}{dr}\right)\left[P^{\text{in}}(r) - \frac{4}{3}\frac{1}{r^2}\frac{d}{dr}(r^2V_f^{\text{in}}) - \frac{\varrho_t(1-\nu_p)}{(1+\nu_p)(1-2\nu_p)}\frac{1}{r^2}\frac{d}{dr}(r^2U_s^{\text{in}})\right] = 0. \tag{5.12}$$

One can compute the analytical solution of Eqs. (5.10)–(5.12) using boundary conditions (2.17). For example, Dey and Raja Sekhar [13] have computed such solutions despite using different boundary conditions. Since the solution procedure remains the same, we do not present the detailed solution here. Using the solution of Eqs. (5.10)–(5.12), we compute normal stresses corresponding to the fluid and solid phases (i.e., $T_{f,rr}^{\text{in}}$ and $T_{s,rr}^{\text{in}}$) and display their variation at each point inside the tumor. We compute $T_{f,rr}^{\text{in}}$ and $T_{s,rr}^{\text{in}}$ as

$$(T_{f,rr}^{\text{in}} + T_{s,rr}^{\text{in}})(r) + 1 = A(X(r) + Y(r)) + BZ(r), \tag{5.13}$$

where

$$X(r) = -\phi_f \mathrm{i}_0(\gamma r) - \frac{4\text{Da}\alpha_t^2}{3\phi_f}(1 + L_r A_r)\mathrm{i}_0(\gamma r) + \frac{4\text{Da}\alpha_t^2}{\phi_f \gamma r}(1 + L_r A_r)\mathrm{i}_1(\gamma r), \tag{5.14}$$

$$Y(r) = -\phi_s \mathrm{i}_0(\gamma r) + \left\{1 + \frac{4\text{Da}\alpha_t^2}{3\phi_f}(1 + L_r A_r)\right\}\left[\mathrm{i}_0(\gamma r) - \frac{(1-2\nu_p)}{(1-\nu_p)\gamma r}\mathrm{i}_1(\gamma r)\right], \tag{5.15}$$

$$Z(r) = \frac{\varrho_t \text{Da}}{3(1-2\nu_p)}, \quad A = \frac{(1+\phi_f)}{X(1)}, \quad B = \frac{1}{Z(1)}\left[\phi_s - \frac{Y(1)(1+\phi_f)}{X(1)}\right]. \tag{5.16}$$

Note that corresponding to the spherical symmetry model, the IFP can be expressed as $P^{\text{in}}(r) = 1 + A\mathrm{i}_0(\gamma r)$. The behavior of IFP towards α_t in this context is similar to an isolated tumor with the imposed ambient pressure (the same as atmospheric pressure) on the boundary. We follow the standard literature on modeling transport phenomena inside tumors [4,25] and identify a range of various parameters involved. Correspondingly, we vary the parameters in the specified range to generate results.

Fig. 2(a) depicts that increase in the IFP can be noted with increase in α_t. At a fixed radius r, for $\alpha_t < 1$, a small increment in α_t causes a significant increment in the magnitude of IFP. In addition, beyond $\alpha_t = 1$, the IFP variation is marginal with increasing α_t. $P^{\text{in}}(r)$ attains the fixed minimum (which is close to 0.25) at $r = 1$ corresponding to $\alpha_t \leqslant 2$. The corresponding minimum value of IFP increases further with α_t. Evidently, tumor center is a region with high IFP. The difference in IFP in the peripheral region and the core region becomes marginal corresponding to larger α_t. This scenario is not favorable for interstitial convection. This situation is quite opposite to the case where IFP meets ambient pressure on the tumor surface [13].

With the one-dimensional spherical symmetry model, we generate some results on the stress fields (solid + fluid phases) inside the tumor. Since in [13], a detailed analysis of the velocity fields is discussed, we focus our attention on the stress fields, which play a crucial role in clinical designs. Fig. 2(b) shows that the magnitude of the normal fluid and solid stresses ($T^{\text{in}}_{f,rr}$ and $T^{\text{in}}_{s,rr}$) increases with the interstitial permeability ($\text{Da} = k_{\text{in}}/R^2$) of the tumor. The inner region of a tumor is a high pressurized zone. Consequently, in order to meet the interstitial flow characteristics, EFV gradients decrease towards the tumor core and hence, the magnitude of fluid stress decays towards the core. Moreover, increasing hydraulic conductivity reduces the interstitial resistance towards the seepage of the fluid. Therefore, $T^{\text{in}}_{f,rr}$ increases with Da. Dey and Raja Sekhar [13] have shown that the tumor core region (spherical) is a necrotic prone zone due to the absence of adequate vascularization and lack of convective transport (EFV goes to zero towards the core). On the other hand, an increase in Da corresponds to increased hydraulic conductivity of the interstitial space. Both the shear and bulk stresses corresponding to the solid phase decrease with the hydraulic conductivity. This can be understood when the stress field is made dimension-free (one can find Da as the common coefficient of shear and bulk stress terms). Moreover, decrease in Da enhances the drag coefficient. Thus, the drag force on the solid phase increases due to the presence of the magnitude of the drag force term in the momentum equations corresponding to the solid phase. We observe a sharp decay in the normal component of solid stress near the tumor boundary due to the corresponding drop in the pressure when the hydraulic conductivity is small.

Fig. 2(c) indicates that the fluid stress is low in the necrotic core region. On the other hand, low values of α_t correspond to a region with low nutrient perfusion. We observe that $T^{\text{in}}_{f,rr}$ increases with decrease in α_t. A rapid decay in the normal stress field with r is observed corresponding to larger α_t. The EFV gradient becomes high towards the core region of a tumor, due to the rapid decrease in the normal stress field. Thus, one can conclude that larger velocity gradient is observed with larger perfusion. Inside a low perfused region, velocity gradient must be low. On the other hand, the strength of the solute perfusion has a potential impact on the normal solid stress field, which is depicted in Fig. 2(c). We observe that, similarly to the radial displacement field, $T^{\text{in}}_{s,rr}$ increases with α_t. An increase in α_t enhances both shear and bulk stresses on the solid phase. Besides, increase in α_t influences

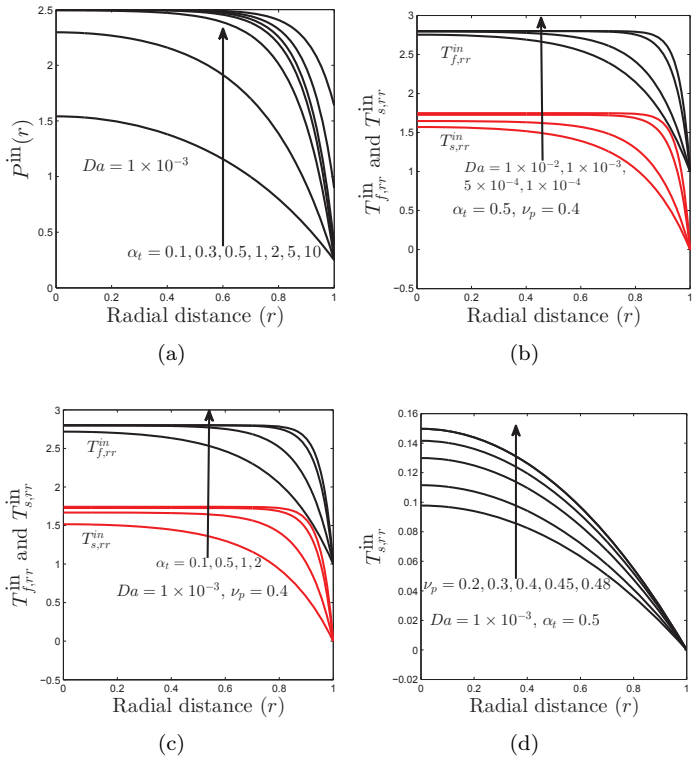

FIGURE 2. (a) Normal component of IFP versus radial distance for different α_t (c) Normal component of fluid and solid stresses versus radial distance for different Da (d) Normal component of fluid and solid stresses versus radial distance for different α_t and (e) Normal component of solid stress versus radial distance for different Poisson ratio of the solid phase.

the normal pressure and EFV. In addition, increase in α_t leads to a saturation such that beyond $\alpha_t = 1$, $T^{\text{in}}_{s,rr}$ becomes more or less independent of α_t.

The behavior of the solid stress field towards the interstitial flow can be discussed in terms of hydraulic conductivity, and elastic moduli corresponding to the isolated solid tumor. Fig. 2(d) shows the variation of the normal component of solid stress ($T^{\text{in}}_{s,rr}$) with Poisson ratio ν_p. The Poisson ratio close to 0 and 0.5 corresponds to the hard and soft tissue phase (cellular phase + extracellular matrix) respectively. The magnitude of $T^{\text{in}}_{s,rr}$ is maximum at the core and decreases to zero at the boundary to meet the zero contact force criteria. Moreover, $T^{\text{in}}_{s,rr}$ increases with ν_p. When $\nu_p = 0$, the coefficient of the bulk stress becomes zero and the coefficient of the shear stress becomes maximum. On the other hand, when $\nu_p = 0.5$ the shear stress is minimum and the corresponding volume strain becomes

maximum (incompressible solid phase). It has been observed that the radial displacement field shows different nature from the normal stress field. The maximum (minimum) normal stress field corresponds to minimum (maximum) displacement in the solid phase. We can state that the magnitude of the solid stress becomes maximum inside the necrotic zone.

6. Energy levels corresponding to L^2 and H^1 norms

In this section, we focus on the insights of L^2 and H^1 norms of the physical quantities EFV and SPD of the corresponding spherical symmetry mode. In general, L^2 norm of the velocity does represent the kinetic energy of the corresponding phase inside the system. On the other hand, H^1 norm of velocity represents a higher state of energy in which the gradient of velocity is involved. In this study, we discuss the formation of necrosis in the light of system energy. For a system in a steady state, deformation of the solid phase is discussed in terms of displacement vector. Equivalent form of the system energy corresponding to the solid phase can be discussed in terms of L^2 and H^1 norms of the displacement vector. For a spherical symmetry system, L^2 and H^1 norms of velocity and displacement for fluid and solid phases are respectively given by

$$
\begin{aligned}
EV_{f_{L^2}} &= \|V_f\|_{L^2_r} = 2\sqrt{\pi}\left[\int_{r=0}^{1}(|V_f(r)|^2)r^2dr\right]^{1/2},\\
EV_{f_{H^1}} &= \|V_f\|_{H^1_r} = 2\sqrt{\pi}\left[\int_{r=0}^{1}(|V_f(r)|^2+|dV_f/dr|^2)r^2dr\right]^{1/2},\\
EU_{s_{L^2}} &= \|U_s\|_{L^2_r} = 2\sqrt{\pi}\left[\int_{r=0}^{1}(|U_s(r)|^2)r^2dr\right]^{1/2},\\
EU_{s_{H^1}} &= \|U_s\|_{H^1_r} = 2\sqrt{\pi}\left[\int_{r=0}^{1}(|U_s(r)|^2+|dU_s/dr|^2)r^2dr\right]^{1/2}.
\end{aligned}
$$

It is observed through Figures 3(a)–3(b) that both $EV_{f_{L^2}}$ and $EV_{f_{H^1}}$ increase with α_t due to increase in EFV. It always holds that the strength $\alpha_t \geqslant 0$. Thus, the higher rate of nutrient proliferation causes increase in internal system energy. At a higher state of system energy, the convective transport of nutrient becomes more significant inside the interstitial space to reduce the necrosis formation. It is obvious that increase in the system energy leads to increase in the cell proliferation. Thus at the higher level of energy, increased volume of cell population leads to increase in the size of the tumor. Increase of $EV_{f_{H^1}}$ is rapid compared to $EV_{f_{L^2}}$. Increasing interstitial permeability (increase in Da) enhances the system internal energy. The low permeable tumor interior possesses less nutrient concentration due to low convective transport and this shows a reduction of the system energy. We choose Da in the range $(10^{-4}, 10^{-3})$, which is appropriate for a deformable Brinkman model. In case of $L_{p_L}A_L/L_pA > 1$, conductivity of a lymph vessel is supposed to be higher than that of a blood vessel. The convective drain timing through the wall of lymph vessel is lesser compared to the filling through the blood vessel. As a result, the system can drain out waste materials (metabolic products)

fast. Such a system possesses higher internal energy. It is also illustrated that increase in the magnitude of $L_{p_L} A_L / L_p A$ results in a fast increment of $EV_{f_{H^1}}$ as compared to the $EV_{f_{L^2}}$.

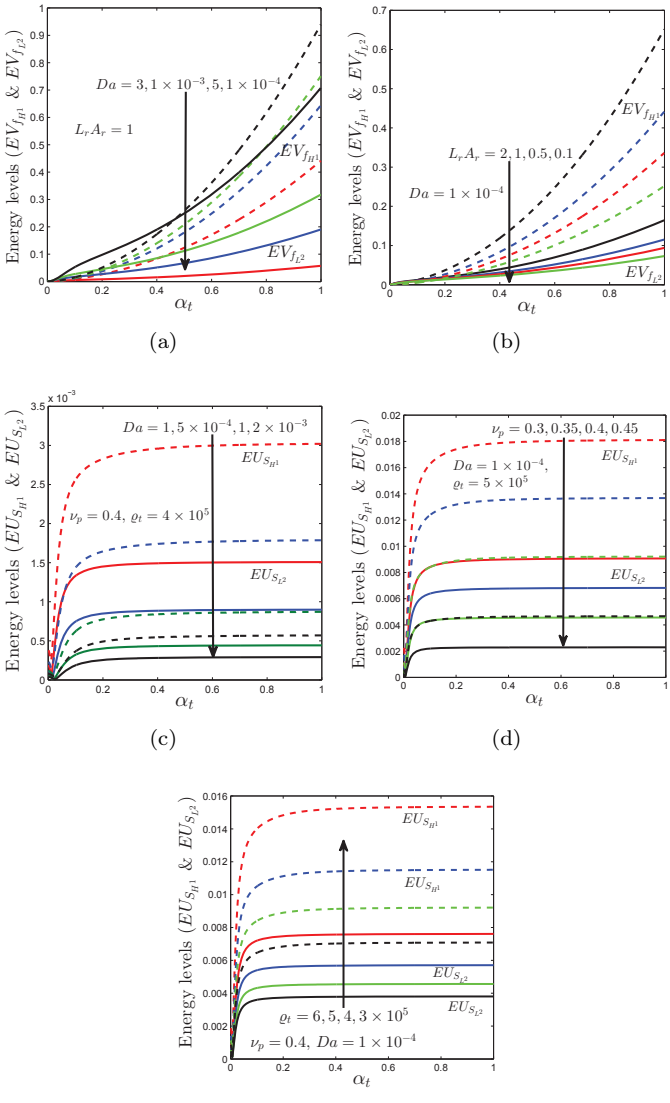

FIGURE 3. One dimensional form of energy levels for EFV and solid phase (cell population + ECM) displacement corresponding to L^2 and H^1 norms: Variation with α_t for different (a) Da (b) $L_r A_r$ (c) Da (d) ν_{p} and (e) ϱ_t.

Figures 3(c)–3(e) depict variation of internal system energy corresponding to the solid phase with respect to Da, ν_p and ϱ_t respectively. We find that both $EU_{s_{L^2}}$ and $EU_{s_{H^1}}$ increase with α_t up to a certain magnitude and thereafter both of them become constant. The increment of $EU_{s_{H^1}}$ is more rapid as compared to $EU_{s_{L^2}}$. Increase in α_t suggests increase in the drag force on the solid phase. The drag force from the fluid phase is found to be only responsible for the deformation of the solid phase. At higher magnitude of solute perfusion, growth of solid phase internal energy becomes stable. On the other hand, decrease in $EU_{s_{L^2}}$ and $EU_{s_{H^1}}$ with increase in Da can be observed. Smaller Da corresponds to the larger surface area constituted by the solid phase of tumor tissue. Also, decrease in Da enhances the Drag coefficient. As a result, increase in the Drag force causes growth in the internal energy of the solid phase. From this discussion, one can claim that the low permeable region inside a tumor possesses high internal energy. On the other hand, with increase in ν_p, decrease in $EU_{s_{L^2}}$ and $EU_{s_{H^1}}$ results. We choose four different Poisson ratios as $\nu_p = 0.3, 0.35, 0.4, 0.45$ and this choice is appropriate for biological tissues. Smaller (larger) values of Poisson ratio correspond to hardness (softness) of the solid phase. The hard (soft) solid matrix of the tumor possesses higher (lower) internal energy and shows higher (lower) tendency to be deformed. The solid phase internal energy varies with the Young's modulus of the solid phase. Here ϱ_t represents the response of the solid phase towards the viscous drag. Based on the choice of Young's modulus in the range $1.46 - 1.74\,\mathrm{kPa}$, plasma viscosity in the range $1.3 - 1.7 \times 10^{-3}\,\mathrm{PaS}$, plasma density equal to $1025\,\mathrm{kg/m^3}$ and tumor radius equal to $0.1\,\mathrm{cm}$, we can consider the following range for ϱ_t is $3 - 6 \times 10^5$. Larger (smaller) Young's modulus of the solid phase corresponds to the smaller (higher) internal energy of the solid phase. Thus, due to increase in the internal energy at low Young's modulus, the solid phase is prone to deform towards the hydrodynamic drag.

7. Conclusion

It is observed that mechanics of tumor growth is mainly dependent on the transport of different fluids and nutrients inside a solid tumor. In the context of mixture theory, one can study the density variations within the components to evaluate the evolution of the stresses and mechanical interactions among the constituents. This was not possible with the previous modeling where the Darcy/Brinkman single phase model was used to describe the hydrodynamics inside a solid tumor. In this paper, we have shown the well-posedness of the poroelastodynamics inside an arbitrary solid tumor in the weak sense. We realize that in the absence of a classical solution of the poroelastodynamics, one can find a weak solution to establish the well-posedness. We have converted the partial differential equations corresponding to the poroelastodyamic model into an equivalent weak formulation. The corresponding abstract formulation has also been obtained by introducing bilinear and linear forms. Using the Lax–Milgram theorem and inf-sup condition, the well-posedness (existence, uniqueness and stability) of the weak solution is shown.

Based on the analytical solution for the one-dimensional tumor model, we have observed that inside a necrotic or low fluid perfused region, normal stresses

corresponding to the fluid and solid phases are minimum and maximum respectively. A high solid phase stress causes less deformation due to increasing rigidity in the solid phase. The solute perfusion strength showed a positive influence on the fluid stress, but the solid stress field was negatively affected by the strength of the perfusion. Increasing hydraulic conductivity enhanced the normal fluid stress and caused the normal solid stress to diminish. Finally, we have observed that increasing softness of the matrix of the tumor causes increased magnitude of the solid stress. Since a solid tumor is a living biological system, we try to get the system internal energy by computing L^2 and H^1 norms of both the EFV and SPD. Later, we define the necrotic zone as a region with less internal system energy. Also, a low permeable interstitial space possesses less system energy. With the increasing strength of solutes, system energy corresponding to the fluid phase shows increasing behavior while stability is noted in case of solid phase system energy. The stiffer solid phase of a biological tissue (when $0.3 \leqslant \nu_p \leqslant 0.5$) possesses significant high internal energy so that deformation is notable.

In general, linear models are first steps to understand non-linear models of tumor growth. On the other hand, non-linear models are more challenging than the linear ones from a mathematical point of view as well as their physical interpretations. In the present model, the processes like nutrient transport, solid phase deformation, and hydrodynamics are very slow, due to which the non-linearity does not appear. Authors believe that these results will give useful insights to understand the non-linear system. We may explore the same in the near future.

8. Appendix

To establish well-posedness, we need the following function spaces and preliminary results.

8.1. Function spaces and some useful results. $M = L^2(\Omega)$ is a space of all measurable functions u defined on Ω for which

$$\|u\|_M = \left(\int_\Omega |u|^2 \, d\Omega \right)^{1/2} < +\infty,$$

$\| \|_M$ defines a norm on M.

For any $\mathbf{u} = (u_1, u_2, \ldots, u_d) \in M^d = L^2(\Omega)^d$, the norm $\|\mathbf{u}\|_{M^d}$ is defined as

$$\|\mathbf{u}\|_{M^d} = \left(\int_\Omega \sum_{i=1}^{d} |u_i|^2 \, d\Omega \right)^{1/2},$$

and for any element $\mathbf{K} = (K_{ij})_{1 \leqslant i,j \leqslant d} \in M^{d^2} = L^2(\Omega)^{d \times d}$, the norm $\|\mathbf{K}\|_{M^{d^2}}$ is defined as

$$\|\mathbf{K}\|_{M^{d^2}} = \left(\int_\Omega \sum_{i=1}^{d} \sum_{j=1}^{d} |K_{ij}|^2 \, d\Omega \right)^{1/2}.$$

$(,)_\Omega$, and $(,)_{\partial\Omega}$ denote the inner products in M, M^d, and M^{d^2} and in corresponding trace spaces $L^2(\partial\Omega)$, $L^2(\partial\Omega)^d$, and $L^2(\partial\Omega)^{d \times d}$.

We choose the space $\mathbf{X} := H^1(\Omega)^d$ where the norm of a function $\mathbf{u} \in \mathbf{X}$ is defined as

$$\|\mathbf{u}\|_{\mathbf{X}} = \left(\int_\Omega \sum_{i=1}^{d} |u_i|^2 \, d\Omega + \int_\Omega \sum_{i=1,j=1}^{d} |\partial_{x_j} u_i|^2 \, d\Omega \right)^{1/2},$$

and $\mathbf{X}' = (H^1(\Omega)^d)'$ denotes the dual space of $\mathbf{X}$. The norm on $\mathbf{X}'$ is defined as

$$\|\mathbf{f}\|_{\mathbf{X}'} = \sup_{0 \neq \mathbf{u} \in \mathbf{X}} \frac{|\langle \mathbf{f}, \mathbf{u} \rangle|}{\|\mathbf{u}\|_{\mathbf{X}}}.$$

$\langle \cdot, \cdot \rangle$ denotes the duality pairing between $\mathbf{X}$ and its dual $\mathbf{X}'$.

Further, $H^{1/2}(\partial\Omega)^d := \{\mathbf{u}|_{\partial\Omega} : \mathbf{u} \in H^1(\Omega)^d\}$ denotes the trace space with the norm

$$\|\mathbf{g}\|_{H^{1/2}(\partial\Omega)^d} = \inf\{\|\mathbf{w}\|_{H^1(\Omega)^d} | \mathbf{w} \in H^1(\Omega)^d, \mathbf{w}|_{\partial\Omega} = \mathbf{g}\}.$$

THEOREM 8.1 (Trace theorem [28]). *Assume Ω is either $\mathbb{R}^n_+$ or a bounded, Lipschitz domain. Then there exists a trace operator $\tau_0 : H^1(\Omega) \to L^2(\partial\Omega)$ such that:*

- $\tau_0 u = u_{|\partial\Omega}$ *if* $u \in \mathcal{C}_0^\infty(\overline{\Omega})$,
- $\|\tau u_0\|_{L^2(\partial\Omega)} \leqslant t_r(n, \Omega)\|u\|_{H^1(\Omega)}$,

where t_r is a constant depending on n and Ω.

The image of the operator τ_0 is given by

$$Im\tau_0 = H^{1/2}(\partial\Omega) = \{\tau_0 u | u \in H^1(\Omega)\}.$$

COROLLARY 8.1. [17] *If we set $\mathbf{Y}_0 = \{\mathbf{v} \in H_0^1(\Omega)^d | \nabla \cdot \mathbf{v} = 0\}$, then*

$$H_0^1(\Omega)^d = \mathbf{Y}_0 \oplus (\mathbf{Y}_0)^\perp$$

and the operator div *(divergence operator) is an isomorphism of $(\mathbf{Y}_0)^\perp$ onto $L^2(\Omega)/\mathbb{R}$.*

THEOREM 8.2 (Korn's Inequality [17]). *Let Ω be a domain in $\mathbb{R}^d$, for $d = 2, 3$. Then there exists a constant $c_0 = c_0(\Omega)$ such that*

$$\|\mathbf{V}\|^2_{H^1(\Omega)^d} \leqslant c_0(\|\mathbf{V}\|^2_{L^2(\Omega)^d} + \|D(\mathbf{V})\|^2_{L^2(\Omega)^{d\times d}}), \quad \forall \mathbf{V} \in H^1(\Omega)^d.$$

THEOREM 8.3 (Poincare's Inequality [28]). *Let Ω be a bounded Lipschitz domain in $\mathbb{R}^d$, for $d = 2,\ 3$. Then there exists a constant $c_p = c_p(\Omega)$ such that*

$$\|\mathbf{V}\|^2_{L^2(\Omega)^d} \leqslant c_p \|\nabla \mathbf{V}\|^2_{L^2(\Omega)^{d\times d}}, \quad \forall \mathbf{V} \in H_0^1(\Omega)^d,$$

where c_p denotes the Poincare's constant.

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МАТЕМАТИЧКА АНАЛИЗА ХИДРОДИНАМИКЕ И ДЕФОРМАЦИЈЕ ТКИВА У ИЗОЛОВАНОМ ЧВРСТОМ ТУМОРУ

Резиме. У овом чланку представљамо математички модел за хидродинамику међукретања флуида и механичког понашања чврсте фазе унутар чврстог тумора. Тумор који се овде разматра је изолована деформабилна биолошка средина. Чврста фаза тумора је састављена од васкулатуре, туморских ћелија и екстрацелуларне мреже, која је овлажена физиолошком екстрацелуларном течности. Пошто је тумор по природи деформабилан, приказане су једначине масе и импулса за обе фазе. Једначине импулса су везане услед силе међудејства (или превлачења). Ове једначине кретања се редукују на једносмерни везани систем под претпоставком инфинитезималне деформације чврсте фазе. Ваљаност овог модела је показана у слабом смислу коришћењем inf-sup (Babuska–Brezzi) услова и Lax–Milgram-ове теореме у 2D и 3D. Даље, дискутујемо једнодимензионални сферно симетрични модел и изводимо резултате о пољу напона и енергије система засноване на L^2 и нормама Соболљева. Дискутујемо тзв. феномене "некрозе" унутар чврстог тумора користећи енергију система.

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