In vivo mimicking model for solid tumor towards hydromechanics of tissue deformation and creation of necrosis

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Abstract The present work addresses transvascular and interstitial fluid transport inside a solid tumor surrounded by normal tissue (close to an in vivo mimicking setup). In general, biological tissues behave like a soft porous material and show mechanical behavior towards the fluid motion through the interstitial space. In general, forces like viscous drag that are associated with the fluid flow may compress the tissue material. On the macroscopic level, we try to model the motion of fluids and macromolecules through the interstitial space of solid tumor and the normal tissue layer. The transvascular fluid transport is assumed to be governed by modified Starling's law. The poroelastohydrodynamics (interstitial hydrodynamics and the deformation of tissue material) inside the tumor and normal tissue regions is modeled using linearized biphasic mixture theory. Correspondingly, the velocity distribution of fluid is coupled to the displacement field of the solid phase (mainly cellular phase and extracellular matrix) in both the normal and tumor tissue regions. The corresponding velocity field is used within the transport reaction equation for fluids and macromolecules through interstitial space to get the overall solute (e.g., nutrients, drug, and other macromolecules) distribution. This study justifies that the presence of the normal tissue layer plays a significant role in delaying/assisting necrosis inside the tumor tissue. It is observed that the exchange process of fluids and macromolecules across the interface of the tumor and normal tissue affects the effectiveness factor corresponding to the tumor tissue.

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1 Introduction

Convective transport of drugs and nutrient molecules through gel-like interstitial space of biological tissues is an important topic of interest while modeling biological tissue mechanics based on suitable mathematical models. There are two popularly known approaches for modeling a soft tissue, namely the theory of poroelasticity [1–6] and theory of mixture [4, 5, 7–12]. In the theory of poroelasticity, soft tissues are considered as fluid-saturated elastic porous solids and exhibit sponge-like behavior. Whereas in the latter [13–17], each soft tissue is contemplated as a continuous binary mixture of solid (s) and fluid (f) phases, respectively. Each point within the binary mixture is occupied simultaneously by a material point of each constituent.

The two approaches above are continuum approximations of the actual structure of soft biological tissues. In addition to cells and the corresponding interstitial spaces inside a biological tissue, continuously distributed blood microvessels and lymphatic networks are found. In order to model hydrodynamics or heat and mass transfer inside a biological tissue, we need to consider more than one constitutive phase (e.g., cell + extracellular fluid) [18]. In order to describe interstitial hydrodynamics inside a biological tissue, three popular models are used viz. Darcy model (tumors, perfused muscle tissues, etc.), Brinkman model (endothelial cell glycocalyx, blood clots, etc.), and Brinkman–Forchheimer–Darcy model (highly perfused skeletal tissues) [19, 20]. Fung [21] described a biological tissue as a fluid-saturated poroelastic medium with uniformly distributed sources/sinks, which represent the transvascular flow to or from the interstitial space. In order to describe the continuous exchange process of solutes among blood vessels, interstitial space, and lymph vessels, one requires not only a vivid knowledge of vascular topology but also microcirculatory fluid dynamics and cell distribution along with their complex interaction [22]. In another study, Netti et al. [23] used the concept of viscoelasticity for modeling fluid transport inside a solid tumor. The solid stress field possesses a viscoelastic term, which is viscoelastic constant multiplied by integral as a product of rate of strain and a memory function. This model also describes distribution of macromolecules using convection–diffusion equation.

The present study deals with the transport of blood-borne solutes like therapeutic agents, nutrients, etc., inside a solid tumor embedded within a normal tissue in the presence of some transportation barriers. Such barriers also exist within the normal tissue region as well. As indicated in earlier studies, a tumor in general consists of (i) 65% of tumor cells, (ii) 5% of the vasculature, and (iii) 30% of interstitial space [24]. A similar structure is also valid for the normal tissue as well but, with an expected proportionate deviations. In general, the peripheral region of a tumor contains enriched vascularization while the core region of the tumor suffers lack of vascularization [25]. Cells present in the avascular or poorly vascularized region suffer the nutrient deficiency. This lack of nutrients forces the cells to die. These groups of dead and nutrient-exhausted cells constitute necrotic region [26, 27]. For a small tumor, tumor cells are expected to receive adequate nutrients through interstitial diffusion. During the growth of the tumor, the nutrient concentration falls below a critical level and triggers necrosis [28]. In case of normal tissue, due to the uniform vascularization, each cell can receive adequate nutrients to survive.

Solute transport to tissues undergoes the following pathways: (i) transport through a blood vessel, (ii) transport across the wall of a blood vessel to the interstitial space of the

tissue, (iii) interstitial transport to reach cells [29, 30]. This transport process depends on the physiochemical properties of a solute, i.e., molecular size, diffusivity, etc. [24, 29]. Apart from the size of the molecules, there are a few factors like conductivity of the blood vessel wall, hydraulic conductivity of the interstitial space (depends on the tissue structure, cell density, etc. [29]), which influence the transport. There are some significant transportation barriers for every solute during perfusion and transport given by (i) low conductivity of the blood vessel wall, (ii) less interstitium permeability [24, 25, 31]. Further, corresponding to a tumor tissue, another barrier is (iii) low perfusion due to vessel compression [32]. Also, the interstitial flow gets restricted by the effective blood viscosity and thickness of the blood vessel [33]. The presence of tumor cells and large protein molecules contribute to the blood viscosity. Low venous pressure is observed inside a tumor tissue in comparison with normal tissue. However, the same arterial pressure is maintained [34]. In contrast to the normal tissue, the blood vessel distribution is not regular inside a tumor. In the peripheral region, blood vessels are constituted of arteries and arterioles, whereas in the tumor core region they are constituted of veins and venules [34]. Correspondingly, the pressure difference across the blood vessel wall is small within the core region. This causes heterogeneous blood flow within a tumor, which is low at the center and high at the periphery. Such an irregular blood flow cannot be expected in the case of normal tissue [34, 35].

Dey and Raja Sekhar [32] have developed a hydrodynamic model for fluid and macromolecule transport inside an isolated solid tumor, using the concept of biphasic mixture theory. Inside the tumor, the effect of the vascular network as solute source and lymph system for drainage from the interstitial space have been captured in detail. For a non-growing tumor, velocities corresponding to each of the phases are obtained for a one-dimensional time-dependent model explicitly by solving the coupled hydrodynamic equations. Explicit solution corresponding to each phase is required to compute the composite velocity, which contributed to the convection term of the solute transport equation [32, 36, 37]. Dey and Raja Sekhar [32] have considered that for an infinitesimal small solid-phase displacement, first-order time derivative of the displacement vector is approximately zero [15]. However, the solid-phase displacement vector helps one to understand the mechanical response towards the interstitial fluid movement. The detailed study done by Dey and Raja Sekhar [32] enlists some essential criteria for the creation of necrosis concerning several transport parameters. Moreover, the dependency of displacement on the elastic parameters associated with the solid phase is discussed. In this study, we attempt an extension of the isolated solid tumor model where the tumor possesses a normal tissue layer surrounding the tumor tissue. This mathematical model is represented as an *in vivo* tumor analogous model [38–41]. There must be some physiological differences between normal and tumor tissues [26, 42, 43]. In this context, our aim is to study the qualitative differences in the transport mechanisms between normal and tumor tissue. In addition, the mechanical interaction between the two tissue regions will be discussed in detail.

2 Problem statement

In this paper, a mathematical model is introduced to describe the transport of blood-borne biochemical components inside a spherical solid tumor, which is surrounded by a normal tissue layer (see Fig. 1). In comparison to normal tissue, a tumor possesses a complex structure. Four essential components of a tumor tissue are (i) tumor cell population, (ii) networks of blood and lymph vessels (vascular network), (iii) extracellular matrix [chief components: fibrous proteins network (e.g., collagen and elastin), polysaccharide (e.g., hyaluronate and

Fig. 1 (Color online) Simplified geometry of a solid tumor surrounded by normal tissue layer

proteoglycan) and lipid], (iv) extracellular fluid (they are mainly the viscous fluid within the “interstitial space”, plasma in the blood and lymph vessels and small a portion of transcellular fluid). Normal tissue in general consists of the monodispersed cell population and well-organized vascular network, which is not the case in case of a tumor tissue. In contrast to normal tissue, tumor tissue grows in multiple layers due to the absence of “contact inhibition” [44], which is responsible for the uniform growth as well as the arrangement of cells. For general biological tissue, interstitial space connects the blood and lymph vessel networks to the cell membrane. Interstitial space consists of three main components: (i) a continuous fluid phase (water, electrolytes, nutrients, plasma proteins, etc.); (ii) collagen or glycoprotein fibrils network; (iii) a group of fine fibrous molecules which remain attached to the network and remain static. These fibrous molecules are mainly glycosaminoglycans (GAG), structural glycoproteins and the fibrous core protein to which sulphated GAGs are bound as proteoglycan (PG) complex. For the sake of simplicity, one can assume that deformable solid phase of biological tissue is the ensemble of interstitial, vascular regions,

and cell population to form a continuous mixture. On the other hand, the fluid phase is the interstitial fluid in which cells survive.

The governing hydrodynamic equations both inside the tumor region and normal tissues are based on the biphasic mixture theory. The difference between interstitial fluid pressure (IFP) and effective vascular pressure (EVP) creates a driving force, which induces the interstitial fluid velocity (IFV). This IFV is coupled with the deformation of the solid phase of both tumor tissue and normal tissue. The drag force associated with the interstitial fluid flow is responsible for this coupling. We discuss the solute transport model inside the tumor and normal tissues, which is concerned with the transport of solutes like oxygen, nutrients, chemoattractants, and so on through the interstitial space to cells.

Due to the heterogeneous blood vessel distribution, the supply of blood-borne biochemical components inside a tumor is mostly heterogeneous. Being motivated by Holmes and Mow [45], Dey and Raja Sekhar [32] have assumed the spatially dependent hydraulic conductivity inside an isolated tumor. By this choice of the permeability, it can be understood that for a tumor, the peripheral region is hypervascular and the central region is hypovascular. The actual structure of tumors may vary based on the location inside an animal body; the hydraulic conductivity may be location specific. However in case of normal tissue, the hydraulic conductivity can behave uniformly throughout. On the other hand, there are experimental pieces of evidence on the constant hydraulic conductivity of tumor tissue [46]. Except for small strain in the solid phase, the hydraulic conductivity shows a nonlinear relation with strain and hence with the deformation. For small strain, interstitial hydraulic conductivity can either be a constant or a linear function of strain [32, 45, 47]. Without loss of generality for the sake of simplicity, we may assume that the hydraulic conductivities of both the tumor and surrounding normal tissue are constant and independent of deformation.

The interstitial hydraulic conductivity of biological tissue is found to have a negative correlation with the concentration of fibrous glycosaminoglycan (GAG) network and collagen fibril network within the interstitium. Moreover, hydraulic resistance in the interstitial space is not only due to the drag effect of the cell wall or membrane, but it also depends on the concentration of fibrous materials which span the intercellular space. The dense network of collagen or glycoprotein fibril and GAG chain, which results in low interstitium permeability, is the primary reason for the small seepage of interstitial fluid. The interstitium hydraulic conductivity maintains a nonlinear relation with the concentration of collagen or glycoprotein and GAG [32, 48].

In the present study, we develop the hydrodynamics of fluid transport through the interstitial space of a homogeneous tumor enclosed with a thick layer of normal tissue (host tissue) over the length scale in order of tumor radius. Normal tissue layer has a role in diffusion and migration of tumor cells during metastasis. This hydrodynamic model does not include the microscopic features like blood vessels, normal and tumor cells, and extracellular matrix (ECM) explicitly. A generalized hydrodynamic model is accompanied with generalized mass transfer model to describe the transport of blood-borne biochemical components to the cells through the interstitial space. This model is presented while treating the corresponding volume fractions varying subject to the total saturation constraint. However for constant volume fractions under standard assumptions, we obtain an analytical solution for the spherical symmetry situation. This assumption forces the generation of radially active flow to take place from the vasculature. We predict some criteria affecting necrosis formation inside the tumor and the role of normal tissue layer on its development. The possibility of necrosis formation is higher in the case of a larger tumor compared to a smaller tumor. Smallbone et al. [49] estimated a critical radius of a tumor at which necrosis begins. Hypoxia and necrosis are more or less similar phenomena due to which tumor cells

die. Recently, Datta et al. [50] have determined the size of hypoxic and necrotic regions using a diffusion and Michaelis–Menten kinetics-based transport model inside a tuberculosis granuloma. Dey and Raja Sekhar [32] have estimated a critical combination of transport parameters which control the formation of necrosis for an isolated tumor. Presently in this paper, we have addressed the effect of normal tissue layer over tumor tissue and this the system is throughout as a representative of an in vivo tumor mimicking model.

3 Hydrodynamics of interstitial fluid transport

In general, living tumor cells occupy 65% volume of a tumor. Similarly, in the case of normal tissue, a significant part of the tissue volume is occupied by normal cells. The cell population collects oxygen, nutrients, and drug molecules from the gel-like interstitium, which is delivered from the blood vessel network. Thus in general, living biological tissue is characterized by a deformable porous structure perfused by blood plasma, which contributes a major part of the interstitial fluid. Relative motion within the cellular phase is observed due to the growth, division, and death of cells. Moreover, relative motion and deformation within the cellular phase are due to the interstitial fluid movement, which is also responsible for small deformation of the fibrous extracellular matrix.

In this present hydrodynamic model, the spherical domain Ω_T represents a tumor which is surrounded by a normal tissue layer that is represented by a concentric outer spherical domain Ω_N of radius R_N and $R_N \gg R_T$ (close to unbounded tissue domain). Both Ω_T and Ω_N are homogeneous deformable porous media. The suffixes N and T denote normal and tumor tissues, respectively. For the sake of simplicity, one can consider that Ω_T is a homogeneous tumor having a single node and a necrotic core.

Let, $\mathbf{V}_f^i(\mathbf{x}, t)$ and $\mathbf{V}_s^i(\mathbf{x}, t)$ denote the interstitial fluid velocity (IFV) and solid-phase velocity vectors, respectively, for $\mathbf{x} \in \Omega_i$ and $i \in \{N, T\}$. $\tilde{\rho}_f^i$ and $\tilde{\rho}_s^i$ are respectively denoting the true densities of fluid and solid phases within the tumor interstitium, φ_f^i and φ_s^i are respective volume fractions of those phases. Note that the solid phase volume is populated by cells, fibrous networks like extracellular matrix (ECM), and vascular space [22]. The major part of this volume fraction φ_s^i is occupied by the cell population, for $i \in \{N, T\}$. In order to reduce complexities in the present mathematical model, we do not consider ECM as a separate phase. On the other hand, we have the interstitial viscous fluid phase, which contains various nutrient and drug molecules, electrolytes, plasma proteins, and so on. We represent the mass balance equations for both the phases (solid and fluid) in the following generic form given by

$$\frac{\partial(\tilde{\rho}_f^i \varphi_f^i)}{\partial t} + \nabla \cdot \left[\left(\tilde{\rho}_f^i \varphi_f^i \right) \mathbf{V}_f^i \right] = \tilde{\rho}_f^i S_f^i(\mathbf{x}, t) \quad \text{in } \Omega_i \subseteq \mathbb{R}^3, \quad (1a)$$

$$\frac{\partial(\tilde{\rho}_s^i \varphi_s^i)}{\partial t} + \nabla \cdot \left[\left(\tilde{\rho}_s^i \varphi_s^i \right) \mathbf{V}_s^i \right] = \tilde{\rho}_s^i S_s^i(\mathbf{x}, t) \quad \text{in } \Omega_i \subseteq \mathbb{R}^3, \quad (1b)$$

where $S_f^i(\mathbf{x}, t)$ and $S_s^i(\mathbf{x}, t)$ represent the generation of fluid and solid phase (precisely, the growth of cell population) respectively, within $\Omega_i \subseteq \mathbb{R}^3$. These sources are continuous, distributed and spatially dependent in Ω_i . The fluid source $S_f^i(\mathbf{x}, t)$ manifests the perfusion of solutes through the blood vessel network within Ω_i . The role of this source is to nourish the tumor and normal cells so that they can survive and produce new cells. The volume

fractions φ_f^i and φ_s^i satisfy the following saturation assumption

$$\varphi_f^i + \varphi_s^i = 1, \quad \text{for } i \in \{N, T\}. \quad (2)$$

When the constant true density of each constituent within Ω_i is constant the saturation constraint help (2), (1a)–(1b) to be summed up to get

$$\nabla \cdot (\varphi_f^i \mathbf{V}_f^i + \varphi_s^i \mathbf{V}_s^i) = S_f^i(\mathbf{x}, t) + S_s^i(\mathbf{x}, t). \quad (3)$$

Note that when

$$S_f^i(\mathbf{x}, t) + S_s^i(\mathbf{x}, t) = 0 \quad \text{in } \Omega_i, \quad (4)$$

we have the biphasic mixture within Ω_i is closed with respect to the mass, which means available solutes (mainly nutrients, electrolytes, plasma proteins, etc.) in the interstitial fluid are only responsible for creation of new cell/fibrous matrix. On the other hand, without any generation of new cell/fibrous matrix during the perfusion of solutes ($S_s^i(\mathbf{x}, t) = 0$), (3) becomes

$$\nabla \cdot (\varphi_f^i \mathbf{V}_f^i + \varphi_s^i \mathbf{V}_s^i) = S_f^i(\mathbf{x}, t). \quad (5)$$

This is the case when Ω_i is not a closed mass. The corresponding model is regarded as a static perfused model, under the assumption that the time scale of growth of the cell population is much larger than the time scale of perfusion from the vasculature and transport to cells. There does exist some literature including some recent on the tumor transport physiology based on the static perfused model [22, 26, 32]. It is defined that

$$\mathbf{V}_{\text{com}}^i = \varphi_f^i \mathbf{V}_f^i + \varphi_s^i \mathbf{V}_s^i \quad (6)$$

is the composite velocity of the binary mixture or weighted average velocity of both the constituents inside Ω_i [32, 37].

$S_f^i(\mathbf{x}, t)$ is the fluid source in Ω_i , which is driven by the average transmural pressure and is expressed as

$$\begin{aligned} S_f^i(\mathbf{x}, t) &= S_V^i(\mathbf{x}, t) - S_L^i(\mathbf{x}, t), \quad \text{for } i \in \{N, T\} \\ &= L_p^i (P_{\text{ev}}^i - P^i) \left(\frac{A}{V} \right)_i - L_{\text{pl}}^i (P^i - P_L^i) \left(\frac{A_L}{V} \right)_i. \end{aligned} \quad (7)$$

Evidently, $S_V^i(\mathbf{x}, t)$ and $S_L^i(\mathbf{x}, t)$ are found to follow Starling's equation. Here, the volumetric flow rate across capillary (fill) and lymphatic wall (drain) are represented through S_V^i and S_L^i , respectively, within Ω_i ; L_p^i and L_{pl}^i are average hydraulic conductivity coefficients of capillary and lymphatic walls within Ω_i , respectively; $(A/V)_i$ and $(A_L/V)_i$ are respectively vascular and lymphatic surface densities within Ω_i . Inside Ω_i , P^i is the average interstitial fluid pressure; $P_{\text{ev}}^i = P_v^i - \sigma_f (\Pi_v^i - \Pi_{\text{int}}^i)$ is the effective vascular pressure; average vascular and lymphatic pressures are respectively denoted by P_v^i and P_L^i ; Π_v^i and Π_{int}^i denote the osmotic pressure of plasma inside the capillary and the interstitial fluid, respectively. The barrier towards the transmural transport in Ω_i is represented by the average osmotic reflection coefficient σ_f . Depending on the solute dispersion and the structure of the micro-vessel, the value of σ_f lies within $(0, 1]$. Impermeability of the capillary wall towards any solute corresponds to $\sigma_f = 1$.

Inside Ω_i , corresponding to the constant apparent density $\tilde{\rho}_j^i$ and the constant volume fraction φ_j^i of each phase (i.e., $j \in \{s, f\}$), the mass conservation equation (5) is given by

$$\nabla \cdot (\varphi_f^i \mathbf{V}_f^i + \varphi_s^i \mathbf{V}_s^i) = -L_p^i \left(\frac{A}{V} \right)_i \{1 + (L_r A_r)_i\} (P^i - P_F^i), \quad (8)$$

where

$$(L_r A_r)_i = \frac{L_{\text{PL}}^i (A_L/V)_i}{L_{\text{p}}^i (A/V)_i}, \quad (9)$$

and

$$P_{\text{F}}^i = \frac{L_{\text{p}}^i P_{\text{ev}}^i (A/V)_i + L_{\text{PL}}^i P_{\text{L}}^i (A_L/V)_i}{L_{\text{p}}^i (A/V)_i + L_{\text{PL}}^i (A_L/V)_i}. \quad (10)$$

Inside Ω_i , $(L_r A_r)_i$ represents the ratio of the strength of solute source through the vasculature and solute sink through the lymph vessels and P_{F}^i denotes weighted vascular pressure. Corresponding to $P = P_{\text{F}}^i$, net efflux from the blood vessel equals net influx into the lymph vessel. Without loss of generality, we can choose $P_{\text{F}}^i = P_{\text{F}}$. The next task is to write the momentum balance equation corresponding to each of the constituent phases (solid and fluid) inside Ω_i as

$$\rho_j^i \left(\frac{\partial \mathbf{V}_j^i}{\partial t} + (\mathbf{V}_j^i \cdot \nabla) \mathbf{V}_j^i \right) = \nabla \cdot \mathbf{T}_j^i + \mathbf{\Pi}_j^i, \quad \text{for } i \in \{N, T\}, \quad j \in \{f, s\}, \quad (11)$$

where $\rho_j^i = \varphi_j^i \tilde{\rho}_j^i$ is the true density of j th phase of the mixture inside Ω_i . In particular, $\rho_f^i = \rho_f$ for $i \in \{N, T\}$. In addition, $\mathbf{T}_j^i$ represents the stress tensor for j th phase and $\mathbf{\Pi}_j^i$ denotes the resultant interaction force on the j th phase with the other phase(s). The derivative term in the left-hand side of (11) is the material derivative. Note that the momentum equation (11) does not contain any body force, however, $\mathbf{\Pi}_j^i$ denotes the interaction forces due to the individual phases or constituents.

Based on the assumption of constituent separation, the constitutive relations for the stress tensor corresponding to each phase are given by

$$\mathbf{T}_f^i = -(\varphi_f^i P^i) \mathbf{I} + \lambda_f (\nabla \cdot \mathbf{V}_f^i) \mathbf{I} + \mu_f \left(\nabla \mathbf{V}_f^i + (\nabla \mathbf{V}_f^i)^T \right), \quad \text{for } i \in \{N, T\}, \quad (12a)$$

and

$$\mathbf{T}_s^i = - \left[(\varphi_s^i P^i) + \Xi^i(\varphi_s^i) - \chi^i(\varphi_s^i) (\nabla \cdot \mathbf{U}_s^i) \right] \mathbf{I} + \mu_s^i(\varphi_s^i) \left(\nabla \mathbf{U}_s^i + (\nabla \mathbf{U}_s^i)^T \right), \quad \text{for } i \in \{N, T\}. \quad (12b)$$

Here, P^i stands for the hydrodynamic IFP (interstitial fluid pressure) within Ω_i ; λ_f and μ_f denote the first and second coefficients of viscosity of the interstitial fluid, which are assumed to be constant [51] and related by the Stokes hypothesis $3\lambda_f + 2\mu_f = 0$ [15]. Note that without any loss of accuracy, the interstitial fluid can be considered as Newtonian fluid [51, 52], since it is very similar to the plasma (recent study reveals that plasma is a Newtonian fluid with viscosity 1.2 mPa s at 37° [53]), which contains 91% of water, 7% of plasma proteins, 2% of inorganic-organic solutes [54, 55]. The solid-phase displacement vector $\mathbf{U}_s$ is related to the corresponding solid phase velocity as $\mathbf{V}_s^i = \partial \mathbf{U}_s^i / \partial t$. In addition, elastic moduli χ^i and μ_s^i corresponding to the solid phase can be expressed in terms of Young's modulus ($\mathcal{Y}^i$) and Poisson's ratio (v_{p}^i) as

$$\chi^i(\varphi_s^i) = \frac{\mathcal{Y}^i(\varphi_s^i) v_{\text{p}}^i}{(1 + v_{\text{p}}^i)(1 - 2v_{\text{p}}^i)} \quad \text{and} \quad \mu_s^i(\varphi_s^i) = \frac{\mathcal{Y}^i(\varphi_s^i)}{2(1 + v_{\text{p}}^i)}.$$

Ξ^i in (12b) satisfies the following relation

$$\frac{\partial \varphi_s^i}{\partial t} - \nabla \cdot \left[\varphi_s^i \lambda_{M_i} \Xi_i'(\varphi_s^i) \nabla \varphi_s^i \right] = S_s^i(\mathbf{x}, t), \quad (13)$$

which corresponds to the interaction of the cells of single type inside Ω_i . Moreover, λ_{M_i} denotes the mobility coefficient corresponding to crawling of a cell upon the fibrous ECM and $(\Xi^i)' = d\Xi^i/d\varphi_s^i$. Using the relation (13), Dey and Raja Sekhar [32] have verified that without generation of any new cells (i.e., $S_s^i(\mathbf{x}, t) = 0$), φ_s^i and Ξ^i become constant. Thus, the contribution of Ξ^i towards the stress field of the solid phase is limited up to a constant only. One can consider this constant elastic cell–cell interaction as insignificant towards the hydrodynamic pore pressure and the corresponding mechanical stress. χ^i and μ_s^i are the average Lamé first and second parameters, respectively, for the solid phase of Ω_i . In general, these two parameters characterize the material nature. Obviously, the material nature must depend on the volume fraction of the solid phase. Thus, for a non-growing tumor with non-growing normal tissue covering, χ^i and μ_s^i show the constant material property.

Next, we would like to pay our attention towards the interaction forces within Ω_i , which are dependent on the relative velocity and the source term [56–60]. These are given by

$$\Pi_f^i = P^i \nabla \varphi_f^i + \Lambda_i (\mathbf{V}_s^i - \mathbf{V}_f^i) + \beta_1^i \tilde{S}_s^i \mathbf{V}_s^i + \beta_2^i \tilde{S}_s^i \mathbf{V}_f^i + \beta_3^i \tilde{S}_f^i \mathbf{V}_s^i + \beta_4^i \tilde{S}_f^i \mathbf{V}_f^i, \quad (14a)$$

and

$$\Pi_s^i = P^i \nabla \varphi_s^i + \Lambda_i (\mathbf{V}_f^i - \mathbf{V}_s^i) + \beta_1^i \tilde{S}_f^i \mathbf{V}_f^i + \beta_2^i \tilde{S}_f^i \mathbf{V}_s^i + \beta_3^i \tilde{S}_s^i \mathbf{V}_f^i + \beta_4^i \tilde{S}_s^i \mathbf{V}_s^i, \quad (14b)$$

where $\tilde{S}_f^i = \rho_f^i S_f^i$ and $\tilde{S}_s^i = \rho_s^i S_s^i$. The above interaction forces must satisfy the following conservation constraints [32, 60]:

$$\Pi_f^i + \Pi_s^i + \tilde{S}_s^i \mathbf{V}_s^i + \tilde{S}_f^i \mathbf{V}_f^i = 0. \quad (15)$$

The above constraint helps one to find the relations which are satisfied by β_j^i . Earlier, Preziosi and Farina [60] have derived those relations in terms of β_j^i in case of closed mixture and derived the following relations

$$\Pi_s^i = P^i \nabla \varphi_s^i + \frac{1}{K_i} \left(1 - \frac{\tilde{S}_f^i K_i}{2} \right) (\mathbf{V}_f^i - \mathbf{V}_s^i), \quad (16a)$$

and

$$\Pi_f^i = P^i \nabla \varphi_f^i + \frac{1}{K_i} \left(1 + \frac{\tilde{S}_f^i K_i}{2} \right) (\mathbf{V}_s^i - \mathbf{V}_f^i). \quad (16b)$$

where $\Lambda_i = 1/K_i$. Recently, Dey and Raja Sekhar [32] have shown that the above relation is also true for the situation when the system is not closed with respect to the mass. In other words, The relations (16a)–(16b) are valid when $S_s^i = 0$ (i.e., without generation of new cells). Moreover, as discussed in the earlier literature [32, 56, 58, 60] that the dimensionless correlation coefficient $\tilde{S}_f^i K_i/2$ has very small contribution towards the momentum transfer between the constitutive phases inside Ω_i by Darcy's drag force in the context of biology. Thus, we have a more simplified relation in terms of the interaction forces:

$$-\Pi_s^i = \Pi_f^i = \frac{1}{K_i} (\mathbf{V}_s^i - \mathbf{V}_f^i) + (\nabla \varphi_f^i) P^i, \quad (17)$$

which is basically Newton's third law with $1/K_i$ as the drag coefficient.

3.1 Assumptions of the mathematical model

In the previous section, the hydrodynamic equations that govern the fluid and macro-molecule transport inside the tumor and surrounding normal tissue layer are presented in a

generic form. The simplified form of governing equations depends on the geometry at hand. Here, a few important assumptions are listed:

- Increase in the rate of solute perfusion through the blood vessels results in adequate nutrient supply, which in turn helps increase the cell population [61]. Nutrient uptake is a continuous process that continues at different phases of the cell cycle. In case of a tumor cell, the total time to complete a cell cycle is less than a normal cell [62]. Moreover, the time scale of solute perfusion is of the order of a second, while the time scale of tumor or normal cell growth is of the order of an hour [22]. Thus, for the sake of simplicity, one can assume that there is no change in the volume of the cellular phase during perfusion of nutrients into the interstitial space. The change in the volume of the cellular phase must include death and birth of the tumor and normal cells inside Ω_T and Ω_N , respectively. In case of a growing tumor and the surrounding normal tissue, the permeability and other elastic parameters corresponding to the tumor must depend on ϕ_s^i . Thus, in the absence of new cells in Ω_i , the right-hand side of (1b) becomes zero. The domain $\Omega_T \cup \Omega_N$ is not closed with respect to the mass [22, 26, 32, 42, 43] (mass source corresponding to the solid phase is neglected).
- The steady-state assumption allows us to ignore the time derivative of the solid and fluid phase velocities from the left-hand side of (11).
- In the absence of the growth of cellular phase, the motion of cells are exhibited by the drag force due to the interstitial fluid movement through the gaps between the cells. This drag force is also responsible for the small deformation within ECM. Indeed, the interstitial fluid motion and solid phase displacement are slow, such that any nonlinear effects or inertial effects like Forchheimer term, convective terms can be ignored [20, 51, 56, 58]. Moreover, with respect to time, the interstitial fluid motion is faster than the deformation rate of the solid phase inside Ω_i . Apparently, this fact is consistent with the infinitesimal strain theory [15]. Consequently one can assume, $\mathbf{V}_s^i = \partial \mathbf{U}_s^i / \partial t \simeq 0$. The solid phases receive infinitesimal strain depending on the specific elastic modulus of the tissue material due to the drag force. In general, solid and fluid phase momentum equations are two-way-coupled via the interaction term Π_j^i in (11). Corresponding to the infinitesimal strain in the solid phase, Π_j^i becomes free from $\mathbf{V}_s^i$ and $\mathbf{U}_s^i$ is connected to the $\mathbf{V}_f^i$ through the solid phase momentum equation in the form of one-way coupling.

Under the above assumptions, we can present the governing hydrodynamic equations in a relatively simpler form given in the next section (Section 3.2).

3.2 Dimensionless form of the governing hydrodynamic equations

Using the following transformations

$$\bar{r} = \frac{r}{R_T}, \quad \bar{p}^i = \frac{P^i}{P_F}, \quad \bar{V}_f^i = \frac{V_f^i}{\frac{K_T P_F}{R_T}}, \quad \bar{U}_s^i = \frac{U_s^i}{\frac{K_T \rho_f P_F R_T}{\mu_f}}, \quad (18)$$

we get the following dimensionless form of the governing equations:

$$\nabla \cdot (\phi_f^N \mathbf{V}_f^N) = -\alpha_N^2 \hat{K} (1 + (L_r A_r)_N) (P^N - 1), \quad (19a)$$

$$\nabla \cdot (\phi_f^T \mathbf{V}_f^T) = -\alpha_T^2 (1 + (L_r A_r)_T) (P^T - 1), \quad (19b)$$

$$-\phi_f^N \nabla P^N + \frac{Da}{3} \nabla \cdot (\nabla \cdot \mathbf{V}_f^N) + Da \nabla^2 \mathbf{V}_f^N - \frac{1}{\hat{K}} \mathbf{V}_f^N = 0, \quad (20a)$$

$$-\varphi_f^T \nabla P^T + \frac{Da}{3} \nabla (\nabla \cdot \mathbf{V}_f^T) + Da \nabla^2 \mathbf{V}_f^T - \mathbf{V}_f^T = 0, \quad (20b)$$

$$-\varphi_s^N \nabla P^N + \frac{Da \varrho_N}{2(1 + \nu_p^N)(1 - 2\nu_p^N)} \nabla (\nabla \cdot \mathbf{U}_s^N) + \frac{Da \varrho_N}{2(1 + \nu_p^N)} \nabla^2 \mathbf{U}_s^N + \frac{1}{\hat{K}} \mathbf{V}_f^N = 0. \quad (20c)$$

$$-\varphi_s^T \nabla P^T + \frac{Da \varrho_T}{2(1 + \nu_p^T)(1 - 2\nu_p^T)} \nabla (\nabla \cdot \mathbf{U}_s^T) + \frac{Da \varrho_T}{2(1 + \nu_p^T)} \nabla^2 \mathbf{U}_s^T + \mathbf{V}_f^T = 0, \quad (20d)$$

where

- $\hat{K} = K_N/K_T$: Ratio of the hydraulic conductivity of normal and tumor tissues.
- $Da = K_T \mu_f / R_T^2$: Darcy number which corresponds to the permeability of the tumor interstitium.
- $\alpha_N = R_T \sqrt{L_p^N(A/V)_N/K_N}$ and $\alpha_T = R_T \sqrt{L_p^T(A/V)_T/K_T}$: The ratio of resistance towards the interstitial fluid movement and the resistance arising during transcapillary fluid exchange inside Ω_N and Ω_T respectively.
- $\varrho_N = \mathcal{Y}_N \rho_f R_T^2 / \mu_f^2$ and $\varrho_T = \mathcal{Y}_T \rho_f R_T^2 / \mu_f^2$: Scaled Young's moduli corresponding to normal and tumor tissues respectively. These parameters characterize the solid character of normal and tumor tissues respectively. Moreover, these parameters represent response of solid phases within Ω_i towards the friction generated due to the movement of fluid through the interstitial space.
- ν_p^N and ν_p^T : Poisson's ratios corresponding to normal and tumor tissues respectively. They measure the softness of the cellular phase and ECM.

There is no coupling observed between the phases in (20a)–(20b) whereas coupling is observed in (20c)–(20d). This form of coupling is one-way coupling [32], but in general, the form of coupling observed between the phases in (11) is a two-way coupling.

Considering the steady poroelastohydrodynamics and infinitesimal time rate of deformation of the solid phase, one can combine (19a)–(19b) and (20a)–(20b) separately to arrive at the corresponding modified equations

$$(\nabla^2 - \chi_N^2)(P^N - 1) = 0, \quad (21a)$$

and

$$(\nabla^2 - \chi_T^2)(P^T - 1) = 0. \quad (21b)$$

Here,

$$\chi_N^2 = \frac{\alpha_N^2(1 + (L_r A_r)_N)}{\left[\left(\varphi_f^N \right)^2 + \frac{4Da\hat{K}\alpha_N^2}{3}(1 + (L_r A_r)_N) \right]}, \quad (22a)$$

and

$$\chi_T^2 = \frac{\alpha_T^2(1 + (L_r A_r)_T)}{\left[\left(\varphi_f^T \right)^2 + \frac{4Da\alpha_T^2}{3}(1 + (L_r A_r)_T) \right]}. \quad (22b)$$

3.3 Hydrodynamic boundary conditions

In this context, we consider the case of a tumor that is enveloped by a layer of normal tissue of uniform thickness. Moreover, the thickness of the tissue layer is assumed to be much

larger compared to the tumor radius. At the interface of the tumor and the normal tissue, i.e., on Γ_{NT} (at R_T), we have the following interface conditions:

$$\mathbf{V}_f^N = \mathbf{V}_f^T, \quad \text{at } r = R_T, \quad (23a)$$

$$\mathbf{T}_f^N \cdot \hat{\mathbf{n}} = \mathbf{T}_f^T \cdot \hat{\mathbf{n}}, \quad \text{at } r = R_T, \quad (23b)$$

$$\mathbf{U}_s^N = \mathbf{U}_s^T, \quad \text{at } r = R_T, \quad (24a)$$

$$\mathbf{T}_s^N \cdot \hat{\mathbf{n}} = \mathbf{T}_s^T \cdot \hat{\mathbf{n}}, \quad \text{at } r = R_T. \quad (24b)$$

The interface Γ_{NT} between the tumor and normal tissue is essentially an interface between two Brinkman media. In this connection, we follow Grosan et al. [63] and Dey and Raja Sekhar [36] to adopt the above interface conditions. Note that in case of two deformable Brinkman media, it is necessary to consider two additional interface conditions on the continuity of the displacements and stresses of the solid phase.

Both the IFP and normal stress reach finite value deep inside the normal tissue (at large distance away from the tumor boundary):

$$P^N \rightarrow \text{finite}, \quad \text{at } r \rightarrow \infty. \quad (25a)$$

and

$$|\mathbf{T}_s^N \cdot \hat{\mathbf{n}}| \rightarrow \text{finite}, \quad \text{at } r \rightarrow \infty. \quad (25b)$$

For an accurate and simplified assumption, one can consider the far field values to be zero for the above cases. We present a one-dimensional solution and details are given in Section 5.

4 Transport and metabolism of blood-borne solutes inside Ω_N and Ω_T

The blood vessel network inside an animal tissue releases blood-borne solutes (nutrients, drugs, etc.) into the interstitial space. Blood-borne biochemical components reach the interstitial space by convective-diffusive transport across the vessel wall. On reaching the interstitial space, biochemical components get transported via interstitial fluid by convective-diffusive transport through the interstitial space to reach the cells. This transport scenario is observed for both normal and tumor tissues. Both the normal and tumor cells consume nutrients at specific rates. We may assume that the overall rate of metabolism is first order in nature. This assumption guarantees creation of no starvation zone inside $\Omega_N \cup \Omega_T$ [64]. The core region of a tumor is a diffusion-dominated zone for all sorts of molecules, but, at the peripheral region of the tumor, the surrounding normal tissue region advective transport plays an important role. The present study assumes that the length scale variations of the intercapillary distances are much smaller compared to the radius of the tumor.

Let us consider the transport of a single solute macromolecule say nutrient “ $\mathcal{N}$ ” through the interstitial space within $\Omega_N \cup \Omega_T$. Let, $C_j^i(\mathbf{x}, t)$, $j \in \{s, f\}$ be the corresponding concentration per unit volume within j th constituent of the mixture inside Ω_i . Moreover, $\varphi_j C_j^i$ becomes the weighted concentration of $\mathcal{N}$ in the j th constituent of the mixture. Thus, the governing transport reaction equation [32, 60, 65] for $\mathcal{N}$ through j th constituent of Ω_i is given by

$$\frac{\partial(\varphi_j^i C_j^i)}{\partial t} + \nabla \cdot (r_f^i \varphi_j^i C_j^i \mathbf{V}_j) = \nabla \cdot (\mathbb{D}_{i,j} \cdot \nabla C_j) + S_{i,j}^{\text{sol}} - K_{i,j}^{\text{rec}} C_j^i,$$

$$(\mathbf{x} \in \Omega_i, j \in \{s, f\}, \text{ and } i \in \{N, T\}), \quad (26)$$

where

- $\mathbb{D}_j^{(i)}$: Effective diffusivity tensor of $\mathcal{N}$ into the j th constituent inside Ω_i . In general, diffusion through j th constituent of the binary mixture depends on Brownian motion and pure molecular dispersion.
- r_f^i : The retardation factor inside Ω_i stands for the ratio of the velocity of $\mathcal{N}$ to the velocity of j th constituent. As a common practice, one can assume $r_f^i = 1$ [26, 32].
- $S_{j,\text{sol}}^i$: Represents source of solute $\mathcal{N}$ in the j th constituent inside Ω_i . Any solute macromolecules like oxygen, nutrients etc., cannot be produced by the constituents inside $\Omega_N \cup \Omega_T$. Solutes are delivered through the vascular network. In some sense, the vascular network is a part of solid phase, but its volume is small compared to that of cell population inside $\Omega_N \cup \Omega_T$.
- $K_{j,\text{rec}}^i$: Rate of metabolism of $\mathcal{N}$ by the j th constituent inside Ω_i . In general, perfused molecules of $\mathcal{N}$ in the interstitial space get consumed by the normal and tumor cells inside Ω_N and Ω_T , respectively.

Next, we assume that for each j , $C_j^i = C^i$. (26) can be summed over j using the saturation constraint (2) and relation (6), to end up with

$$\frac{\partial C^i}{\partial t} + \nabla \cdot (C^i \mathbf{V}_{\text{com}}) = \nabla \cdot (\mathbb{D}^{(i)} \cdot \nabla C) + S_{\text{sol}}^i - K_{\text{rec}}^i C^i, \quad \mathbf{x} \in \Omega_i, \quad (27)$$

where $\mathbb{D}^{(i)} = \sum_{j \in \{s, f\}} \mathbb{D}_j^{(i)}$, $S_{\text{sol}}^i = \sum_{j \in \{s, f\}} S_{j,\text{sol}}^i$, and $K_{\text{rec}}^i = \sum_{j \in \{s, f\}} K_{j,\text{rec}}^i$. For an isotropic and homogeneous diffusivity $D^{(i)}$ of $\mathcal{N}$ inside Ω_i , (27) becomes

$$\frac{\partial C^i}{\partial t} + \nabla \cdot (C^i \mathbf{V}_{\text{com}}) = D^{(i)} \nabla^2 C^i + S_{\text{sol}}^i - K_{\text{rec}}^i C^i, \quad \mathbf{x} \in \Omega_i. \quad (28)$$

Further, the assumption $\mathbf{V}_s^i = \partial \mathbf{U}_s^i / \partial t \simeq 0$ results $\mathbf{V}_{\text{com}}^i \approx \mathbf{V}_f^i$.

In general, S_i^{sol} follows the Patlak equation [26, 32, 65] which is given by

$$S_i^{\text{sol}} = (1 - \sigma_f) C_p S_V^i + P_c \left(\frac{A}{V} \right)_i (C_p - C^i) \left(\frac{Pe_v^i}{\exp(Pe_v^i) - 1} \right) - S_L^i C^i. \quad (29)$$

The above equation governs the diffusive-convective transport across the blood vessel or capillary and drainage through lymph vessel within Ω_i . In this approach, one can assume the wall of a blood or lymph vessel as a uniform porous membrane. Thus, use of Patlak equation is found in order to describe the convective and diffusive transport across a membrane. In (29), σ_f is known as osmotic reflection coefficient for transport of $\mathcal{N}$ across capillaries, P_c is the uniform vascular permeability coefficient for tumor and normal tissue region, and Pe_v^i is the Peclet number corresponding to the vascular transport, which is the ratio of convective transport to the diffusive transport across the blood vessel wall. Pe_v^i is expressed as

$$Pe_v^i = \frac{S_V^i (1 - \sigma_f)}{P_c \left(\frac{A}{V} \right)_i} = \frac{L_p^i (1 - \sigma_f) (P_{\text{ev}}^i - P^i)}{P_c}. \quad (30)$$

Inside Ω_N , Pe_v^N can be arranged as follows

$$Pe_v^N = \frac{\alpha_N^2 Pe \widehat{K} \widehat{D} (1 - \sigma_f)}{S_N^2} \left[(P_{\text{ev}}^N / P_F) - \widehat{P}^N \right]. \quad (31)$$

Moreover, Pe_v^T takes the following form

$$Pe_v^T = \frac{\alpha_T^2 Pe(1 - \sigma_f)}{\varsigma_T^2} \left[\frac{(1 + (L_r A_r)_T)}{1 + (L_r A_r)_T(P_L^T/P_{ev})} - \widehat{P}^T \right], \quad (32)$$

where

- $Pe = K_T P_F/D_T$: This is called the Peclet number, which represents the competition between the diffusive and convective transport through the interstitial space inside the tumor tissue Ω_T .
- $\widehat{D} = D_T/D_N$: Ratio of diffusivities inside Ω_T and Ω_N .
- $\varsigma_N = R_T \sqrt{P_c(A/V)_N/D_N}$: This dimensionless parameter is analogous to the Thiele modulus. This represents the competition between the diffusive transport of solutes across the blood vessel wall and diffusion through the interstitial space inside Ω_N .
- $\varsigma_T = R_T \sqrt{P_c(A/V)_T/D_T}$: Similar interpretation as above inside Ω_T .

For the sake of simplicity, S_i^{sol} can be simplified for a single mode of transport (diffusion or convection) across the wall of blood vessel [26, 32, 36]:

$$\text{for low } Pe_v^i, \quad S_i^{\text{sol}} \approx \frac{P_c A}{V} (C_p - C^i) - S_L^i C^i, \quad (33a)$$

and

$$\text{for high } Pe_v^i, \quad S_i^{\text{sol}} \approx (1 - \sigma_f) C_p S_V^i - S_L^i C^i. \quad (33b)$$

Dey and Raja Sekhar [32, 36] have proposed that the conditions $Pe_v^i \gg 1$ and $Pe_v^i \ll 1$ may correspond to high and low vascularization inside a tumor domain, respectively. On the other hand, a normal tissue possesses uniform vascularization. The complete expression for S_i^{sol} given in (29) is valid for the simultaneous diffusive and convective transport across the wall of a blood vessel. But, due to the complex nature of S_i^{sol} , a simplification is required for the analytical treatment. Dey and Raja Sekhar [32] have observed that there is a marginal difference in concentration near the core region between the cases $Pe_v^T \gg 1$ and $Pe_v^T \ll 1$. This infers that there is only marginal dependency of interstitial transport on the mode of transport across the wall of a blood vessel. Besides, S_i^{sol} needs similar simplification on the basis of $Pe_v^i \gg 1$ and $Pe_v^i \ll 1$.

4.1 Mass transfer boundary conditions

At the interface of normal and tumor tissue, i.e., at Γ_{NT} , the concentration of solute macro-molecules of $\mathcal{N}$ is continuous and in addition, sum of the convective and diffusive fluxes (total flux) are equal. Thus, at $r = R_T$,

$$C^N = C^T, \quad (34a)$$

and

$$-D_T \nabla C^T + V_f^T C^T = -D_N \nabla C^N + V_f^N C^N. \quad (34b)$$

The net flux of $\mathcal{N}$ is zero at the center of the tumor Ω_T :

$$-D_T \nabla C^T + V_f^T C^T = 0, \quad r = 0. \quad (35)$$

Moreover, C^N is finite at a large distance from the tumor within the normal tissue region.

4.2 Solution technique for the solute transport equation inside Ω_i

Basically, (28) is a linear partial differential equation with first order in time and corresponding solution is manageable by Fourier analysis [32, 36, 66]. Accordingly, Fourier components corresponding to the concentration of fluids and macromolecules inside Ω_i are defined as

$$C^i(\mathbf{x}, t) = \sum_{n=-\infty}^{\infty} C_n^i(\mathbf{x}) \exp(i\omega_n t), \quad \mathbf{x} \in \Omega_i. \quad (36)$$

In addition, the plasma concentration C_p inside $\Omega_N \cup \Omega_T$ is expressed in terms of the following Fourier series

$$C_p = \sum_{n=-\infty}^{\infty} C_p^0 \exp(i\omega_n t), \quad (37)$$

where C_p^0 is the initial plasma concentration that remains constant throughout $\Omega_N \cup \Omega_T$. The transformations defined in (36)–(37) change the time domain to the frequency domain.

4.3 Dimensionless form of the solute transport equation inside Ω_i

We first introduced the expansions (36) and (37) into (28), and then non-dimensionalized using (18) and $\tilde{C}_n^i = C_n^i / C_p^0$. The obtained dimensionless forms of mass transfer equation for two different modes of solute transport across the blood vessel are given by

(when Pe_v^i is high)

$$(\nabla^2 - \lambda_{N,n,1}^2)C^N - \beta_N(1 - \sigma_f) = Pe\hat{D} \left[\nabla \cdot (\mathbf{V}_f^N C^N) - \frac{(1 - \sigma_f)}{(1 + (L_r A_r)_N)} \nabla \cdot (\varphi_f^N \mathbf{V}_f^N) \right] \quad (38a)$$

$$- \frac{(L_r A_r)_N}{(1 + (L_r A_r)_N)} \nabla \cdot (\varphi_f^N \mathbf{V}_f^N) C^N \Big], \quad (38b)$$

and

$$(\nabla^2 - \lambda_{T,n,1}^2)C^T + \frac{\beta_T}{(1 + (L_r A_r)_T)}(1 - \sigma_f) = Pe \left[\nabla \cdot (\mathbf{V}_f^T C^T) - \frac{(1 - \sigma_f)}{(1 + (L_r A_r)_T)} \nabla \cdot (\varphi_f^T \mathbf{V}_f^T) \right. \\ \left. - \frac{(L_r A_r)_T}{(1 + (L_r A_r)_T)} \nabla \cdot (\varphi_f^T \mathbf{V}_f^T) C^T \right]. \quad (38c)$$

(when Pe_v^i is low)

$$(\nabla^2 - \lambda_{N,n,2}^2)C^N + \varsigma_N^2 = Pe\hat{D} \left[\nabla \cdot (\mathbf{V}_f^N C^N) - \frac{(L_r A_r)_N}{(1 + (L_r A_r)_N)} \nabla \cdot (\varphi_f^N \mathbf{V}_f^N) C^N \right], \quad (39a)$$

and

$$(\nabla^2 - \lambda_{T,n,2}^2)C^T + \varsigma_T^2 = Pe \left[\nabla \cdot (\mathbf{V}_f^T C^T) - \frac{(L_r A_r)_T}{(1 + (L_r A_r)_T)} \nabla \cdot (\varphi_f^T \mathbf{V}_f^T) C^T \right], \quad (39b)$$

where

$$\lambda_{N,n,1}^2 = i\bar{\omega}_n \hat{D} + \phi_N^2 - \beta_N^2, \quad (40a)$$

$$\lambda_{T_{n,1}}^2 = i\bar{\omega}_n + \phi_T^2 + \frac{\beta_T^2}{(1 + (L_r A_r)_T)}, \quad (40b)$$

$$\lambda_{N_{n,2}}^2 = i\bar{\omega}_n \widehat{D} + \varsigma_N^2 + \phi_N^2 - \beta_N^2, \quad (40c)$$

and

$$\lambda_{T_{n,2}}^2 = i\bar{\omega}_n + \varsigma_T^2 + \phi_T^2 + \frac{\beta_T^2}{(1 + (L_r A_r)_T)}. \quad (40d)$$

Here,

- $\phi_N = \sqrt{K_{\text{rec}}^N R_T^2 / D_N}$: Ratio of metabolism rate to the diffusion rate through the interstitial space inside Ω_N .
- $\phi_T = \sqrt{K_{\text{rec}}^T R_T^2 / D_T}$: Ratio of metabolism rate to the diffusion rate through the interstitial space inside Ω_T .
- $\beta_N = \sqrt{R_T^2 L_{pL}^N (A_L / V)_N P_L}$: Ratio of drainage rate through the lymph vessel to the diffusion rate through the interstitial space inside Ω_N .
- $\beta_T = \sqrt{R_T^2 L_{pL}^T (A_L / V)_T (P_{\text{ev}} - P_L)}$: Ratio of drainage rate through the lymph vessel to the rate of interstitial diffusion inside Ω_T .
- $\bar{\omega}_n = \omega_n R_T^2 / D_T$: Denotes the frequency of perfusion and transport of macromolecules of $\mathcal{N}$ inside $\Omega_N \cup \Omega_T$.

4.4 Low Peclet number (Pe) solution

In this paper, we follow Preziosi and Farina [60]; Dey and Raja Sekhar [32] to consider the transport of those solutes which possess much smaller diffusion time compared to the time of advection. In other words, one can infer that the molecules of $\mathcal{N}$ possess high diffusivity. Thus, we consider the Peclet number (Pe) to be small corresponding to the interstitial transport inside the interstitial space of Ω_i . It is obvious that obtaining a general solution of the (38a)–(39b) is a challenging task. We realize that this problem admits a regular perturbation with respect to low Peclet number. Considering Pe as a regular perturbation parameter, we can write the following expansion in terms of Pe as

$$C_n^i = C_{n,0}^i + Pe C_{n,1}^i + Pe^2 C_{n,2}^i + \mathcal{O}(Pe^3), \quad i \in \{N, T\}. \quad (41)$$

The above expansion is substituted in (38a)–(39b) and collecting the terms of $\mathcal{O}(1)$ and $\mathcal{O}(Pe)$, we obtain the leading and first-order equations. Substituting the expansion (41) into the boundary conditions (34a)–(35), one can obtain the conditions corresponding to the leading and first-order equations.

5 One-dimensional solution (radial symmetry)

After describing the generic model, our immediate task is to discuss the transport phenomena of blood-borne solutes in terms of some graphical illustrations. Accordingly, we obtain the one-dimensional solution corresponding to the poroelastohydrodynamics and transport reaction model inside the spherical tumor Ω_T and the surrounding annular normal tissue region Ω_N . The corresponding solution is obtained under the assumption of spherical sym-

metry flow and small deformation. Thus, for $\mathbf{x} \in \mathbb{R}^3$, the one-dimensional IFP in the overall tissue region is given by

$$P(\mathbf{x}) = \begin{cases} P^N(r), & 1 \leq r < \infty \\ P^T(r), & 0 \leq r \leq 1. \end{cases} \quad (42)$$

The overall IFV can be given as

$$\mathbf{V}_f(\mathbf{x}) = \begin{cases} \mathbf{V}_f^N(r), & 1 \leq r < \infty \\ \mathbf{V}_f^T(r), & 0 \leq r \leq 1. \end{cases} \quad (43)$$

Similarly, one-dimensional displacement field of the solid phase can be represented in the following way

$$\mathbf{U}_s(\mathbf{x}) = \begin{cases} \mathbf{U}_s^N(r), & 1 \leq r < \infty \\ \mathbf{U}_s^T(r), & 0 \leq r \leq 1. \end{cases} \quad (44)$$

The arbitrary constants present within (42)–(44) can be evaluated using the boundary conditions (23a)–(25b) and the following volumetric flux balance condition across Γ_{NT} :

$$\int_{\Gamma_{NT}} \mathbf{V}_f^N \cdot \hat{\mathbf{n}} d\Gamma = \int_{\Gamma_{NT}} \mathbf{V}_f^T \cdot \hat{\mathbf{n}} d\Gamma. \quad (45)$$

On the other hand, the transport reaction model is also simplified under the assumption of spherical symmetry $C_n^i(\mathbf{x}; \bar{\omega}_n) = C_n^i(r; \bar{\omega}_n)$. Therefore, the interstitial solute concentration for one-dimensional transport inside $\Omega_N \cup \Omega_T$ is described as

$$C_n(\mathbf{x}) = \begin{cases} C_n^N(r), & 1 \leq r < \infty \\ C_n^T(r), & 0 \leq r \leq 1. \end{cases} \quad (46)$$

The details of the one-dimensional solution is presented in the Appendix A.

6 Results and discussion on the interstitial hydrodynamics and tissue deformation

The interstitial fluid transport parameters and tissue material parameters inside the tumor and normal tissue regions are chosen based on their physical significance and previous experimental or theoretical studies. For a vivid reference about realistic values of physical parameters, one can follow [22, 26, 46]. The porous structure of $\Omega_T \cup \Omega_N$ is characterized by Da and the ratio K_N/K_T . The softness of tumor tissue may differ from the surrounding normal tissue thus, $\nu_p^N \neq \nu_p^T$ in general. Since the entire tissue domain $\Omega_T \cup \Omega_N$ is soft, each of ν_p^N and ν_p^T lies within the interval (0.45, 0.49) [67]. In particular, two realistic Poisson ratios are: 0.2 and 0.45 (approx.) for compressible and incompressible tumors [68]. Based on the choice of Young's modulus in the range 1.0 – 60 kPa (for wide varieties of soft tissues) [67, 69], plasma viscosity and plasma density in the range $1.3\text{--}1.7 \times 10^{-3}$ PaS and $1020\text{--}1030$ kg/m³ and tumor radius equal to 0.1 cm, we can consider $1 \times 10^2 - 1 \times 10^5$ as the range for ϱ_T and ϱ_N . Finally, $(L_r A_r)_N$ and $(L_r A_r)_T$ are the conductivity ratios of the lymph and blood vessel walls, and for the present analysis we chose $(L_r A_r)_i = 1$. For a quick review, we propose Table 1 with summary of all the interstitial hydrodynamic parameters and tissue material parameters employed in this paper. Since these parameters have different forms in two different tissue regions, it is more convenient to discuss their impact in the form of their ratio.

Table 1 Suitable ranges of various interstitial hydrodynamic parameters and elasticity parameters for tissue material

Parameter	Description	Range
$\hat{K}$	Hydraulic conductivity ratio	$10^{-1} \leq \hat{K} \leq 10$
Da	Darcy number	$10^{-4} \leq Da \leq 10^{-3}$ [32]
α_N and α_T	Nutrient source strength inside Ω_N and Ω_T respectively	$\alpha_N, \alpha_T \geq 0$ [22, 32]
ϱ_N and ϱ_T	Scaled Young's moduli inside Ω_N and Ω_T respectively	$10^2 < \varrho_N, \varrho_T \leq 10^5$ [67, 69]
ν_p^N and ν_p^T	Measures softness of normal and tumor tissue respectively	$0.2 \leq \nu_p^N, \nu_p^T \leq 0.49$ [67, 68]
φ_f^N and φ_f^T	Volume fraction of fluid phases inside Ω_N and Ω_T respectively	$0.6 \leq \varphi_f^N, \varphi_f^T \leq 0.8$

6.1 Impact of α_N/α_T and K_N/K_T on the interstitial fluid pressure (IFP)

The variation in the IFP within normal and tumor tissue depends on the physiological properties like solute proliferation rate and interstitial hydraulic conductivity, etc. However due to the difference in the blood vessel distribution, the strength of the solute supply differs within these regions. Figure 2a includes three situations like $\alpha_T \gtrless \alpha_N$ when $K_N/K_T = 1$. The interstitial pressures are continuous at the interface between the tumor and the normal tissue. Moreover, the interface region is a low-pressure region (or pressure drop region) as compared to the tumor interior and the surrounding normal tissue. The exchange of fluids and solutes macromolecules between two tissue regions takes place through the interface Γ_{NT} . Corresponding to $\alpha_T < \alpha_N$, a larger IFP is observed in the overall tissue region $\Omega_T \cup \Omega_N$ compared to the other two cases $\alpha_T \geq \alpha_N$. Moreover, a larger drop in the IFP is observed inside Ω_T compared to that in Ω_N . One can realize a significant pressure difference between two different points inside Ω_T and Ω_N . This difference in IFP creates a larger rate of extravasation from Ω_T towards Ω_N through the interface Γ_{NT} . Thus, one can infer that there is a high possibility of transport of interstitial fluid from the interstitial space of

Fig. 2 (Color online) Dimensionless interstitial fluid pressure distribution in Ω_N and Ω_T along radial distance (r) for different **a** α_N/α_T **b** K_N/K_T

Ω_T to that of Ω_N when $\alpha_T > \alpha_N$ due to the leakage through Γ_{NT} . This possibility is minimal corresponding to $\alpha_T \leq \alpha_N$.

When $\alpha_N/\alpha_T = 1$, Fig. 2b shows that for $K_T < K_N$, the IFP within the overall tissue region is found to be higher compared to the other situations. We find that average IFP is higher in the tumor tissue region compared to the normal tissue region when $K_T \leq K_N$. Due to this pressure difference, the rate of extravasation from the interstitial space of the tumor tissue (Ω_T) to the normal tissue (Ω_N) is high. On the other hand, the average IFP is higher inside Ω_N compared to that of Ω_T when $K_T > K_N$. In this situation, the rate of extravasation from Ω_T becomes limited. However, nutrients and other molecules can reach the tumor tissue from the surrounding normal tissue in favor of this pressure gradient. On the other hand when $K_T \leq K_N$, one may observe nutrient deficiency due to leakage from the tumor surface.

6.2 Impact of α_N/α_T and K_N/K_T on the interstitial fluid velocity (IFV)

Figure 3b depicts that IFV increases with the ratio α_T/α_N when $K_N/K_T = 1$. Thus, a higher overall flow rate can be guaranteed when the ratio α_T/α_N is large. Correspondingly, the volume of solutes generated from the vascular network within the interstitial space of Ω_T is larger than that of Ω_N . From Fig. 2a, one can observe that due to large average pressure difference and significant pressure drop at the interface, IFV becomes high. Thus, the overall flow rate increases within the interstitial space of $\Omega_T \cup \Omega_N$, which may prevent tumor cell damage/necrosis. This situation is not supported in case of $\alpha_T/\alpha_N < 1$. The flow rate from Ω_N to Ω_T becomes retarded due to the small difference in the average IFP across the interface. As a result, proliferated fluids and macromolecules within Ω_N cannot seep towards the tumor tissue.

In general, IFV increases with the interstitial hydraulic conductivity. Figure 3a suggests that the magnitude of IFV corresponding to $K_N/K_T < 1$ is found to attain high values compared to the other cases ($K_N/K_T \geq 1$). The interstitial convective transport must depend on the IFV. Correspondingly, when $K_N/K_T < 1$, a significant convective mass transport

Fig. 3 (Color online) Dimensionless IFV component (V_f) versus the dimensionless radial distance (r) for different ratios **a** K_N/K_T **b** α_N/α_T

through the overall tissue region (tumor tissue+ surrounding normal tissue) is expected. In each case, the IFV in the normal tissue region increases from the interface value with distance to attain the maximum. Consequently, it decreases with the distance from the interface and becomes asymptotic. There is a significant difference in the convective transport between the cases $K_N/K_T < 1$ and $K_N/K_T > 1$. Corresponding to the latter situation, the convective transport becomes slower in Ω_T as compared to the former. The convective transport becomes insignificant towards the tumor core, whereas it becomes constant deep in the normal tissue. The higher magnitude of IFV that is attained near the interface is due to high IFP. The interstitial spaces of two different tissue regions are connected by the interface Γ_{NT} where the continuity of IFV maintains the exchange of solutes.

6.3 Impact of α_N/α_T , K_N/K_T , v_p^N and v_p^T on the displacement field

In a recent study, Dey and Raja Sekhar [32, 36] have discussed the solid phase deformation inside an isolated solid tumor in terms of the radial component of the displacement vector. In the current study due to presence of normal tissue layer, it would be more sensible to discuss the deformation issue in terms of radial stresses. Overall, Fig. 4a–c suggests that the magnitude of solid stress becomes minimum at the interface for the overall tissue region. From this minimum value, the magnitude of normal solid stress increases with the depth inside both tissue regions. This behavior is quite opposite to the behavior of displacement field at each point of the overall tissue region. Therefore, the maximum deformation can be noted at the interface region Γ_N . A larger (smaller) magnitude of solid stress field corresponds to larger (smaller) pressure region for each combination of α_N and α_T . Figure 4a depicts that higher magnitude of normal solid stress is noted corresponding to $\alpha_N/\alpha_T > 1$ compared to the cases $\alpha_N \leq \alpha_T$. This is due to the increase in the IFP with the ratio α_N/α_T throughout the whole tissue region. The pressure field has a linear relationship with the stress field.

Figure 4b indicates the variation of the solid stress with the hydraulic conductivity ratio K_N/K_T . Among the three possible cases $K_N/K_T \gtrless 1$, the magnitude of the solid stress is maximum and minimum for $K_N/K_T > 1$ and $K_N/K_T < 1$ respectively. This is primarily due to the pressure field which also attains maximum and minimum for $K_N/K_T > 1$ and $K_N/K_T < 1$, respectively. According to [48], the hydraulic conductivity of the interstitial space of a biological medium is inversely related to the concentration of collagen + GAGs inside. Thus, if the volume concentration of collagen + GAGs is higher inside Ω_T than that of inside Ω_N , the interstitial fluid experiences larger resistance from the solid phase and exerts a significant drag on the solid phase. As a result, the magnitude of small deformation of the solid phase inside Ω_T is higher than that of Ω_N and vice versa. Dey and Raja Sekhar [34] argued that increase in the concentration of collagen + GAGs can be correlated with the increase in the solid-phase displacement field [32]. The gradual decay in the concentration of collagen + GAGs and cellular phase is correlated with the gradual increase in the stress field starting from the interface. On the other hand, a sharp decay in the solid stress curve suggests increasing the average concentration of collagen + GAGs and cellular phase towards the interface region. Note that the core region is supposed to contain a large number of dead cells.

Figure 4c illustrates the behavior of the ratio v_p^N/v_p^T towards the solid stress field. For a biological tissue, the Poisson ratio varies between 0.4 and 0.45. In case of $v_p^N/v_p^T < 1$, the collagen + GAGs protein structure and the cellular phase inside Ω_T are softer than those inside Ω_N . Similar inferences are valid for $v_p^N/v_p^T > 1$. As described by Dey and Raja

Fig. 4 (Color online) Dimensionless solid-phase displacement component ($T_{s,rr}^i$) versus the dimensionless radial distance (r) for **a** K_N/K_T **b** α_N/α_T , and **c** $\nu_p^N \gtrless \nu_p^T$

Sekhar [32], the radial strain becomes maximum and minimum corresponding to $\nu_p^i = 0$ and $\nu_p^i = 0.5$, respectively. In this study, the radial stress (mechanical contact force along the radius) in the overall region would be higher in the case of $\nu_p^i = 0.4$ compared to the case $\nu_p^i = 0.45$. Corresponding to these situations $\nu_p^T = 0.4, \nu_p^N = 0.45$ (magenta line) and $\nu_p^T = \nu_p^N = 0.4$ (blue line), $T_{s,rr}^T$ dominates $T_{s,rr}^N$ to produce more deformation in the normal tissue layer. As a reaction, $T_{s,rr}^N$ does not affect $T_{s,rr}^T$ due to the negligible momentum transfer. On the other hand, comparing the cases $\nu_p^N = \nu_p^T = 0.4$ (blue line) and $\nu_p^N = 0.4, \nu_p^T = 0.45$ (green line), $T_{s,rr}^N$ dominates $T_{s,rr}^T$ to produces larger deformation in the tumor tissue region. Consequently, the reaction force is also large enough to produce small deformation in the normal tissue.

Table 2 Various mass transport and metabolism parameters with suitable ranges

Pe	Peclet number	$0 < Pe < 0.1$ [32, 37]
$\widehat{D}$	Diffusivity ratio	$10^{-1} \leq \widehat{D} \leq 10$
ς_N and ς_T	Strength of diffusive nutrient source inside Ω_N and Ω_T	$10^{-1} \leq \varsigma_N \leq 10$ [32, 36]
ϕ_N and ϕ_T	Thiele moduli inside Ω_N and Ω_T	$10^{-1} \leq \phi_N, \phi_T \leq 10$ [32, 36, 64]
β_N and β_T	Strengths of lymphatic drainage inside Ω_N and Ω_T	$\beta_N, \beta_T \geq 0$ [32]

7 Results and discussion on the transport of fluids and macromolecules

For the transport of albumin-like plasma protein, Peclet number (Pe) corresponding to the diffusion-dominated interstitial transport is a small perturbation parameter so that higher powers are extremely small. Transport across the wall of a blood vessel is convection and diffusion-dominated corresponding to $Pe_v^i \gg 1$ and $Pe_v^i \ll 1$, respectively. The osmotic barrier from the blood vessel wall towards the transvascular transport is characterized by σ_f , which is 0.91 in case of albumin transport in normal tissues [70]. In both the modes of transport across blood vessels, blood-borne solutes exhibit diffusion-dominated transport through the interstitial space under low convection to reach the cells. Dey and Raja Sekhar [32] show that the concentration profiles corresponding to these cases do not differ significantly from each other for an isolated tumor (only some quantitative variation has been observed). Consequently, the physics behind the transport mechanisms corresponding to $Pe_v^i \gg 1$ and $Pe_v^i \ll 1$ is expected to be the same.

Due to the varied characteristics of the lymph vessel structure inside tumor and normal tissue regions, the rates of drain of blood-borne fluids and molecules through the lymph vessel wall may differ (i.e., $\beta_N \neq \beta_T$). In addition, the transvascular diffusion depends on the characteristics of blood vessels inside tumor and normal tissue regions. Consequently, in case of $Pe_v^i \ll 1$, $\varsigma_N \neq \varsigma_T$. On the other hand, due to the structural difference of the interstitial spaces inside tumor and normal tissue regions and difference in the metabolic rates of the tumor and normal cells, $D_N \neq D_T$ and $\phi_N \neq \phi_T$. Table 2 provides the possible ranges of blood-borne solute transport and metabolism parameters introduced above.

7.1 Impact of α_T and α_N on C_n/C_p^0 inside $\Omega_T \cup \Omega_N$

Figure 5a represents the variation of interstitial fluid concentration (IFC) with respect to the solute source parameters α_T and α_N corresponding to $Pe_v^i \gg 1$. These parameters are similar to the Damkohler number and represent the ratio of the interstitial resistance and the resistance across the vascular wall. We find similar observation corresponding to $Pe_v^i \ll 1$.

When $K_N/K_T = 1$, $\alpha_T \neq \alpha_N$ suggests that the strength of the solute sources inside Ω_T is different from Ω_N . Depending on the blood vessel density, the magnitude of α_T may vary from one tumor to the other, but the uniform vascularization inside Ω_N gives a hint to assume a constant value of α_N throughout the study. Overall nutrient concentration within $\Omega_T \cup \Omega_N$ increases with α_T when α_N is fixed. Due to the continuity in the solute concentration and the total mass flux at the interface, solutes from the interstitial space of Ω_T reach that of Ω_N . As $r \rightarrow \infty$, $C_n^N/C_p^0 \rightarrow C_\infty^N$, where C_∞^N is the uniform solute concentration deep in the normal tissue. C_∞^N depends on α_N . This incident helps us to conclude that corresponding to the uniform vascularization, nutrient deficiency does not take place. Corresponding to large α_T (Ω_T does not undergo nutrient deficiency), different solutes from the interstitial space of Ω_T reaches Ω_N .

Fig. 5 (Color online) Dimensionless interstitial solute concentration C_n^i versus the dimensionless radial distance (r) corresponding to different **a** α_N/α_T and **b** β_N/β_T when $Pe_V^i \gg 1$

Analogous to the overall velocity field, we observe that the overall solute concentration attains maximum inside Ω_N at a point close to the interface Γ_{NT} . Therefore, the concentration attains its maximum due to the maximum convection near the interface. Away from the tumor, deep in the normal tissue, we find that the concentration profile becomes uniform. On the contrary, the solute concentration decays towards the core inside Ω_T . Moreover for small magnitudes of α_T , C_n^T/C_p^0 reaches a value close to zero near the core region of Ω_T . This guarantees that the core region of Ω_T undergoes deficiency of nutrients (necrosis) due to the decaying solute concentration.

7.2 Impact of β_T and β_N on C_n/C_p^0 inside $\Omega_T \cup \Omega_N$

Figure 5b illustrates the impacts of β_T and β_N on the overall concentration C_n/C_p^0 when $Pe_V^i \gg 1$ (or $Pe_V^i \ll 1$). β_i corresponds to the ratio of resistance for the interstitial fluid to percolate the interstitial space to the resistance due to the drainage through the lymph vessel inside Ω_i . We observe that C_n/C_p^0 increases with decreasing β_T when $\beta_N = 1$. The increase in β_T beyond unity results in a significant drainage of fluids and solute macromolecules from the interstitial space of Ω_T . Consequently, the nutrient deficiency is observed inside Ω_T . Moreover, one can understand that there is no significant increment in C_n/C_p^0 with decrease in β_T satisfying $\beta_T \leq \beta_N$. Beyond $\beta_T > 1$, an increase in β_T causes deficiency of fluids and solute macromolecules inside β_T due to the drainage. Subsequently, fluids and solute macromolecules from Ω_N exhibit convective-diffusive transport to reach the interstitial space of Ω_T in order to maintain the interstitial concentration to a specific level.

7.3 Impact of D_N/D_T and K_N/K_T on C_n/C_p^0 inside $\Omega_T \cup \Omega_N$

Figure 6a and b illustrates that with increasing magnitude of the ratios D_N/D_T and K_N/K_T , the overall concentration C_n/C_p^0 decreases when $Pe_V^i \gg 1$. Similar observations are found corresponding to $Pe_V^i \ll 1$. For a particular solute $\mathcal{N}$, $D_N/D_T < 1$ implies low diffusivity of the same inside Ω_N as compared to Ω_T . We observe a higher concentration of $\mathcal{N}$

Fig. 6 (Color online) Dimensionless interstitial solute concentration C_n^i/C_p^0 versus the dimensionless radial distance (r) corresponding to different **a** D_N/D_T and **b** K_N/K_T when $Pe_V^i \gg 1$

within the interstitial space of Ω_N compared to Ω_T when $D_N/D_T < 1$. In this situation, a small portion of molecules of $\mathcal{N}$ would diffuse into Ω_T . This phenomenon results in only a marginal change in the concentration profile inside Ω_T corresponding to each D_N/D_T satisfying $D_N/D_T < 1$. On the other hand, when $D_N/D_T > 1$, molecules of $\mathcal{N}$ exhibit faster diffusional transport inside Ω_N compared to Ω_T . Consequently, molecules of $\mathcal{N}$ move towards Ω_T from Ω_N , but the interstitial transport of $\mathcal{N}$ in the opposite direction is hardly possible.

On the other hand, one may notice that a decrease in K_N/K_T beyond unity can lead to a significant increase in C_n/C_p^0 . Moreover, a marginal decrease in C_n/C_p^0 is observed when K_N/K_T is increased significantly beyond unity. If the hydraulic conductivity of the tumor interstitium is higher than that of the surrounding normal tissue, higher convection in the interstitial fluid is noted compared to the other possible situations (overall velocity field maximizes for $K_N/K_T < 1$, see Fig. 3a). Due to low hydraulic conductivity of the tumor tissue compared to surrounding normal tissue, overall convective transport reduces. Interstitial fluid along with solute macromolecules from Ω_N cannot reach efficiently to Ω_T .

7.4 Impact of ϕ_T and ϕ_N on C_n/C_p^0 inside $\Omega_T \cup \Omega_N$

In this study, solute metabolism process inside $\Omega_T \cup \Omega_N$ is considered to be first order in nature. Blood-borne solutes and macromolecules supplied into the interstitial space of $\Omega_T \cup \Omega_N$ from the existing blood vessel network gets metabolized by the cell population [32]. In general, normal and tumor cells in Ω_N and Ω_T respectively possess different metabolic rates. Figure 7a and b highlight the variation of C_n/C_p^0 with ϕ_T for fixed ϕ_N . One can observe different behaviors of C_n/C_p^0 corresponding to the situations (i) $\phi_T \leq 1$ and $\phi_N = 1$ (dotted line) (ii) $\phi_T > 1$ and $\phi_N = 1$ (dashed line).

- In case (i), an increase in ϕ_T is responsible for a marginal increment in C_n/C_p^0 . In general, a small increment in the concentration within Ω_T shows saturation with decreasing metabolic rate. With decreasing ϕ_T satisfying $\phi_T \leq \phi_N (= 1)$, normal cells possess

Fig. 7 (Color online) Dimensionless interstitial solute concentration C_n^i versus the dimensionless radial distance (r) corresponding to different ϕ_T when **a** $Pe_V^i \gg 1$ and **b** $Pe_V^i \ll 1$

a high metabolic rate compared to the tumor cells. Nutrients and other bio-chemicals from the interstitial space of Ω_T get diffused to reach that of Ω_N in order to get consumed by the normal cells. As a result, a small increment in the magnitude of the overall concentration is noted with increase in ϕ_T .

- Corresponding to case (ii), it is observed that the slope of the concentration curve in Ω_T becomes steeper near the interface for increasing values of $\phi_T > 1$. Due to a higher metabolic rate, except the cells present in the peripheral region of the tumor, others do not get sufficient nutrients in order to survive. Consequently, the core region suffers nutrient deficiency and necrosis is triggered. Corresponding to $\phi_T = 5$ and $\phi_T = 10$, a drop in the concentration is observed within Ω_N near the interface. This suggests that nutrients from the normal tissue region move to the tumor tissue region when it undergoes necrosis.

7.5 Impact of ς_T and ς_N on C_n/C_p^0 inside $\Omega_T \cup \Omega_N$

In case of $Pe_V^i \ll 1$, ς_T and ς_N represent the strength of diffusive solute source inside Ω_T and Ω_N , respectively. An increase in ς_i beyond unity corresponds to enhanced diffusion of nutrients through the wall of the vascular network. Here we will discuss two cases (i) $\varsigma_T > \varsigma_N (= 1)$ (dashed line) (ii) $\varsigma_N > \varsigma_T (= 1)$ (dotted line). Increase in ς_i may enhance the blood-borne solute concentration level within $\Omega_T \cup \Omega_N$. In this context, Fig. 8 shows that

- Case (i): the magnitude of C_n/C_p^0 increases with ς_T . No significant change in C_n/C_p^0 is observed due to the increase in ς_T satisfying $\varsigma_T \leq 1$. We observe that $\varsigma_T = 0.1$ is the critical strength beyond which C_n/C_p^0 remains independent of ς_T . This corresponds to the maximum nutrient deficiency. At larger values of ς_T , IFC inside Ω_T maintains a constant magnitude towards the core. This may correspond to uniform vascularization towards the tumor core. Corresponding to $\varsigma_T > \varsigma_N (= 1)$, interstitial diffusion from Ω_T to Ω_N forces exchange of solutes through the interface. Therefore, the delay in necrosis within Ω_T is possible in this case.

Fig. 8 (Color online) Dimensionless interstitial solute concentration C_n^i versus the dimensionless radial distance (r) corresponding to different ς_T when $Pe_v^i \ll 1$

- Case (ii): increase in IFC is observed due to increasing ς_N satisfying $\varsigma_N > \varsigma_T (= 1)$. Each concentration profile shows a decaying nature from a constant value within the normal tissue towards the tumor core. This situation is much relevant because constant concentration profile at deep in the normal tissue may characterize uniform vascularization inside Ω_N . Corresponding to the larger ς_N , necrosis gets delayed due to the transport of nutrients from Ω_N to Ω_T .

7.6 Effectiveness factor

The study of effectiveness factor is very essential in order to understand the interplay of the rate of metabolism (ϕ_T) inside Ω_T with the parameters α_T , β_T , and ς_T along with the ratios D_N/D_T and K_N/K_T when α_N , β_N , and ς_N are fixed. Recently, Dey and Raja Sekhar [32, 36] have observed that ϕ_T and ς_T show opposite behavior in the transport of blood-borne nutrients. We have the following expression to compute the effectiveness factor on the boundary of the tumor

$$\eta_T = \frac{4\pi R_T^2 D}{K_{rec}^T C_p \frac{4}{3}\pi R_T^3} \left. \frac{\partial C^T}{\partial r} \right|_{r=R_T}, \quad (47)$$

which in non-dimensional form is given by

$$\eta_T = \frac{3}{\phi_T^2} \left. \frac{dC^T}{dr} \right|_{r=1}. \quad (48)$$

We compute the same corresponding to $Pe_v^i \gg 1$ and $Pe_v^i \ll 1$. It is observed that corresponding to the Dirichlet boundary (isolated tumor [32]), the effectiveness factor remains bounded between (0, 1] corresponding to zero strength of the source and the drainage

Fig. 9 (Color online) Comparative study in terms of η_{T_n} between the cases $Pe_v^i \ll 1$ and $Pe_v^i \gg 1$, $\phi_N = 1$, $\alpha_N = 1$, and different α_T when $Pe_v^i \gg 1$

parameter. In the present context, at the boundary of Ω_T , we have imposed the continuity of net flux. Thus, the behavior of the effectiveness factor (η_{T_n}) is expected to be different from the isolated tumor case. Similar to an isolated tumor, η_{T_n} measures the diffusive character of a solute macromolecule (nutrient or drug) through the interstitial space before it gets metabolized by the tumor cells. In order to show the behavior of η_{T_n} against ϕ_T , we use a logarithmic scale for both of the axes. Throughout the discussion, we assume $\phi_N = 1$. The general behavior indicates a decreasing pattern of η_{T_n} for $\phi_T \in [10^{-1}, 10^1]$ corresponding to the cases $Pe_v^i \gg 1$ and $Pe_v^i \ll 1$. However, one may observe the difference in the nature of the curves representing η_{T_n} within the ranges $[10^{-1}, 10^0]$ ($\phi_N \geq \phi_T$) and $[10^0, 10^1]$ ($\phi_N \leq \phi_T$).

Figure 9b indicates that η_{T_n} increases with α_T for $Pe_v^i \gg 1$ ($Pe_v^i \ll 1$) when $\alpha_N = 1$. A significant increment in η_{T_n} is noted between $\alpha_T = 1$ and $\alpha_T = 2$. Beyond $\alpha_T = 1$, an increase in α_T shows marginal impact on η_{T_n} . Corresponding to $\alpha_T > \alpha_N$, the convective perfusion rate of the solute macromolecules from blood vessel network is high within Ω_T as compared to α_N . This high perfusion rate is responsible for the enhanced effectiveness factor due to the excess solutes and macromolecules available in the interstitial space of Ω_T . On the other hand corresponding to $\alpha_T < \alpha_N$, the interstitial space of Ω_T may suffer nutrient deficiency due to reduced concentration. Consequently, η_{T_n} is reduced in both the cases $Pe_v^i \gg 1$ and $Pe_v^i \ll 1$ due to the effective reduction of metabolic process within the cell population towards available solutes and macromolecules.

Figure 10a illustrates the increasing behavior of η_{T_n} with β_T for $Pe_v^i \gg 1$ ($Pe_v^i \ll 1$) when $\beta_N = 1$. In this context, β_T and ϕ_T are two parameters corresponding to the reduction in the concentration level inside Ω_T . It is observed that corresponding to higher β_T satisfying $\beta_T > \beta_N$ (when $\beta_N = 1$), a strictly decreasing nature of η_{T_n} is exhibited with respect to ϕ_T . With increase in β_T satisfying $\beta_T > \beta_N$, a decrease in the concentration level makes the tumor tissue to show a faster tendency towards the metabolism process. As a result, decreased η_{T_n} is noted. On the other hand corresponding to $\beta_T < \beta_N$, low drainage rate from the interstitial space of Ω_T through the lymph network makes the transport of biochemical components towards Ω_N . Thus, one may note a reduced effectiveness factor.

Fig. 10 (Color online) Effectiveness factor η_{T_n} versus ϕ_T for **a** $\phi_N = 1$, $\beta_N = 1$, and different β_T when $Pe_V^i \gg 1$ **b** $\zeta_N = 1$, and different ζ_T when $Pe_V^i \ll 1$

The interplay between ζ_T and ϕ_T can be interpreted using η_{T_n} . The corresponding behavior is shown in Fig. 10b. It may be noted that ζ_T corresponds to the rate of diffusive proliferation across the wall of the blood vessel. We observed that increase in the diffusive proliferation rate inside Ω_T enhances η_{T_n} when the corresponding rate is fixed for the surrounding normal tissue. Note that corresponding to $\zeta_T < \zeta_N (= 1)$, a small increment in ζ_T can result in a significant increase in η_{T_n} . However for $\zeta_T > \zeta_N (= 1)$, an increment in η_{T_n} reaches a saturation at large ζ_T . Thus, larger ζ_T dominates the intake rate inside Ω_T . Again, corresponding to the larger intake rate inside Ω_T ($\phi_T > 1$), one can observe that the impact of ζ_T becomes insignificant. Thus, ζ_T and ϕ_T complement each other.

The effect of D_N/D_T and K_N/K_T on η_{T_n} are depicted through Fig. 11a and b, respectively when the rate of metabolism and the supply strength remains fixed. For both of the cases, $Pe_V^i \gg 1$ and $Pe_V^i \ll 1$, η_{T_n} increases with a decrease in D_N/D_T when $K_N/K_T = 1$. Solute macromolecules $\mathcal{N}$ with high D_N/D_T ratio exhibit low concentration inside $\Omega_T \cup \Omega_N$ (see Fig. 6a). In addition, the diffusive transport of the biochemical components of $\mathcal{N}$ becomes significantly low from Ω_N to Ω_T . Consequently, the lack of concentration of $\mathcal{N}$ inside Ω_T reduces η_{T_n} .

On the other hand, η_{T_n} increases with decrease in the ratio K_N/K_T for both the cases $Pe_V^i \gg 1$ and $Pe_V^i \ll 1$. The concentration of fluids and macromolecules becomes low inside Ω_T in case of $K_N/K_T > 1$ as compared to $K_N/K_T < 1$ from the point of view of convective transport. An increase in the convective transport enhances η_{T_n} . Thus, corresponding to $K_N/K_T > 1$, the convective transport becomes low from Ω_N to Ω_T .

8 Comparison with the clinical study

Lankelma et al. [71] have performed a clinical study of patients with breast cancer treated with the drug doxorubicin. On the basis of this clinical study, a mathematical model on doxorubicin transport inside a tumor cell islet have been developed by them. From the simulated graphical results, we have obtained the concentration data of injected doxorubicin

Fig. 11 (Color online) Effectiveness factor η_{T_n} versus ϕ_T when $\phi_N = 1$ and $Pe_V^i \gg 1$, for different **a** D_N/D_T **b** K_N/K_T

with tumor islet of radii 75, 105, 150 μm using grabit toolbox of MATLAB R2009b corresponding to two different time levels 2 h and 24 h. The extracted data has been normalized. Figure 12a–b correspond to doxorubicin concentration inside a tumor islet after 2 h and 24 h of injection respectively. The steady state concentration profiles of $\mathcal{N}$ corresponding to the present study shows nice qualitative agreement for higher rate of metabolism (say, $\phi_T = 3, 5$) when $Pe_V^i \gg 1$ and $Pe_V^i \ll 1$. This comparison shows that intake of doxorubicin inside a tumor islet shows a similar behavior as the metabolism of nutrients inside tumor in the present study. The decaying nature of concentration in both the studies justify that the outer cell compartment of tumor islet [71] and cells at the peripheral region of

Fig. 12 (Color online) The situations $Pe_V^i \gg 1$ and $Pe_V^i \ll 1$ in the present study are compared with the clinical study (C.S.) done by Lankelma et al. [71] corresponding to **a** 2 h of after doxorubicin injection (Dox. Inj.) **b** 24 h after doxorubicin injection (Dox. Inj.) for different tumor islet radius (I.R)

the tumor (present study) follow similar efficiency towards the intake of doxorubicin and nutrient $\mathcal{N}$ respectively.

9 Comparison with previous theoretical model

Researchers have set up several theoretical models on transport phenomena inside solid tumor from the last few decades. Since this present theoretical investigation proposes an in vivo mimicking model on a solid tumor, it would be more significant if we can compare the present model with another theoretical model on an in vitro-type solid tumor. Accordingly, we compare the effectiveness factor (η_{T_n}) corresponding to $Pe_v^i \gg 1$ and $Pe_v^i \ll 1$ with that of from the study of Dey and Raja Sekhar [32]. One can observe that for an in vitro type, there is an only marginal difference in the effectiveness factors corresponding to the cases $Pe_v^i \ll 1$ and $Pe_v^i \gg 1$. This said difference is much significant for an in vivo type in the present study when $\phi_T > 1$. However, a significant qualitative difference in the behaviors cannot be observed. The perfusion across the blood vessel wall is convection or diffusion based in accordance with $Pe_v^i \gg 1$ and $Pe_v^i \ll 1$, respectively. For high intake rate (large ϕ_T), the modes of transport across the blood vessel wall have a significant impact on the interstitial transport in case of in vivo type, but such behavior is not seen for in vitro type. However, there is a much qualitative agreement in the behavior of effectiveness factor with metabolic rate that can be observed between in vivo and in vitro type.

10 Limitations of this study

The assumption of the infinitesimal time rate of strain in the solid phase ensures the decoupling of solid phase from the fluid phase. This decoupling is the one-way coupling, since the solid phase displacement field depends on the fluid phase velocity and the pore pressure. The composite velocity defined in (6) becomes free from the solid phase velocity. Therefore, the contribution towards the biochemical components concentration field is limited up to fluid phase velocity only.

11 Conclusions

In this study, we have presented a mathematical model to understand the poroelastodynamics and transport of biochemical components inside a tumor that is surrounded by a normal tissue layer. The hydraulic conductivities of the interstitial space of both the tissues are assumed to be constant. Interstitial fluid flow is incompressible in nature. The vascular network (blood and lymph vessels) inside $\Omega_N \cup \Omega_T$ acts as source and drain of biochemical components from the interstitial space. The overall solute transport model inside $\Omega_N \cup \Omega_T$ is studied for those molecules that have high diffusivity. Different biochemical component molecules from the surrounding tissue get transported to the tumor tissue via interstitial convective and diffusional transport. In a similar way, several solutes from the interstitial space of the tumor tissue may reach the normal tissue layer.

$\alpha_T > \alpha_N$ and $K_T > K_N$ are the situations when one can expect the maximum IFP inside $\Omega_N \cup \Omega_T$ compared to the other cases. Similarly, IFV is found to be maximum corresponding to the situations $\alpha_T > \alpha_N$ and $K_T > K_N$ as compared to the other possibilities. Corresponding to $\alpha_T < \alpha_N$ and $K_T < K_N$, larger drag is experienced by the solid phase (collagen +

GAGs protein-based network) of the overall tissue region compared to the remaining cases. Increased radial stress (decrease in Poisson ratio corresponding to the solid phase) within the normal tissue region does not affect the solid phase deformation inside tumor tissue region, but the converse may not be true.

This study shows how the presence of the normal tissue layer over a solid tumor affects the necrosis creation within it. Low solute proliferation rate and high drainage rate within the tumor tissue compared to the surrounding normal tissue (i.e., corresponding to these situations $\alpha_T < \alpha_N$ and $\beta_T > \beta_N$) can be thought of as significant causes for the formation of necrosis inside the tumor. Necrosis formation gets assisted within Ω_T for those perfused biochemical components which follow the diffusivity relation $D_N > D_T$. The low hydraulic conductivity of tumor tissue compared to the surrounding normal tissue disallows biochemical components to transport inside the tumor tissue Ω_T . This is another important cause for the nutrient deficiency inside Ω_T . The necrosis creation depends on the higher intake rate of tumor cells inside Ω_T than the surrounding normal cells inside Ω_N . Thus, an increase in ϕ_T satisfying $\phi_T > \phi_N (= 1)$ causes nutrient deficiency. In addition, the opposite behavior in the nutrient concentration is observed with an increase in ϕ_T satisfying $0 < \phi_T \leq 1, \phi_N = 1$. Lastly corresponding to $Pe_v \ll 1$, the creation of necrosis gets delayed if ς_T increases satisfying $\varsigma_T > \varsigma_N (= 1)$. Moreover, necrosis gets delayed corresponding to higher values of ς_N satisfying $\varsigma_N > \varsigma_T (= 1)$.

The present study shows that the behavior of effectiveness factor η_{T_n} is different from the isolated solid tumor for both the cases $Pe_v^i \gg 1$ and $Pe_v^i \ll 1$. The behavior of η_{T_n} is comparable for these two cases. For a given proliferation and drainage rates inside the normal tissue, increasing the proliferation and drainage rates inside the tumor tissue enhances η_{T_n} . Negative impact of the ratios D_N/D_T and K_N/K_T on η_{T_n} is justified through this study. Higher diffusive proliferation rate corresponding to the situation $Pe_v^i \ll 1$ (larger ς_T) shows positive impact on η_{T_n} . The mode of transvascular transport inside both the tumor and normal tissue does not have a significant impact on the effectiveness factor corresponding to the tumor tissue.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest.

Appendix A

One dimensional solution of the above hydrodynamic equations are given by

(when $1 \leq r < \infty$),

$$P^N = 1 + A_1^N k_0(\chi_N r), \quad (49a)$$

$$V_f^N = \frac{A_2^N}{r^2} + \frac{\alpha_N^2 \hat{K}}{\varphi_f^N \chi_N} (1 + (L_r A_r)_N) A_1^N k_1(\chi_N r), \quad (49b)$$

$$U_s^N = \frac{A_3^N}{r^2} - \frac{(1 + v_p^N)(1 - 2v_p^N)}{\varrho_N(1 - v_p^N)} \left[\frac{4}{3} + \frac{\varphi_f^N}{\alpha_N^2 \hat{K} Da(1 + (L_r A_r)_N)} \right] V_f^N, \quad (49c)$$

(when $0 < r \leq 1$)

$$P^T = 1 + A_1^T i_0(\chi_T r), \quad (50a)$$

$$V_f^T = -\frac{\alpha_T^2(1 + (L_r A_r)_T)}{\varphi_f^T \chi_T} A_1^T i_1(\chi_T r), \quad (50b)$$

$$U_s^T = \frac{A_2^T}{3} r - \frac{(1 + v_p^T)(1 - 2v_p^T)}{\varrho_T(1 - v_p^T)} \left[\frac{4}{3} + \frac{\varphi_f^T}{\alpha_T^2 Da(1 + (L_r A_r)_T)} \right] V_f^T. \quad (50c)$$

The arbitrary constants in the above solutions are evaluated as

$$A_1^T = -\frac{X_1^N (\varphi_f^N - \varphi_f^T)}{(8DaX_1^N + X_3^N)X_1^T - X_1^N X_3^T}, \quad (51a)$$

$$A_2^T = \frac{1}{(X_5^T - \frac{1}{3}X_6^N)} \left[(X_4^N A_1^N + X_5^N A_2^N + (\varphi_s^T - \varphi_s^N) - X_4^T A_1^T) \right. \\ \left. + X_6^N (X_2^N A_2^N + X_1^N X_2^N A_1^N + X_1^T X_2^T A_1^T) \right], \quad (51b)$$

$$A_1^N = -\frac{(\varphi_f^N - \varphi_f^T) X_1^T}{(8DaX_1^N X_1^T + X_1^T X_3^N - X_1^N X_3^T)}, \quad (51c)$$

$$A_2^N = \frac{2(\varphi_f^T - \varphi_f^N) X_1^T X_1^N}{(8DaX_1^N X_1^T + X_1^T X_3^N - X_1^N X_3^T)}, \quad (51d)$$

$$A_3^N = \frac{1}{3} A_2^T + (X_2^N A_2^N + X_1^N X_2^N A_1^N + X_1^T X_2^T A_1^T), \quad (51e)$$

where

$$X_1^N = \frac{\alpha_N^2 \hat{K}}{\varphi_f^N \chi_N} (1 + (L_r A_r)_N) k_1(\chi_N), \quad (52a)$$

$$X_1^T = \frac{\alpha_T^2}{\varphi_f^T \chi_T} (1 + (L_r A_r)_T) i_1(\chi_T), \quad (52b)$$

$$X_2^N = \frac{(1 + v_p^N)(1 - 2v_p^N)}{\varrho_N(1 - v_p^N)} \left[\frac{4}{3} + \frac{\varphi_f^N}{\alpha_N^2 \hat{K} Da(1 + (L_r A_r)_N)} \right], \quad (52c)$$

$$X_2^T = \frac{(1 + v_p^T)(1 - 2v_p^T)}{\varrho_T(1 - v_p^T)} \left[\frac{4}{3} + \frac{\varphi_f^T}{\alpha_T^2 Da(1 + (L_r A_r)_T)} \right]. \quad (52d)$$

$$X_3^N = \left[-\varphi_f^N k_0(\chi_N) - \frac{4\alpha_N^2 \hat{K} Da}{3\varphi_f^N} (1 + (L_r A_r)_N) k_0(\chi_N) \right. \\ \left. - \frac{4\alpha_N^2 \hat{K} Da}{\varphi_f^N \chi_N} (1 + (L_r A_r)_N) k_1(\chi_N) \right], \quad (52e)$$

$$X_3^T = \left[-\varphi_f^T i_0(\chi_T) - \frac{4\alpha_T^2 Da}{3\varphi_f^T} (1 + (L_r A_r)_T) i_0(\chi_T) - \frac{4\alpha_T^2 Da}{\varphi_f^T \chi_T} (1 + (L_r A_r)_T) i_1(\chi_T) \right], \quad (52f)$$

$$X_4^N = \left[-\varphi_s^N k_0(\chi_N) + \left\{ 1 + \frac{4\alpha_N^2 \hat{K} Da}{3\varphi_f^N} (1 + (L_r A_r)_N) \right\} \times \left\{ k_0(\chi_N) + \frac{2}{\chi_N} \frac{(1 - 2\nu_p^N)}{(1 - \nu_p^N)} k_1(\chi_N) \right\} \right], \quad (52g)$$

$$X_4^T = \left[-\varphi_s^T i_0(\chi_T) + \left\{ 1 + \frac{4\alpha_T^2 Da}{3\varphi_f^T} (1 + (L_r A_r)_T) \right\} \right] \quad (52h)$$

$$\times \left\{ i_0(\chi_T) - \frac{2}{\chi_T} \frac{(1 - 2\nu_p^T)}{(1 - \nu_p^T)} i_1(\chi_T) \right\}, \quad (52i)$$

$$X_5^N = \frac{2(1 - 2\nu_p^N)}{(1 - \nu_p^N)} \left\{ \frac{4}{3} Da + \frac{\varphi_f^N}{\alpha_N^2 \hat{K} (1 + (L_r A_r)_N)} \right\} \quad (52j)$$

$$X_5^T = \frac{\varrho_T Da}{3(1 - 2\nu_p^T)} \quad (52k)$$

$$X_6^N = -\frac{2\varrho_N Da}{(1 + \varrho_N)} \quad (52l)$$

One dimensional solution of transport reaction model can be obtained with the help of boundary conditions (34a)–(35) for two different modes of transport across the blood vessel wall inside $\Omega_N \cup \Omega_T$. Accordingly, we have

Leading Order Solution:

(when Pe_v^i is high)

$$C_{n,0}^N = a_{01}^N i_0(\lambda_{N_{n,1}} r) + a_{02}^N k_0(\lambda_{N_{n,1}} r) - \frac{\beta_N^2}{\lambda_{N_{n,1}}^2} (1 - \sigma_f), \quad (53a)$$

$$C_{n,0}^T = a_{01}^T i_0(\lambda_{T_{n,1}} r) + a_{02}^T k_0(\lambda_{T_{n,1}} r) + \frac{\beta_T^2}{\lambda_{T_1}^2 (1 + (L_r A_r)_T)} (1 - \sigma_f), \quad (53b)$$

and

(when Pe_v^i is low)

$$C_{n,0}^N = b_{01}^N i_0(\lambda_{N_{n,2}} r) + b_{02}^N k_0(\lambda_{N_{n,2}} r) + \left(\frac{\varsigma_N}{\lambda_{N_{n,2}}} \right)^2, \quad (54a)$$

$$C_{n,0}^T = b_{01}^T i_0(\lambda_{T_{n,2}} r) + b_{02}^T k_0(\lambda_{T_{n,2}} r) + \left(\frac{\varsigma_T}{\lambda_{T_{n,2}}} \right)^2. \quad (54b)$$

First-Order Solution:(when Pe_v^i is high)

$$C_{n,1}^N = a_{11}^N i_0(\lambda_{N_{n,1}} r) + a_{12}^N k_0(\lambda_{N_{n,1}} r) + \mathcal{P}_{Pe_v \gg 1}^N(r; \chi_N, \lambda_{N_{n,1}}, \lambda_{N_{n,3}}), \quad (55a)$$

$$C_{n,1}^T = a_{11}^T i_0(\lambda_{T_{n,1}} r) + a_{12}^T k_0(\lambda_{T_{n,1}} r) + \mathcal{P}_{Pe_v \gg 1}^T(r; \chi_T, \lambda_{T_{n,1}}), \quad (55b)$$

and

(when Pe_v^i is low)

$$C_{n,1}^N = b_{11}^N i_0(\lambda_{N_{n,2}} r) + b_{12}^N k_0(\lambda_{N_{n,2}} r) + \mathcal{P}_{Pe_v \ll 1}^N(r; \chi_N, \lambda_{N_{n,2}}, \lambda_{N_{n,4}}), \quad (56a)$$

$$C_{n,1}^T = b_{11}^T i_0(\lambda_{T_{n,2}} r) + b_{12}^T k_0(\lambda_{T_{n,2}} r) + \mathcal{P}_{Pe_v \ll 1}^T(r; \chi_T, \lambda_{T_{n,2}}), \quad (56b)$$

where

$$\begin{aligned} \mathcal{P}_{Pe_v \gg 1}^N(r; \chi_N, \lambda_{N_{n,1}}, \lambda_{N_{n,3}}) = & \frac{F_{N_3}}{2} \left\{ \frac{1}{(\lambda_{N_{n,1}} r)^2} + \frac{1}{2(\lambda_{N_{n,1}} r)^3} \right\} \exp(-\lambda_{N_{n,1}} r) \\ & + \frac{F_{N_2}}{\chi_N(\chi_N^2 - \lambda_{N_{n,1}}^2)} \frac{1}{r} \exp(-\lambda_{N_{n,1}} r) \\ & + \frac{1}{\chi_N \lambda_{N_{n,1}}} (F_{N_1} + F_{N_4}) f_{N_1}(r; \lambda_{N_{n,1}}, \lambda_{N_{n,3}}) \\ & + \frac{F_{N_4}}{\chi_N^2 \lambda_{N_{n,1}}^2} \{ \lambda_{N_{n,1}} f_{N_2}(r; \lambda_{N_{n,1}}, \lambda_{N_{n,3}}) \\ & + f_{N_3}(r; \lambda_{N_{n,1}}, \lambda_{N_{n,3}}) \}, \end{aligned} \quad (57a)$$

$$\begin{aligned} \mathcal{P}_{Pe_v \gg 1}^T(r; \chi_T, \lambda_{T_{n,1}}) = & F_{T_1} f_{T_1}(r; \chi_T, \lambda_{T_{n,1}}) \\ & + F_{T_2} f_{T_2}(r; \chi_T, \lambda_{T_{n,1}}) + F_{T_3} f_{T_3}(r; \chi_T, \lambda_{T_{n,1}}), \end{aligned} \quad (57b)$$

$$\begin{aligned} \mathcal{P}_{Pe_v \ll 1}^N(r; \chi_N, \lambda_{N_{n,2}}, \lambda_{N_{n,4}}) = & \frac{G_{N_3}}{2} \left\{ \frac{1}{(\lambda_{N_{n,2}} r)^2} + \frac{1}{2(\lambda_{N_{n,2}} r)^3} \right\} \exp(-\lambda_{N_{n,2}} r) \\ & + \frac{G_{N_2}}{\chi_N(\chi_N^2 - \lambda_{N_{n,2}}^2)} \frac{1}{r} \exp(-\lambda_{N_{n,2}} r) \\ & + \frac{1}{\chi_N \lambda_{N_{n,2}}} (G_{N_1} + G_{N_4}) g_{N_1}(r; \lambda_{N_{n,2}}, \lambda_{N_{n,4}}) \\ & + \frac{G_{N_4}}{\chi_N^2 \lambda_{N_{n,2}}^2} \{ \lambda_{N_{n,2}} g_{N_2}(r; \lambda_{N_{n,2}}, \lambda_{N_{n,4}}) \\ & + g_{N_3}(r; \lambda_{N_{n,2}}, \lambda_{N_{n,4}}) \}, \end{aligned} \quad (57c)$$

$$\begin{aligned} \mathcal{P}_{Pe_v \ll 1}^T(r; \chi_T, \lambda_{T_{n,2}}) = & G_{T_1} g_{T_1}(r; \chi_T, \lambda_{T_{n,1}}) \\ & + G_{T_2} g_{T_2}(r; \chi_T, \lambda_{T_{n,1}}) + G_{T_3} g_{T_3}(r; \chi_T, \lambda_{T_{n,1}}). \end{aligned} \quad (57d)$$

For the details on functions F_* , G_* (* denotes relevant suffix) in (57b) and (57d) respectively, please refer Appendix B. For the particular integrals f_* and g_* in (57b) and (57d) respectively, please refer Appendix C. Note that the arbitrary constants a_{01}^N , a_{02}^T , a_{11}^N , a_{12}^T ,

$b_{01}^N, b_{02}^T, b_{11}^N$ and b_{12}^T turn out to be zero in order to avoid singularity. The remaining constants are evaluated and presented in Appendix D.

Appendix B

$$F_{N_1} = -\frac{a_{02}^N A_2^N \widehat{D} \alpha_N^2 \widehat{K} (1 + \varphi_s^N (L_r A_r)_N)}{\varphi_f^N}, \quad (58a)$$

$$F_{N_2} = \alpha_N^2 \widehat{K} \widehat{D} (1 - \sigma_f) A_2^N \left[1 + \frac{(1 + \varphi_s^N (L_r A_r)_N) \beta_N^2}{\varphi_f^N \chi_N} \right], \quad (58b)$$

$$F_{N_3} = -a_{02}^N A_3^N \widehat{D} \lambda_{N_{n,1}}, \quad (58c)$$

$$F_{N_4} = -\frac{a_{02}^N A_2^N \widehat{D} \lambda_{N_{n,1}} \alpha_N^2 \widehat{K}}{\varphi_s^N \chi_N} (1 + (L_r A_r)_N), \quad (58d)$$

$$F_{T_1} = \frac{\alpha_T^2 A_1^T (1 - \sigma_f)}{\chi_T} \left[1 - \frac{(1 + \varphi_s^T (L_r A_r)_T) \beta_T^2}{\varphi_f^T \lambda_{T_{n,1}}^2 (1 + (L_r A_r)_T)} \right] \quad (58e)$$

$$F_{T_2} = -\frac{A_1^T a_{01}^T \alpha_T^2}{\varphi_f^T \chi_T} (1 + \varphi_s^T (L_r A_r)_T) \quad (58f)$$

$$F_{T_3} = -\frac{A_1^T a_{01}^T \alpha_T^2 \lambda_{T_{n,1}}}{\varphi_f^T \chi_T^2} (1 + (L_r A_r)_T) \quad (58g)$$

$$G_{N_1} = -\frac{b_{02}^N A_2^N \alpha_N^2 \widehat{K} \widehat{D}}{\varphi_f^N \chi_N} (1 + \varphi_s^N (L_r A_r)_N), \quad (58h)$$

$$G_{N_2} = -\frac{A_2^N \alpha_N^2 \widehat{K} \widehat{D} \varsigma_N^2}{\varphi_f^N \lambda_{N_2}^2} (1 + \varphi_s^N (L_r A_r)_N), \quad (58i)$$

$$G_{N_3} = -b_{02}^N A_3^N \widehat{D} \lambda_{N_{n,2}}, \quad (58j)$$

$$G_{N_4} = -\frac{b_{02}^N A_2^N \alpha_N^2 \widehat{K} \widehat{D} \lambda_{N_{n,2}}}{\varphi_f^N \chi_N} (1 + (L_r A_r)_N), \quad (58k)$$

$$G_{T_1} = -\frac{A_1^T \alpha_T^2 \varsigma_T^2}{\varphi_f^T \chi_T \lambda_{T_{n,2}}^2} (1 + \varphi_s^T (L_r A_r)_T), \quad (58l)$$

$$G_{T_2} = -\frac{A_1^T b_{01}^T \alpha_T^2}{\varphi_f^T \chi_T} (1 + \varphi_s^T (L_r A_r)_T), \quad (58m)$$

$$G_{T_3} = -\frac{A_1^T b_{01}^T \alpha_T^2 \lambda_{T_{n,2}}}{\varphi_f^T \chi_T^2} (1 + (L_r A_r)_T). \quad (58n)$$

Appendix C

$$f_{N_m} : \frac{1}{r} \left[\frac{1}{(D^2 - \lambda_{N_{n,1}}^2)} \frac{1}{r^m} \exp(-\lambda_{N_{n,3}}^2 r) \right], \quad m \in \mathbb{N}. \quad (59a)$$

$$g_{N_m} : \frac{1}{r} \left[\frac{1}{(D^2 - \lambda_{N_{n,2}}^2)} \frac{1}{r^m} \exp(-\lambda_{N_{n,4}}^2 r) \right], \quad m \in \mathbb{N}. \quad (59b)$$

$$f_{T_1} : \frac{1}{r} \frac{1}{(D^2 - \lambda_{T_{n,1}}^2)} (\chi_{Tr}) i_0(\chi_{Tr}) \quad (59c)$$

$$f_{T_2} : \frac{1}{r} \frac{1}{(D^2 - \lambda_{T_{n,1}}^2)} (\chi_{Tr}) i_0(\chi_{Tr}) i_0(\lambda_{T_{n,1}} r) \quad (59d)$$

$$f_{T_3} : \frac{1}{r} \frac{1}{(D^2 - \lambda_{T_{n,1}}^2)} (\chi_{Tr}) i_1(\chi_{Tr}) i_1(\lambda_{T_{n,1}} r) \quad (59e)$$

$$g_{T_1} : \frac{1}{r} \frac{1}{(D^2 - \lambda_{T_{n,2}}^2)} (\chi_{Tr}) i_0(\chi_{Tr}) \quad (59f)$$

$$g_{T_2} : \frac{1}{r} \frac{1}{(D^2 - \lambda_{T_{n,2}}^2)} (\chi_{Tr}) i_0(\chi_{Tr}) i_0(\lambda_{T_{n,2}} r) \quad (59g)$$

$$g_{T_3} : \frac{1}{r} \frac{1}{(D^2 - \lambda_{T_{n,2}}^2)} (\chi_{Tr}) i_1(\chi_{Tr}) i_1(\lambda_{T_{n,2}} r) \quad (59h)$$

Appendix D

$$\begin{aligned} a_{01}^T &= -(1 - \sigma_f) \left[\frac{\beta_N^2}{\lambda_{N_{n,1}}} + \frac{\beta_T^2}{\lambda_{T_{n,1}}(1 + (L_r A_r)_T)} \right] k_1(\lambda_{N_{n,1}}) \\ &\times \left[\frac{\lambda_{T_{n,1}}}{\lambda_{N_{n,1}}} i_1(\lambda_{T_{n,1}}) k_0(\lambda_{N_{n,1}}) + i_0(\lambda_{T_{n,1}}) k_1(\lambda_{N_{n,1}}) \right]^{-1} \end{aligned} \quad (60a)$$

$$\begin{aligned} a_{02}^N &= (1 - \sigma_f) \left[\frac{\beta_N^2}{\lambda_{N_{n,1}}} + \frac{\beta_T^2}{\lambda_{T_{n,1}}(1 + (L_r A_r)_T)} \right] i_1(\lambda_{T_{n,1}}) \\ &\times \left[i_1(\lambda_{T_{n,1}}) k_0(\lambda_{N_{n,1}}) + \frac{\lambda_{N_{n,1}}}{\lambda_{T_{n,1}}} i_0(\lambda_{T_{n,1}}) k_1(\lambda_{N_{n,1}}) \right]^{-1} \end{aligned} \quad (60b)$$

$$b_{01}^T = \left(\frac{\varsigma_N^2}{\lambda_{N_{n,2}}^2} - \frac{\varsigma_T^2}{\lambda_{T_{n,2}}^2} \right) k_1(\lambda_{N_{n,2}}) \times \left[i_0(\lambda_{T_{n,2}}) k_1(\lambda_{N_{n,2}}) + \frac{\lambda_{T_{n,2}}}{\lambda_{N_{n,2}}} i_1(\lambda_{T_{n,2}}) k_0(\lambda_{N_{n,2}}) \right]^{-1} \quad (60c)$$

$$b_{02}^N = \left(\frac{\varsigma_N^2}{\lambda_{N_{n,2}}^2} - \frac{\varsigma_T^2}{\lambda_{T_{n,2}}^2} \right) i_1(\lambda_{T_{n,2}}) \times \left[\frac{\lambda_{T_{n,2}}}{\lambda_{N_{n,2}}} i_0(\lambda_{T_{n,2}}) k_1(\lambda_{N_{n,2}}) + i_1(\lambda_{T_{n,2}}) k_0(\lambda_{N_{n,2}}) \right]^{-1} \quad (60d)$$

$$\begin{aligned}
 a_{11}^T = & \left[\frac{\lambda_{N_{n,1}}}{\widehat{D}} \left\{ \mathcal{P}_{P_{ev} \gg 1}^N(\chi_N, \lambda_{N_{n,1}}, \lambda_{N_{n,3}}) - \mathcal{P}_{P_{ev} \gg 1}^T(\chi_T, \lambda_{T_{n,1}}) \right\} \right. \\
 & \times k_1(\lambda_{N_{n,1}}) \\
 & + \left\{ \frac{1}{\widehat{D}} \mathcal{P}_{P_{ev} \gg 1}^{N'}(\chi_N, \lambda_{N_{n,1}}, \lambda_{N_{n,3}}) - \mathcal{P}_{P_{ev} \gg 1}^{T'}(\chi_T, \lambda_{T_{n,1}}) \right\} \\
 & \times k_0(\lambda_{N_{n,1}}) \\
 & - \frac{\alpha_T^2(1 + (L_r A_r)_T) A_1^T}{\varphi_f^T \chi_T} \\
 & \times \left\{ a_{01}^T i_0(\lambda_{T_{n,1}}) + \frac{\beta_T^2}{\lambda_{T_1}^2(1 + (L_r A_r)_T)}(1 - \sigma_f) \right\} k_0(\lambda_{N_{n,1}}) \\
 & - \left\{ A_3^N + \frac{\alpha_N^2 \widehat{K} A_2^N}{\varphi_f^N \chi_N} (1 + (L_r A_r)_N) k_1(\chi_N) \right\} \\
 & \times \left\{ a_{02}^N k_0(\lambda_{N_{n,1}}) - \frac{\beta_N^2}{\lambda_{N_{n,1}}^2} (1 - \sigma_f) \right\} k_0(\lambda_{N_{n,1}}) \Big] \\
 & \Big/ \left[\frac{\lambda_{N_1}}{\widehat{D}} i_0(\lambda_{T_{n,1}}) k_1(\lambda_{N_{n,1}}) + \lambda_{T_{n,1}} i_1(\lambda_{T_{n,1}}) k_0(\lambda_{N_{n,1}}) \right] \quad (60e)
 \end{aligned}$$

$$\begin{aligned}
 a_{12}^N = & \frac{1}{k_0(\lambda_{N_{n,1}})} \left[\mathcal{P}_{P_{ev} \gg 1}^T(\chi_T, \lambda_{T_{n,1}}) \right. \\
 & \left. - \mathcal{P}_{P_{ev} \gg 1}^N(\chi_N, \lambda_{N_{n,1}}, \lambda_{N_{n,3}}) + a_{11}^T i_0(\lambda_{T_{n,1}}) \right], \quad (60f)
 \end{aligned}$$

$$\begin{aligned}
 b_{11}^T = & \left[\frac{\lambda_{N_{n,2}}}{\widehat{D}} \left\{ \mathcal{P}_{P_{ev} \ll 1}^N(\chi_N, \lambda_{N_{n,2}}, \lambda_{N_{n,4}}) - \mathcal{P}_{P_{ev} \ll 1}^T(\chi_T, \lambda_{T_{n,2}}) \right\} \right. \\
 & \times k_1(\lambda_{N_{n,2}}) \\
 & + \left\{ \frac{1}{\widehat{D}} \mathcal{P}_{P_{ev} \gg 1}^{N'}(\chi_N, \lambda_{N_{n,1}}, \lambda_{N_{n,3}}) - \mathcal{P}_{P_{ev} \gg 1}^{T'}(\chi_T, \lambda_{T_{n,1}}) \right\} \\
 & \times k_0(\lambda_{N_{n,2}}) \\
 & - \frac{\alpha_T^2(1 + (L_r A_r)_T) A_1^T}{\varphi_f^T \chi_T} \times \left\{ b_{01}^T i_0(\lambda_{T_{n,2}}) + \left(\frac{\varsigma_T}{\lambda_{T_{n,2}}} \right)^2 \right\} k_0(\lambda_{N_{n,2}}) \\
 & - \left\{ A_3^N + \frac{\alpha_N^2 \widehat{K} A_2^N}{\varphi_f^N \chi_N} (1 + (L_r A_r)_N) k_1(\chi_N) \right\} \\
 & \times \left\{ b_{02}^N k_0(\lambda_{N_{n,2}}) + \left(\frac{\varsigma_N}{\lambda_{N_{n,2}}} \right)^2 \right\} k_0(\lambda_{N_{n,2}}) \Big] \\
 & \Big/ \left[\frac{\lambda_{N_{n,2}}}{\widehat{D}} i_0(\lambda_{T_{n,2}}) k_1(\lambda_{N_{n,2}}) + \lambda_{T_{n,2}} i_1(\lambda_{T_{n,2}}) k_0(\lambda_{N_{n,2}}) \right] \quad (60g)
 \end{aligned}$$

$$b_{12}^N = \frac{1}{k_0(\lambda_{N_{n,2}})} \left[\mathcal{P}_{P_{ev} \ll 1}^T(\chi_T, \lambda_{T_{n,2}}) - \mathcal{P}_{P_{ev} \ll 1}^N(\chi_N, \lambda_{N_{n,2}}, \lambda_{N_{n,4}}) + b_{11}^T i_0(\lambda_{T_{n,2}}) \right]$$

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