Theoret. Appl. Mech., Vol.34, No.1, pp. 51–86, Belgrade 2007

A multiscale description of growth and transport in biological tissues

A.Grillo * **G.Zingali** † **D.Borrello** †
S.Federico ‡ **W.Herzog** ‡ **G.Giaquinta** *

Abstract

We study a growing biological tissue as an open biphasic mixture with mass exchange between phases. The solid phase is identified with the matrix of a porous medium, while the fluid phase is comprised of water, together with all the dissolved chemical substances coexisting in the pore space. We assume that chemical substances evolve according to transport mechanisms determined by kinematic and constitutive relations, and we propose to consider growth as a process able to influence transport by continuously varying the thermo-mechanic state of the tissue. By focussing on the case of anisotropic growth, we show that such an influence occurs through a continuous rearrangement of the tissue material symmetries. In order to illustrate this interaction, we restrict ourselves to diffusion-dominated transport, and we assume that the time-scales associated with growth and the transport process of interest are largely separated. This allows for performing an asymptotic analysis of the "field equations" of the system. In this framework, we provide a formal solution of the transport equation in terms of its associated Green's function, and we show how the macroscopic concentration of a given chemical substance is "modulated" by anisotropic growth.

Keywords: multi-scale, homogenization, mixtures theory, growth, transport.

---

*CNISM, DMFCI, University of Catania. Viale Andrea Doria 6, 95125 Catania, Italy, e-mail: agrillo@dmfci.unict.it

†Dottorato di Ricerca in Ingegneria Fisica, University of Catania, Italy

‡HPL, The University of Calgary, 2500 University Drive NW, Calgary, Alberta, T2N 1N4, Canada

1 Introduction

Biological growth is the mass variation of a living tissue in response to the concurrency of various phenomena which take place at several scales of observation. As a result, the tissue may either increase (positive growth) or decrease (negative growth, or resorption) its mass [1]. At the molecular and cellular level, growth is dictated by chemical reactions and cellular processes involving transport mechanisms of both cells and chemical species [2][3]. At the scale at which the tissue can be regarded as a macroscopic complex continuum system, growth is influenced by environmental factors [1], identified with thermo-mechanical stimuli that participate with growth in the changes of geometry, internal structure, thermo-mechanic state, and material properties of the tissue. This continuous transformation of the tissue implies that chemical substances evolve in a continuously varying thermo-mechanical environment.

Despite the separation of scales between the molecular and the tissue levels, the transport processes experienced by chemical substances, and the thermo-mechanical processes undergone by the tissue as a whole are interconnected. Mixture Theory offers a useful tool for studying the coupling between transport processes and thermo-mechanics in biological systems [3]-[6]. Mixtures can be either assumed to be composed by a solid phase, a fluid phase and an arbitrary number of chemical species dissolved in the fluid [2], or can be assumed to consist of an arbitrary number of solid and "fluid" constituents [5][6].

We regard a biological tissue experiencing growth as a porous medium made of a solid matrix saturated by a fluid, i.e., the saturation condition, $\phi_F + \phi_S = 1$, is assumed to hold true (ϕ_F and ϕ_S being the volume fractions of the fluid and solid phase, respectively). The fluid phase consists of a number of chemical species, which behave as solutes in an aqueous solution, and filtrate the solid porous matrix. This description is consistent with Biot's picture [7]. We first consider the balance laws of chemical substances at the pore scale. Then, by averaging these balance equations [8], we "bring" chemical substances to the scale at which the porous material is treated as a macroscopic continuum mixture. This technique, called *upscaling*, is consistent with the macroscopic description of the mixture given, for example, in [2][5], and can be made consistent with the results shown in [6] by considering the case of a system open with respect to mass, momentum, energy, and entropy even at the pore scale. However, for the sake of simplicity, we shall deal with the case of a system open with respect to mass only.

The macroscopic thermo-mechanic characterisation of the mixture given in this paper follows the constitutive assumptions suggested in [8]. This provides the expressions for Darcy's law of flow and Fick's law of diffusion in porous materials. It is worth to notice that in the framework followed in the present paper, the *caveat* put forward by Rajagopal [9] seems to be not so stringent for our purposes.

The introduction of Fick's law enables us to treat the macroscopic mass balance of a given chemical substance in terms of an advection-diffusion-reaction equation. The investigation of the possible interaction between these transport mechanisms and growth is the main goal of this paper. In order to do that, we write the advection-diffusion-reaction equation in material form [10], and we follow the idea put forward by Epstein and Maugin [11] to consider growth as development of material inhomogeneities. Particular emphasis is given to anisotropic growth. In this case, we interpret the growth-induced evolution of transport properties in terms of a continuous rearrangement of material symmetries and inhomogeneities. On the trail of a previous paper [12], we assume that growth is characterized by a time-scale much slower than that of the transport process of interest, we suggest a formal solution of the transport equation in terms of its associated Green's function, and we show how the macroscopic concentration of a certain chemical substance is "modulated" by anisotropic growth.

2 Pore scale description and upscaling

The overall behaviour of a porous material depends on both its internal structure and the interaction with the environment. In order to investigate the role played by the former, it is necessary to start the analysis of a porous medium from the pore scale description. Indeed, since this paper deals with growth (i.e., a macroscopic phenomenon which requires the presence of source terms in general balance laws), we need to determine the macroscopic sources of mass, momentum, energy and entropy consistently with the formulation of balance laws at the pore scale. This is possible if all the "ingredients" accounted for at the *mesoscopic* scale (or pore scale) are retrieved within the macroscopic framework in accordance with a thermodynamically appropriate *upscaling* (or *homogenization*) procedure. The upscaling "philosophy" allows for determining a Fick-like macroscopic description of transport that incorporates pore scale structure and phenomenology.

We consider a system made of a porous solid matrix (i.e., the solid phase) and a fluid phase filling the pores. We represent the fluid phase as an "ensemble" of N chemical substances ($N-1$ solutes plus the N-th component, identified with water) coexisting in the pore space. By invoking phase separation, we describe the evolution of the chemical constituents by considering, for each species, separate balance of mass, momentum, energy, and entropy, and accounting for appropriate interaction and exchange terms. By attaching at any point $\boldsymbol{r}$ of the system a given mesoscopic physical quantity ψ_m (that can be either a scalar, a vector or a tensor field), the associated mesoscopic balance law reads [8][13]-[15]:

$$\frac{\partial(\rho_m \psi_m)}{\partial t} + \nabla_{\mathbf{r}} \cdot (\rho_m \psi_m \mathbf{v}_m) - \nabla_{\mathbf{r}} \cdot \Im_m - \rho_m f_m = \rho_m g_m, \tag{1}$$

where ρ_m and $\mathbf{v}_m$ are the mesoscopic mass density and velocity of the medium, respectively, $\nabla_{\mathbf{r}}$ denotes differentiation with respect to the mesoscopic space variable $\boldsymbol{r}$, $\Im_m$ is the flux associated with ψ_m, f_m is the internal source, and g_m is the net production rate. By labelling each of these physical quantities with the indices $k = S, F, \alpha$, Eq. (1) can be specialized to the solid phase (index S), fluid phase (index F) and the generic chemical constituent (index α) of the fluid phase. The specialization of Eq. (1) to the subsets of the porous material occupied by the solid and fluid is necessary because physical quantities are assumed to be smooth inside each component of the medium, but experience jump conditions at the fluid-solid interface [8]. These jump conditions yield certain constraints on the thermo-mechanical quantities, and can be stated as balance laws at the fluid-solid interface, i.e.,

$$\begin{aligned} &\textstyle\sum_{\alpha=1}^{N} \left[\rho_{m,\alpha}\psi_{m,\alpha}(\mathbf{u} - \mathbf{v}_{m,\alpha}) - \Im_{m,\alpha}\right]\big|_F \cdot \mathbf{n}_{FS} + \\ &\left[\rho_{m,S}\psi_{m,S}(\mathbf{u} - \mathbf{v}_{m,S}) - \Im_{m,S}\right]\big|_S \cdot \mathbf{n}_{SF} \geq 0, \end{aligned} \tag{2}$$

where $\mathbf{u}$ is the interface velocity, $\mathbf{n}_{FS}$ and $\mathbf{n}_{SF}$ ($\mathbf{n}_{FS} = -\mathbf{n}_{SF}$) are the unit normal vectors pointing out of the fluid and solid phase, respectively, and the symbols $[...]|_F$ and $[...]|_S$ indicate that, at the interface, the limit of the expressions within brackets is to be evaluated from the fluid and solid side, respectively. It is worth to remark that Eq. (2) is satisfied as an inequality only in the case of entropy.

Quantity	ψ_m	$\Im_m$	f_m	g_m
Mass	1	0	0	$\hat{r}^{gr}_{m,S}$
Momentum	$\mathbf{v}_{m,S}$	$\sigma_{m,S}$	$\mathbf{g}_{m,S}$	$\hat{r}^{gr}_{m,S}\hat{\mathbf{v}}_{m,S} + \hat{\lambda}^{gr}_{m,S}$
Energy	$U_{m,S}+$ $\frac{1}{2}v^2_{m,S}$	$\sigma_{m,S}.\mathbf{v}_{m,S}+$ $\mathbf{q}_{m,S}$	$\mathbf{g}_{m,S}\cdot\mathbf{v}_{m,S}+$ $h_{m,S}$	$\hat{r}^{gr}_{m,S}(\hat{U}_{m,S} + \frac{1}{2}\hat{v}^2_{m,S})$ $+\hat{\lambda}^{gr}_{m,S}\cdot\mathbf{v}_S + \hat{\theta}_{m,S}$
Entropy	$S_{m,S}$	$\varphi_{m,S}$	$b_{m,S}$	$\hat{r}^{gr}_{m,S}\hat{S}_{m,S} + \hat{\zeta}_{m,S} +$ $\Gamma_{m,S}$

Table 1: Mesoscopic variables referred to the solid phase.

Quantity	ψ_m	$\Im_m$	f_m	g_m
Mass	1	0	0	$\hat{r}^{ch}_{m,\alpha}$
Momentum	$\mathbf{v}_{m,\alpha}$	$\sigma_{m,\alpha}$	$\mathbf{g}_{m,\alpha}$	$\hat{r}^{ch}_{m,\alpha}\hat{\mathbf{v}}_{m,\alpha} + \hat{\lambda}^{ch}_{m,\alpha}$
Energy	$U_{m,\alpha}+$ $\frac{1}{2}v^2_{m,\alpha}$	$\sigma_{m,\alpha}.\mathbf{v}_{m,\alpha}+$ $\mathbf{q}_{m,\alpha}$	$\mathbf{g}_{m,\alpha}\cdot\mathbf{v}_{m,\alpha}+$ $h_{m,\alpha}$	$\hat{r}^{ch}_{m,\alpha}(\hat{U}_{m,\alpha} + \frac{1}{2}\hat{v}^2_{m,\alpha})$ $+\hat{\lambda}^{ch}_{m,\alpha}\cdot\mathbf{v}_\alpha + \hat{\theta}_{m,\alpha}$
Entropy	$S_{m,\alpha}$	$\varphi_{m,\alpha}$	$b_{m,\alpha}$	$\hat{r}^{ch}_{m,\alpha}\hat{S}_{m,\alpha} + \hat{\zeta}_{m,\alpha} +$ $\Gamma_{m,\alpha}$

Table 2: Mesoscopic variables referred to the α-th chemical substance.

In order to refer Eqs. (1) and (2) to the mesoscopic balance of mass, momentum, energy and entropy, it suffices to use the physical quantities defined in Tables 1 and 2. In Tables 1 and 2, $U_{m,\alpha}$, $U_{m,S}$ and $S_{m,\alpha}$, $S_{m,S}$ are the internal energy and entropy densities per unit mass, respectively, $\sigma_{m,\alpha}$, $\sigma_{m,S}$ are the Cauchy stress tensors, $\mathbf{q}_{m,\alpha}$, $\mathbf{q}_{m,S}$ and $\varphi_{m,\alpha}$, $\varphi_{m,S}$ are the heat and entropy flux, respectively, $\mathbf{g}_{m,\alpha}$, $\mathbf{g}_{m,S}$ are body forces per unit mass, $h_{m,\alpha}$, $h_{m,S}$ and $b_{m,\alpha}$, $b_{m,S}$ are the internal sources of internal energy and entropy, $\hat{r}^{ch}_{m,\alpha}$ and $\hat{r}^{gr}_{m,S}$ are mass net production rates, $\hat{\lambda}^{ch}_{m,\alpha}$ and $\hat{\lambda}^{gr}_{m,S}$ denote the intrinsic productions of momentum, $\hat{\theta}_{m,\alpha}$, $\hat{\theta}_{m,S}$ and $\hat{\zeta}_{m,\alpha}$, $\hat{\zeta}_{m,S}$ are the net productions of energy and entropy, respectively, and $\Gamma_{m,\alpha}$, $\Gamma_{m,S}$ are the entropy net production rates. It is worth to notice that the production rates of mass and momentum of the solid phase, $\hat{r}^{gr}_{m,S}$ and $\hat{r}^{gr}_{m,S}\hat{\mathbf{v}}_{m,S} + \hat{\lambda}^{gr}_{m,S}$, are due to growth (i.e., these two quantities would vanish in the absence of growth), while the production rates of mass and momentum of the α-th chemical species, $\hat{r}^{ch}_{m,\alpha}$ and $\hat{r}^{ch}_{\alpha,m}\hat{\mathbf{v}}_{\alpha,m} + \hat{\lambda}^{ch}_{m,\alpha}$, are assumed to be due to chemical processes only. We introduced the velocities $\hat{\mathbf{v}}_{\alpha,m}$ and $\hat{\mathbf{v}}_{m,S}$, the energies $\hat{U}_{\alpha,m}$ and $\hat{U}_{m,S}$, and the entropies $\hat{S}_{\alpha,m}$ and $\hat{S}_{m,S}$ because, as suggested by [6], the mass production rates $\hat{r}^{ch}_{m,\alpha}$ and $\hat{r}^{gr}_{m,S}$ may be endowed with their own velocities, energies, and entropies, respectively (thus, in general, $\hat{\mathbf{v}}_{\alpha,m} \neq \mathbf{v}_{\alpha,m}$, $\hat{\mathbf{v}}_{m,S} \neq \mathbf{v}_{m,S}$, $\hat{U}_{\alpha,m} \neq U_{\alpha,m}$, $\hat{U}_{m,S} \neq U_{m,S}$, $\hat{S}_{\alpha,m} \neq S_{\alpha,m}$, and $\hat{S}_{m,S} \neq S_{m,S}$,).

By hypothesizing that chemical reactions take place within the pore space, the net production of mass, momentum, energy, and entropy referred to the fluid phase as a whole must equal zero. This implies the following set of constraints on the mesoscopic source terms:

$$\begin{aligned}
&\textstyle\sum_{\alpha=1}^{N} \rho_{m,\alpha}\hat{r}^{ch}_{m,\alpha} = 0,\\
&\textstyle\sum_{\alpha=1}^{N} \rho_{m,\alpha}(\hat{r}^{ch}_{m,\alpha}\hat{\mathbf{v}}_{m,\alpha} + \hat{\lambda}^{ch}_{m,\alpha}) = 0,\\
&\textstyle\sum_{\alpha=1}^{N} \rho_{m,\alpha}[\hat{r}^{ch}_{m,\alpha}(\hat{U}_{m,\alpha} + \dfrac{1}{2}\hat{v}^2_{m,\alpha}) + \hat{\lambda}^{ch}_{m,\alpha}\cdot\mathbf{v}_{m,\alpha} + \hat{\theta}_{m,\alpha}] = 0,\\
&\textstyle\sum_{\alpha=1}^{N} \rho_{m,\alpha}(\hat{r}^{ch}_{m,\alpha}\hat{S}_{m,\alpha} + \hat{\zeta}_{m,\alpha}) = 0.
\end{aligned} \tag{3}$$

In order to "bring" the mesoscopic balance laws (1), (2), and (3) to the scale at which the porous material is regarded as a macroscopic mixture, we postulate the existence of a suitable Representative Elementary Volume (REV), Ω, and we average each physical quantity by employing averaging operators [8][13]-[15][16] defined on Ω. An REV is a subset of the porous material such that its size, represented by its measure $|\Omega|$, defines a length-scale which is much larger than the typical length-scale of mesoscopic heterogeneities, and much smaller than the length-scale of the macroscopic inhomogeneities.

We undertake the upscaling (or homogenization) procedure by introducing an averaging operator which provides the average of a given physical quantity ψ_m over the REV, $\Omega(\mathbf{x})$, centred at $\boldsymbol{x}$ ($\boldsymbol{x}$ can be identified with the centroid of the REV), i.e.,

$$\begin{aligned}\langle\psi_m\rangle_\Omega(t,\mathbf{x}) &= \frac{1}{|\Omega(\mathbf{x})|}\int_{\Omega(\mathbf{x})}\psi_m(t,\mathbf{x}+\xi)d\varpi_\xi = \\ &\frac{1}{|\Omega(\mathbf{x})|}\int_{\mathcal{B}_t}\psi_m(t,\mathbf{x}+\xi)\gamma_\Omega(\xi)d\varpi_\xi, \qquad (4)\end{aligned}$$

where $\xi = \mathbf{r} - \mathbf{x} \in \Omega(\mathbf{x})$ is the relative vector coordinate of a point lying inside the REV centred at $\mathbf{x} \in \mathcal{B}_t$, $\mathcal{B}_t$ is the portion of space occupied by the mixture at time t, and γ_Ω is the characteristic function of the REV, defined by

$$\gamma_\Omega(\xi) = \begin{cases} 1, & \forall\xi \in \Omega(\mathbf{x}) \cap \mathcal{B}(t), \\ 0, & \texttt{elsewhere}. \end{cases} \qquad (5)$$

We also define the *apparent* and *intrinsic* volume averages,

$$\langle\psi_m\rangle_k(t,\mathbf{x}) = \langle\gamma_k\psi_m\rangle_\Omega(t,\mathbf{x}), \qquad (6)$$

$$\langle\psi_m\rangle_k^k(t,\mathbf{x}) = \frac{1}{\phi_k(t,\mathbf{x})}\langle\psi_m\rangle_k(t,\mathbf{x}), \qquad (7)$$

the *mass* average of ψ_m with respect to the k-th phase (i.e., $k = S, F$),

$$\overline{\psi_{m,k}}^k(t,\mathbf{x}) = \frac{1}{\langle\gamma_k\rho_{m,k}\rangle_\Omega(t,\mathbf{x})}\langle\gamma_k\rho_{m,k}\psi_{m,k}\rangle_\Omega(t,\mathbf{x}), \qquad (8)$$

and the mass average of ψ_m with respect to the α-th chemical substance,

$$\overline{\psi_{m,\alpha}}^\alpha(t,\mathbf{x}) = \frac{1}{\langle\gamma_F\rho_{m,\alpha}\rangle_\Omega(t,\mathbf{x})}\langle\gamma_F\rho_{m,\alpha}\psi_{m,\alpha}\rangle_\Omega(t,\mathbf{x}). \qquad (9)$$

In Eqs. (6)-(9), $\gamma_k(t,\mathbf{r})$ is the characteristic function of the set $\Omega_k(t,\mathbf{x}) \subset \Omega(\mathbf{x})$ occupied by the k-th phase at time t, and $\phi_k(t,\mathbf{x})$ is the *volume fraction* of the k-th phase, i.e., $\phi_k(t,\mathbf{x}) = |\Omega_k(t,\mathbf{x})|/|\Omega(\mathbf{x})|$.

The "upscaled" version of the mesoscopic balance law (1) can be obtained by using the definitions given in Eqs. (4)-(9), and appealing for two theorems [13]-[15] that provide the result of the application of the apparent volume averaging operator, $\langle . \rangle_k$, to the time and space derivatives of a given mesoscopic field, respectively, i.e. [8][13]-[15],

$$\begin{aligned}\frac{\partial}{\partial t}\left[\phi_F \left\langle \rho_{m,\alpha}\right\rangle_F^F \overline{\psi_{m,\alpha}}^{\alpha}\right] + \nabla_{\mathbf{x}} \cdot \left[\phi_F \left\langle \rho_{m,\alpha}\right\rangle_F^F \overline{\psi_{m,\alpha}}^{\alpha} \overline{\mathbf{v}_{m,\alpha}}^{\alpha}\right] - \nabla_{\mathbf{x}} \cdot \mathbf{J}_\alpha \\ = \phi_F \left\langle \rho_{m,\alpha}\right\rangle_F^F [\overline{f_{m,\alpha}}^{\alpha} + \overline{g_{m,\alpha}}^{\alpha} + \mathcal{E}_\alpha(\rho_{m,\alpha}\psi_{m,\alpha}) + \Re_\alpha],\end{aligned} \tag{10}$$

$$\begin{aligned}\frac{\partial}{\partial t}\left[\phi_S \left\langle \rho_{m,S}\right\rangle_S^S \overline{\psi_{m,S}}^{S}\right] + \nabla_{\mathbf{x}} \cdot \left[\phi_S \left\langle \rho_{m,S}\right\rangle_S^S \overline{\psi_{m,S}}^{S} \overline{\mathbf{v}_{m,S}}^{S}\right] - \nabla_{\mathbf{x}} \cdot \mathbf{J}_S \\ = \phi_S \left\langle \rho_{m,S}\right\rangle_S^S [\overline{f_{m,S}}^{S} + \overline{g_{m,S}}^{S} + \mathcal{E}_S(\rho_{m,S}\psi_{m,S}) + \Re_S].\end{aligned} \tag{11}$$

In Eqs. (10) and (11), $\nabla_{\mathbf{x}}$ denotes differentiation with respect to the centroid of the REV, $\mathbf{x}$, $\mathbf{J}_\alpha$ and $\mathbf{J}_S$ represent macroscopic fluxes, and the quantities $\mathcal{E}_S(\rho_{m,S}\psi_{m,S})$, $\mathcal{E}_\alpha(\rho_{m,\alpha}\psi_{m,\alpha})$, $\Re_S$, and $\Re_\alpha$ are macroscopic source terms accounting for the transfer of the fields $\psi_{m,S}$ and $\psi_{m,\alpha}$ across the solid-fluid interface [8] (see Appendix A for details).

3 Macroscopic description

Macroscopic balance laws of mass, momentum, energy, and entropy must be studied for the N fluid components (or chemical species), and the solid phase. Alternatively, we can write, for each balance law, $N-1$ equations referring to the $N-1$ chemical species (we recall that the N-th fluid component is water), one equation for the mean thermodynamic properties of the fluid phase as a whole, and one equation for the solid phase. In order to do that, it suffices to substitute the macroscopic thermodynamic quantities reported in Tables 3, 4 and 5 into Eqs. (10) and (11). The quantities in Tables 3 and 5 are the macroscopic counterparts of the mesoscopic fields defined in Tables 1 and 2, respectively, while the quantities in Table 4 describe the overall behaviour of the fluid phase. The explicit form for all these quantities is given in Appendix B.

It is also necessary to provide the upscaled version of the constraints stated in Eqs. (2) and (3). By employing the averaging operators defined

Quantity	$\overline{\psi_{m,\alpha}}^{\alpha}$	$\mathbf{J}_\alpha$	$G_\alpha = \overline{g_{m,\alpha}}^{\alpha} + \mathcal{E}_\alpha(\rho_{m,\alpha}\psi_{m,\alpha}) + \Re_\alpha = G^{ch}_\alpha + G^{tr}_\alpha$	
			G^{ch}_α	G^{tr}_α
Mass	1	0	$\hat{r}^{ch}_\alpha$	$\hat{r}^{tr}_\alpha$
Momentum	$\mathbf{v}_\alpha$	σ_α	$\hat{r}^{ch}_\alpha\hat{\mathbf{v}}_\alpha + \hat{\lambda}^{ch}_\alpha$	$\hat{r}^{tr}_\alpha\mathbf{v}_\alpha + \hat{\mathbf{m}}_\alpha$
Energy	$U_\alpha + \frac{1}{2}v^2_\alpha$	$\sigma_\alpha.\mathbf{v}_\alpha + \mathbf{q}_\alpha$	$\hat{r}^{ch}_\alpha(\hat{U}_\alpha + \frac{1}{2}\hat{v}^2_\alpha)$ $+\hat{\lambda}^{ch}_\alpha \cdot \mathbf{v}_\alpha + \hat{\theta}_\alpha$	$\hat{r}^{tr}_\alpha(U_\alpha + \frac{1}{2}v^2_\alpha)$ $+\hat{\mathbf{m}}_\alpha \cdot \mathbf{v}_\alpha + \hat{e}_\alpha$
Entropy	S_α	φ_α	$\hat{r}^{ch}_\alpha\hat{S}_\alpha + \hat{\zeta}_\alpha + \Gamma_\alpha$	$\hat{r}^{tr}_\alpha S_\alpha + \hat{\eta}_\alpha$

Table 3: Macroscopic thermodynamic quantities associated with the α-th chemical substance

Quantity	$\overline{\psi_F}^{F}$	$\mathbf{J}_F$	$G_F = G^{ch}_F + G^{tr}_F$	
			G^{ch}_F	G^{tr}_F
Mass	1	0	0	$\phi_F\rho_F\hat{R}^{tr}_F$
Momentum	$\mathbf{v}_F$	σ_F	0	$\phi_F\rho_F\hat{R}^{tr}_F\mathbf{v}_F + \phi_F\rho_F\hat{\mathbf{T}}_F$
Energy	$U_F + \frac{1}{2}v^2_F$	$\sigma_F.\mathbf{v}_F + \mathbf{q}_F$	0	$\phi_F\rho_F\hat{R}^{tr}_F(U_F + \frac{1}{2}v^2_F)$ $+\phi_F\rho_F\hat{\mathrm{T}}_F \cdot \mathbf{v}_F + \phi_F\rho_F\hat{Q}_F$
Entropy	S_F	φ_F	$\phi_F\rho_F\Gamma_F$	$\phi_F\rho_F\hat{R}^{tr}_F S_F + \hat{\Phi}_F$

Table 4: Macroscopic thermodynamic quantities associated with the fluid phase as a whole

Quantity	$\overline{\psi_S}^{S}$	$\mathbf{J}_S$	$G_S = G^{tr}_S + G^{gr}_S$	
			G^{tr}_S	G^{gr}_S
Mass	1	0	$\phi_S\rho_S\hat{R}^{tr}_S$	$\phi_S\rho_S\hat{R}^{gr}_S$
Momentum	$\mathbf{v}_S$	σ_S	$\phi_S\rho_S\hat{R}^{tr}_S\mathbf{v}_S + \phi_S\rho_S\hat{\mathbf{T}}_S$	$\phi_S\rho_S\hat{R}^{gr}_S\hat{\mathbf{v}}_S$
Energy	$U_S + \frac{1}{2}v^2_S$	$\sigma_S.\mathbf{v}_S + \mathbf{q}_S$	$\phi_S\rho_S\hat{R}^{tr}_S(U_S + \frac{1}{2}v^2_S)$ $+\phi_S\rho_S\hat{\mathrm{T}}_S \cdot \mathbf{v}_S + \phi_S\rho_S\hat{Q}_S$	$\phi_S\rho_S\hat{R}^{gr}_S(\hat{U}_S + \frac{1}{2}\hat{v}^2_S)$
Entropy	S_S	φ_S	$\phi_S\rho_S\hat{R}^{tr}_S S_S + \hat{\Phi}_S + \phi_S\rho_S\Gamma_S$	$\phi_S\rho_S\hat{R}^{gr}_S\hat{S}_S$

Table 5: Macroscopic thermodynamic quantities associated with the solid phase

in section 2, the macroscopic balance laws at the fluid-solid interface read (cfr. Eq. (2))

$$\textit{Mass} \qquad \phi_F \rho_F \hat{R}^{tr}_F = -\phi_S \rho_S \hat{R}^{tr}_S \tag{12}$$

$$\textit{Momentum} \qquad \begin{array}{l} \phi_F \rho_F \hat{R}^{tr}_F \mathbf{v}_F + \phi_F \rho_F \hat{\mathbf{T}}_F = \\ -(\phi_S \rho_S \hat{R}^{tr}_S \mathbf{v}_S + \phi_S \rho_S \hat{\mathbf{T}}_S), \end{array} \tag{13}$$

$$\textit{Energy} \qquad \begin{array}{l} \phi_F \rho_F \hat{Q}_F + \phi_F \rho_F \hat{\mathbf{T}}_F \cdot \mathbf{v}_F + \\ \phi_F \rho_F \hat{R}^{tr}_F (U_F + \frac{1}{2} v_F^2) = -[\phi_S \rho_S \hat{Q}_S + \\ \phi_S \rho_S \hat{\mathbf{T}}_S \cdot \mathbf{v}_S + \phi_S \rho_S \hat{R}^{tr}_S (U_S + \frac{1}{2} v_S^2)], \end{array} \tag{14}$$

$$\textit{Entropy} \qquad \begin{array}{l} \phi_F \sum_{\alpha=1}^N \rho_\alpha (\hat{r}^{tr}_\alpha S_\alpha + \hat{\eta}_\alpha) + \\ \phi_S \rho_S (\hat{R}^{tr}_S S_S + \hat{\Phi}_S) \geq 0. \end{array} \tag{15}$$

Analogously, it is possible to obtain the macroscopic representation of Eq. (3), i.e.,

$$\textit{Mass} \qquad \phi_F \sum_{\alpha=1}^N \rho_\alpha \hat{r}^{ch}_\alpha = 0, \tag{16}$$

$$\textit{Momentum} \qquad \phi_F \sum_{\alpha=1}^N \rho_\alpha (\hat{r}^{ch}_\alpha \hat{\mathbf{v}}_\alpha + \hat{\lambda}^{ch}_\alpha) = 0, \tag{17}$$

$$\textit{Energy} \qquad \phi_F \sum_{\alpha=1}^N \rho_\alpha \left[\hat{r}^{ch}_\alpha (\hat{U}_\alpha + \tfrac{1}{2} \hat{v}_\alpha^2) + \hat{\lambda}^{ch}_\alpha \cdot \mathbf{v}_\alpha + \hat{\theta}_\alpha \right] = 0, \tag{18}$$

$$\textit{Entropy} \qquad \phi_F \sum_{\alpha=1}^N \rho_\alpha (\hat{r}^{ch}_\alpha \hat{S}_\alpha + \hat{\zeta}_\alpha) = 0. \tag{19}$$

In order to reduce the number of unknowns featuring in the macroscopic balance laws, it is necessary to set up a constitutive theory fulfilling the Second Law of Thermodynamics and consistent with the continuum theory of mixtures. This is achieved by exploiting the Clausius-Duhem inequality, and selecting appropriate independent constitutive variables on the basis of specific hypotheses about the behaviour of fluid components, the fluid phase as a whole, and the solid phase. In this paper, we adhere to the constitutive framework established in [8]. We regard the fluid as inviscid, and the solid as an incompressible thermo-elastic material (i.e., the substantial derivative $D_S \rho_S / Dt = \partial_t \rho_S + \mathbf{v}_S \cdot \nabla_{\mathbf{x}} \rho_S$ is equal to zero). The latter assumption is acceptable as long as we deal with a saturated biological porous material [6]. Indeed, in this case, it is reasonable to admit that growth is able to change the solid phase volume fraction while "preserving" its intrinsic mass density [6][17]. Furthermore, we assume that all chemical substances are at the same temperature (i.e., $\Theta_F = \Theta_\alpha$, $\forall \alpha = 1, ..., N$), and the solid and fluid phase are in thermal equilibrium (i.e., $\Theta_F = \Theta_S = \Theta$). Although we are aware that multi-temperature models have recently been proposed in Mixture Theory (cfr., for example, [18][19]), we maintain this hypothesis because it simplifies the thermo-mechanical treatment of our problem. The elastic deformation of the solid is described by the solid phase motion, χ_S [20], i.e., a field mapping each material point $\mathbf{X}$ in the reference configuration of the mixture, $\mathcal{B}_R$, onto $\mathcal{B}_t$ (i.e., $\mathbf{x} = \chi_S(t, \mathbf{X}) \in \mathcal{B}_t$), and such that the components of velocity are $\mathrm{v}_S^a(t, \mathbf{x}) = \partial_t \chi_S^a(t, \mathbf{X})$. By virtue of the hypotheses stated above, the variables to be treated as unknowns are: *i*) the fluid phase mass density, ρ_F; *ii*) the solid phase volume fraction, ϕ_S (or, equivalently, $\phi_F = 1 - \phi_S$); *iii*) the temperature, Θ; *iv*) the $S-$motion, χ_S; *v*) the filtration velocity, $\mathbf{v}_{FS} = \mathbf{v}_F - \mathbf{v}_S$; *vi*) the mass fractions of chemical constituents, $c_\beta = \rho_\beta / \rho_F$ ($\beta = 1, ..., N-1$); *vii*) the diffusive velocities of constituents relative to the fluid phase, $\mathbf{v}_{\beta F} = \mathbf{v}_\beta - \mathbf{v}_F$ ($\beta = 1, ..., N-1$).

We start the constitutive description of the material with the definition of the Helmholtz free energy densities:

$$
\begin{aligned}
A_F &= A_F(\rho_F, c_\beta, \Theta), \\
A_S &= A_S(\mathbf{E}_S, \Theta, \mathbf{X}), \\
A_\beta - A_N = A_{\beta N} &= A_{\beta N}(\rho_F, c_\beta, \Theta)
\end{aligned}
\tag{20}
$$

Here, $\mathbf{E}_S = \frac{1}{2}(\mathbf{F}_S^T \mathbf{F}_S - \mathbf{I}_R)$ is the Green-Lagrange strain tensor of the solid phase, $\mathbf{F}_S = \nabla_{\mathbf{X}} \chi_S$ is the solid phase deformation gradient tensor, $\mathbf{I}_R$ is the identity tensor in the reference configuration, $\mathcal{B}_R$. By virtue of these relations, the entropy of the mixture is given by

$$
\rho S = \phi_F \rho_F S_F + \phi_S \rho_S S_S = -\phi_F \rho_F \frac{\partial A_F}{\partial \Theta} - \phi_S \rho_S \frac{\partial A_S}{\partial \Theta}, \tag{21}
$$

and the Cauchy stress tensor of the fluid and solid phase can be written as

$$
\begin{aligned}
\sigma_S &= -\phi_S p \mathbf{I} + \sigma_S^{el}, \\
\sigma_F &= -\phi_F p \mathbf{I} - \phi_F \rho_F \textstyle\sum_{\beta=1}^{N-1} c_\beta \mathbf{v}_{\beta F} \otimes \mathbf{v}_{\beta F},
\end{aligned}
\tag{22}
$$

where $\mathbf{I}$ is the identity tensor in the current configuration of the mixture, $\mathcal{B}_t$, the thermodynamic pressure, p, is given by:

$$p = \rho_F^2 \frac{\partial A_F}{\partial \rho_F}, \tag{23}$$

and the tensor σ_S^{el} represents the elastic part of σ_S. By expressing the solid phase Helmholtz free energy density, A_S, as a function of $\mathbf{F}_S$, and introducing the first Piola-Kirchhoff stress tensor,

$$\mathbf{P}_S^{el} = J_S \phi_S \rho_S \frac{\partial A_S}{\partial \mathbf{F}_S}, \tag{24}$$

where $J_S = \det(\mathbf{F}_S)$, tensor σ_S^{el} can be written as

$$\sigma_S^{el} = \frac{1}{J_S} \mathbf{P}_S^{el} \mathbf{F}_S^{-T}. \tag{25}$$

The variation of the fluid phase Helmholtz free energy density, A_F, with respect to concentration (or mass fraction) c_β of the β-th chemical substance enables us to define the “relative” chemical potential

$$Y_{\beta N} = Y_\beta - Y_N = \frac{\partial A_F}{\partial c_\beta}(\rho_F, c_\beta, \Theta), \tag{26}$$

where Y_β and Y_N are the chemical potentials for the β-th chemical constituent and water, respectively. On account of Eq. (26), it is possible to prove that the Cauchy stress tensors associated with chemical species are spherical (hydrostatic) tensors [8], i.e.,

$$\sigma_{\beta N} = \sigma_\beta - \frac{c_\beta}{c_N} \sigma_N = -\phi_F \rho_F c_\beta (Y_{\beta N} - A_{\beta N}) \mathbf{I}. \tag{27}$$

Finally, the constitutive expressions defining the momentum exchange terms referred to the fluid phase and chemical substances are given by

$$\begin{gathered}
\phi_F \rho_F \hat{\mathbf{T}}_F = \phi_F \rho_F \mathbf{f}_F + p \nabla_{\mathbf{x}} \phi_F, \\
\phi_F \rho_F (\hat{\mathbf{T}}_\beta - \hat{\mathbf{T}}_N) = \phi_F \rho_F c_\beta \mathbf{f}_\beta + \nabla_{\mathbf{x}} [\phi_F \rho_F c_\beta (Y_{\beta N} - A_{\beta N})] - \\
\phi_F \rho_F c_\beta \nabla_{\mathbf{x}} Y_{\beta N} - \sigma_N . \nabla_{\mathbf{x}} \left(\tfrac{c_\beta}{c_N} \right),
\end{gathered} \tag{28}$$

where $\phi_F\rho_F\mathbf{f}_F$ and $\phi_F\rho_F c_\beta\mathbf{f}_\beta$ represent dissipative terms describing the drag forces exerted on the fluid phase and the β-th chemical substance, respectively. In Ref. [8], a detailed derivation of explicit formulae for $\mathbf{f}_F$ and $\mathbf{f}_\beta$ is presented, and it is shown how $\mathbf{f}_F$ and $\mathbf{f}_\beta$ can be given a linearised expression depending linearly on the filtration velocity, $\mathbf{v}_{FS}$, the diffusive velocities, $\mathbf{v}_{\beta F}$, of chemical substances, and the temperature gradient, $\nabla_{\mathbf{x}}\Theta$. However, by assuming, for the sake of simplicity, that temperature, Θ, is a constant (i.e., $\Theta = \Theta_0$), we can write $\mathbf{f}_F$ and $\mathbf{f}_\beta$ as

$$\begin{aligned}\mathbf{f}_F &= -\Lambda_F.\mathbf{v}_{FS} + \textstyle\sum_{\beta=1}^{N-1}\Lambda_{F\beta}.\mathbf{v}_{\beta F},\\ \mathbf{f}_\beta &= \Lambda_\beta.\mathbf{v}_{FS} - \textstyle\sum_{\gamma=1}^{N-1}\Lambda_{\beta\gamma}.\mathbf{v}_{\gamma F},\end{aligned} \tag{29}$$

where the tensors Λ_F, $\{\Lambda_{F\beta}\}_{\beta=1}^{N-1}$, $\{\Lambda_\beta\}_{\beta=1}^{N-1}$, and $\{\Lambda_{\beta\gamma}\}_{\beta,\gamma=1}^{N-1}$ are material coefficients depending on ρ_F, ϕ_F, $\{c_\delta\}_{\delta=1}^{N}$, and Θ_0. Equations (29) can be used to derive the expressions of Darcy's law of flow, and Fick's diffusion law in the context of porous materials. In order to resume this procedure, we first write the momentum balance laws of the fluid phase and chemical substances:

$$\begin{gathered}\frac{\partial(\phi_F\rho_F\mathbf{v}_F)}{\partial t} + \nabla_{\mathbf{x}}\cdot(\phi_F\rho_F\mathbf{v}_F\otimes\mathbf{v}_F) - \nabla_{\mathbf{x}}\cdot\sigma_F =\\ \phi_F\rho_F\hat{R}_F^{tr}\mathbf{v}_F + \phi_F\rho_F\hat{\mathbf{T}}_F,\end{gathered} \tag{30}$$

$$\begin{gathered}\frac{\partial(\phi_F\rho_F c_\beta\mathbf{v}_\beta)}{\partial t} + \nabla_{\mathbf{x}}\cdot(\phi_F\rho_F c_\beta\mathbf{v}_\beta\otimes\mathbf{v}_\beta) - \nabla_{\mathbf{x}}\cdot\sigma_\beta =\\ \phi_F\rho_F c_\beta\hat{R}_\beta\mathbf{v}_F + \phi_F\rho_F c_\beta\hat{\mathbf{T}}_\beta.\end{gathered} \tag{31}$$

By invoking the mass balance law, after some manipulations, Eqs. (30) and (31) can be rewritten as [8]

$$\phi_F\rho_F\frac{D_F\mathbf{v}_F}{Dt} = \nabla_{\mathbf{x}}\cdot\sigma_F + \phi_F\rho_F\hat{\mathbf{T}}_F, \tag{32}$$

$$\begin{gathered}\phi_F\rho_F c_\beta\left(\tfrac{D_\beta\mathbf{v}_\beta}{Dt} - \tfrac{D_N\mathbf{v}_N}{Dt}\right) =\\ \nabla_{\mathbf{x}}\cdot\sigma_\beta - \tfrac{c_\beta}{c_N}\nabla_{\mathbf{x}}\cdot\sigma_N + \phi_F\rho_F c_\beta(\hat{\mathbf{T}}_\beta - \hat{\mathbf{T}}_N).\end{gathered} \tag{33}$$

By substituting Eqs. (22), (27), and (28) into Eqs. (32) and (33), and assuming that inertial contributions are negligible for the class of biological phenomena of interest, we obtain:

$$\begin{aligned}-\phi_F\rho_F\Lambda_F.\mathbf{v}_{FS}+\phi_F\rho_F\textstyle\sum_{\beta=1}^{N-1}\Lambda_{F\beta}.\mathbf{v}_{\beta F} &= \\ &\phi_F\nabla_{\mathbf{x}}p+\nabla_{\mathbf{x}}\cdot[\phi_F\rho_F\textstyle\sum_{\alpha=1}^{N}c_\alpha\mathbf{v}_{\alpha F}\otimes\mathbf{v}_{\alpha F}],\end{aligned} \tag{34}$$

$$\Lambda_\beta.\mathbf{v}_{FS}-\sum_{\gamma=1}^{N-1}\Lambda_{\beta\gamma}.\mathbf{v}_{\gamma F}=\nabla_{\mathbf{x}}Y_{\beta N}=\frac{\partial Y_{\beta N}}{\partial\rho_F}\nabla_{\mathbf{x}}\rho_F+\sum_{\gamma=1}^{N-1}\frac{\partial Y_{\beta N}}{\partial c_\gamma}\nabla_{\mathbf{x}}c_\gamma. \tag{35}$$

If diffusive velocities, $\mathbf{v}_{\alpha F}$, are sufficiently small, and the non-equilibrium part of the fluid phase Cauchy stress tensor can be disregarded, Eqs. (34) and (35) become a set of linear equations involving the unknowns $\mathbf{v}_{FS}$ and $\{\mathbf{v}_{\beta F}\}_{\beta=1}^{N-1}$. A simple solution to this set is obtained in the case in which, at the pore scale, all chemical substances are present in the interstitial water at a very low concentration. This assumption implies that, at the macroscale, the overall fluid phase mass density can be safely approximated by the constant mass density of water, i.e. $\rho_F\approx\rho_N$, and the fluid phase can be thus considered as incompressible (i.e., $D_F\rho_F/Dt=\partial_t\rho_F+\mathbf{v}_F\cdot\nabla_{\mathbf{x}}\rho_F=0$). Moreover, since in this paper the fluid phase is also assumed to be macroscopically inviscid, its mass density ρ_F can be replaced by the thermodynamic pressure p in the list of unknowns treated as independent constitutive variables. By introducing the diffusive current $\mathcal{J}_\beta=\phi_F\rho_F c_\beta\mathbf{v}_{\beta F}$, the formal solution to the set (34)-(35) can be written as

$$\mathbf{v}_{FS}=-\mathbf{K}_F.\nabla_{\mathbf{x}}p-\sum_{\beta=1}^{N-1}\mathbf{D}_{F\beta}.\nabla_{\mathbf{x}}c_\beta, \tag{36}$$

$$\mathcal{J}_\beta=\phi_F\rho_F c_\beta\mathbf{v}_{\beta F}=-\mathbf{K}_\beta.\nabla_{\mathbf{x}}p-\sum_{\gamma=1}^{N-1}\mathbf{D}_{\beta\gamma}.\nabla_{\mathbf{x}}c_\gamma. \tag{37}$$

Here, tensors $\mathbf{K}_F$, $\mathbf{K}_\beta$, and $\mathbf{D}_{F\beta}$, $\mathbf{D}_{\beta\gamma}$ are the *permeability*, and *diffusivity-dispersivity* tensors of the fluid phase and chemical substances, respectively. In particular, tensors $\mathbf{D}_{F\beta}$ and $\mathbf{D}_{\beta\gamma}$ are defined by

$$\mathbf{D}_{F\beta} = \textstyle\sum_{\gamma=1}^{N-1} \mathcal{D}_{F\gamma} \frac{\partial Y_{\gamma N}}{\partial c_\beta}, \quad \mathbf{D}_{\beta\gamma} = \textstyle\sum_{\delta=1}^{N-1} \mathcal{D}_{\beta\delta} \frac{\partial Y_{\delta N}}{\partial c_\gamma} \ , \tag{38}$$

where $\mathcal{D}_{F\gamma}$ and $\mathcal{D}_{\beta\delta}$ are material coefficients [8]. If, in the limit of very low concentration of chemical substances, tensors $\mathbf{D}_{F\beta}$ tend towards the null tensor, tensors $\mathbf{D}_{\beta\gamma}$ vanish when indices β and γ are different, and pressure effects on the diffusivity current $\mathcal{J}_\beta$ are negligible, we can write the "classic" expressions of Darcy's and Fick's laws, i.e.,

$$\mathbf{v}_{FS} = -\mathbf{K}_F.\nabla_{\mathbf{x}} p, \tag{39}$$

$$\mathcal{J}_\beta = -\mathbf{D}_\beta.\nabla_{\mathbf{x}} c_\beta. \tag{40}$$

Here, $\mathbf{D}_\beta$ replaces the tensors $\mathbf{D}_{\beta\gamma}$ featuring in Eq. (37). By virtue of Eqs. (39) and (40), the unknown fields reduce to volume fraction ϕ_S (or ϕ_F), pressure p, the $S-$motion χ_S, and the mass fractions $\{c_\beta\}_{\beta=1}^{N-1}$. These quantities are to be determined by solving the following set of field equations:

$$\frac{\partial(\phi_S\rho_S)}{\partial t} + \nabla_{\mathbf{x}} \cdot (\phi_S\rho_S\mathbf{v}_S) = \phi_S\rho_S(\hat{R}_S^{tr} + \hat{R}_S^{gr}) = \phi_S\rho_S\hat{R}_S, \tag{41}$$

$$\frac{\partial(\phi_F\rho_F)}{\partial t} + \nabla_{\mathbf{x}} \cdot (\phi_F\rho_F\mathbf{v}_F) = \phi_F\rho_F\hat{R}_F^{tr}, \tag{42}$$

$$\nabla_{\mathbf{x}} \cdot \sigma_S^{el} = \nabla_{\mathbf{x}} p - \phi_F\rho_F\hat{R}_F^{tr}\mathbf{K}_F.\nabla_{\mathbf{x}} p, \tag{43}$$

$$\frac{\partial(\phi_F\rho_F c_\beta)}{\partial t} + \nabla_{\mathbf{x}} \cdot (\phi_F\rho_F c_\beta\mathbf{v}_F) = \nabla_{\mathbf{x}} \cdot [\mathbf{D}_\beta\nabla_{\mathbf{x}} c_\beta] + \phi_F\rho_F c_\beta\hat{R}_\beta. \tag{44}$$

Equation (44) provides the macroscopic description of the transport processes experienced by the chemical substances in the pore space of a porous medium. Because of the presence of the advective current, $\phi_F\rho_F c_\beta\mathbf{v}_F$, the Fick-type diffusive current, $-\mathbf{D}_\beta\nabla_{\mathbf{x}} c_\beta$, and the reaction term, $\phi_F\rho_F c_\beta\hat{R}_\beta$, we refer to Eq. (44) as to an advection-diffusion-reaction equation.

4 Material form of the field equations

In order to bring the theory exposed so far into contact with the Continuum Physics treatment of growth, it is convenient to write the field equations (41)-(44) in material form. This is done by employing the formalism presented in [20]. In particular, since we aim at investigating how growth influences the transport coefficients featuring in the advection-diffusion-reaction equation of chemical substances, we put special emphasis on the material formulation of Eq. (44). In the literature, the study of the transport equation in material form can be found, for example, in [10][21][22].

In Mixture Theory, the material field Ψ_k $(k = \alpha, F, S)$ associated with a given physical quantity ψ_k, defined on the domain $\mathcal{B}_t \subset \mathbb{E}$ ($\mathbb{E} = \mathbb{R}^3$ being the three-dimensional Euclidean space) occupied by the mixture at time t, is determined by performing the Piola transformation of ψ_k with respect to the $S-$motion χ_S [20]. By virtue of the $S-$motion, for every material point $\mathbf{X} \in \mathcal{B}_R$, there exists a point $\mathbf{x} \in \mathcal{B}_t$ such that $\psi_k(t, \mathbf{x}) = \psi_k(t, \chi_S(t, \mathbf{X}))$. This identity implies that the gradient and substantial derivative of ψ_k with respect to the $n-$th mixture component $(n = \alpha, F, S)$ can be written as

$$\nabla_{\mathbf{x}}\psi_k(t,\mathbf{x}) = \mathbf{F}_S^{-T}(t,\mathbf{X}).\nabla_{\mathbf{X}}\psi_k(t,\mathbf{X}), \tag{45}$$

$$\begin{aligned}\frac{D_n\psi_k}{Dt}(t,\mathbf{x}) = \frac{D_S\psi_k}{Dt}(t,\mathbf{x}) + \mathbf{v}_{nS}(t,\mathbf{x}) \cdot \nabla_{\mathbf{x}}\psi_k(t,\mathbf{x}) = \\ \frac{\partial\psi_k}{\partial t}(t,\mathbf{X}) + \mathbf{V}_{nS}(t,\mathbf{X}) \cdot \nabla_{\mathbf{X}}\psi_k(t,\mathbf{X}),\end{aligned} \tag{46}$$

where $\mathbf{V}_{nS} = \mathbf{F}_S^{-1}.\mathbf{v}_{nS}$ is the material form of the relative velocity $\mathbf{v}_{nS} = \mathbf{v}_n - \mathbf{v}_S$.

By using Eqs. (45) and (46), accounting for the identity $\nabla_{\mathbf{x}} \cdot \mathbf{v}_S = J_S^{-1}\partial_t J_S$, and applying the Piola transformations to Eqs. (41)-(44), we can rewrite the field equations as

$$\frac{\partial(\rho_S\Phi_S)}{\partial t} = \rho_S\Phi_S\hat{R}_S, \tag{47}$$

$$\frac{\partial(\rho_F\Phi_F)}{\partial t} + \nabla_{\mathbf{X}} \cdot (\rho_F\Phi_F\mathbf{V}_{FS}) = \rho_F\Phi_F\hat{R}_F^{tr}, \tag{48}$$

$$\nabla_{\mathbf{X}} \cdot [\mathbf{P}_S^{el} - J_S p \mathbf{F}_S^{-T}] = -\rho_F \Phi_F \hat{R}_F^{tr} (\mathbf{F}_S^{-1} \mathbf{K}_F \mathbf{F}_S^{-T}).\nabla_{\mathbf{X}} p, \tag{49}$$

$$\frac{\partial C_\beta}{\partial t} + \nabla_{\mathbf{X}} \cdot (C_\beta \mathbf{V}_{FS}) = \nabla_{\mathbf{X}} \cdot [\Delta_\beta . \nabla_{\mathbf{X}} C_\beta - C_\beta \mathcal{V}_\beta] + C_\beta \hat{R}_\beta, \tag{50}$$

where $\Phi_S = J_S \phi_S$ and $\Phi_F = J_S \phi_F$ are the Piola transforms of the volume fractions ϕ_S and ϕ_F, respectively, $\mathbf{V}_{FS} = \mathbf{F}_S^{-1}.\mathbf{v}_{FS}$ is the material form of Darcy's velocity $\mathbf{v}_{FS}$, $\mathbf{P}_S^{el}$ is the first Piola-Kirchhoff stress tensor, $\mathbf{F}_S^{-1} \mathbf{K}_F \mathbf{F}_S^{-T}$ is the material form of the permeability tensor, $C_\beta = \rho_F \Phi_F c_\beta$ is the macroscopic concentration of the $\beta-$th chemical substance in the reference configuration $\mathcal{B}_R$, Δ_β is the material form of the *diffusivity tensor*, and $\mathcal{V}_\beta$ is an additional drift term due to the material inhomogeneity of the fluid phase volume fraction. These two quantities are said to be the *material transport coefficients*, and their expressions are given by

$$\Delta_\beta = J_S \mathbf{F}_S^{-1} \frac{\mathbf{D}_\beta}{\rho_F \Phi_F} \mathbf{F}_S^{-T}, \tag{51}$$

$$\mathcal{V}_\beta = \Delta_\beta . \nabla_{\mathbf{X}} \ln(\Phi_F). \tag{52}$$

We remark that the term $\mathcal{V}_\beta$ vanishes identically if, and only if, the Piola transform of the fluid phase volume fraction, Φ_F, does not depend on material points $\boldsymbol{X}$. Since $\nabla_{\mathbf{X}} \Phi_F = \nabla_{\mathbf{X}} J_S - \nabla_{\mathbf{X}} \Phi_S$, we conclude that, when growth is considered, this can be true only in the following two special cases: *i*) neither volume fractions ϕ_F and ϕ_S depend on material points, nor does the determinant of $\mathbf{F}_S$, J_S; *ii*) the "packing" of material points, ascribable to $\nabla_{\mathbf{X}} J_S$ in entirely compensated for by the spatial variation of Φ_S. When these conditions are not respected, the term $\mathcal{V}_\beta$ reflects the rearrangement of material inhomogeneities developed by growth, and represents the spatial variation of the fluid phase volume fraction due to the mass transfer and growth between the fluid and the solid phase.

Equations (47)-(50) can be recast in a form in which only the unknown fields are put in evidence, i.e., Φ_S, p, $\mathbf{F}_S$, and $\{C_\beta\}_{\beta=1}^{N-1}$. For this purpose, by assuming that the intrinsic mass densities ρ_S and ρ_F are constants, dividing Eq. (47) and Eq. (48) by ρ_S and ρ_F, respectively, and summing up the resulting expressions, we may write

$$\frac{\partial \Phi_S}{\partial t} = \Phi_S \hat{R}_S, \tag{53}$$

$$J_S tr(\mathbf{L}_S) - \nabla_{\mathbf{X}} \cdot [(J_S - \Phi_S)(\mathbf{F}_S^{-1}\mathbf{K}_F \mathbf{F}_S^{-T}).\nabla_{\mathbf{X}} p] = \Phi_S \hat{R}_S + (J_S - \Phi_S)\hat{R}_F^{tr}, \tag{54}$$

$$\nabla_{\mathbf{X}} \cdot [\mathbf{P}_S^{el} - J_S p \mathbf{F}_S^{-T}] = -\rho_F (J_S - \Phi_S)\hat{R}_F^{tr}(\mathbf{F}_S^{-1}\mathbf{K}_F \mathbf{F}_S^{-T}).\nabla_{\mathbf{X}} p, \tag{55}$$

$$\frac{\partial C_\beta}{\partial t} = \nabla_{\mathbf{X}} \cdot [\Delta_\beta . \nabla_{\mathbf{X}} C_\beta - C_\beta \mathcal{V}_\beta + C_\beta (\mathbf{F}_S^{-1}\mathbf{K}_F \mathbf{F}_S^{-T}).\nabla_{\mathbf{X}} p] + C_\beta \hat{R}_\beta. \tag{56}$$

In order to close Eqs. (53)-(56), it is necessary to provide self-consistent expressions for the sources $\{\hat{R}_\beta\}_{\beta=1}^{N-1}$, $\hat{R}_F^{tr}$, and $\hat{R}_S$. Since $\hat{R}_F^{tr}$ is bound to satisfy the constraint

$$\hat{R}_F^{tr} = \sum\nolimits_{\alpha=1}^{N} c_\alpha \hat{R}_\alpha, \tag{57}$$

we can conveniently assign the sources $\{\hat{R}_\alpha\}_{\alpha=1}^{N}$ on the basis of phenomenological laws that involve the unknown variables mentioned above [8]. On the other hand, it is possible to prove that the source $\hat{R}_S$ has to fulfil a relation based on the kinematics of growth. This is done by introducing the multiplicative decomposition of the deformation gradient tensor [1][4][11][20]

$$\mathbf{F}_S = \mathbf{F}_S^{el}\mathbf{G}_S, \tag{58}$$

where $\mathbf{F}_S^{el}$ is a purely elastic deformation tensor, and $\mathbf{G}_S$ is said to be the *growth tensor* because it describes the anelastic deformation induced by growth through the production of material inhomogeneities and continuous rearrangement of material symmetries [11]. The growth tensor is relative to an elastically released configuration $\mathcal{B}_G$, which is obtained by applying the linear map $\mathbf{G}_S$ to the tangent space $T_{\mathbf{X}}\mathcal{B}_R$ of $\mathcal{B}_R$, for any $\mathbf{X} \in \mathcal{B}_R$. It can be shown that, in the case of density preserving growth [6], Eq. (58) implies the kinematic relation

$$\hat{R}_S = tr(\mathbf{L}_S^G), \tag{59}$$

where $\mathbf{L}_S^G = (\partial_t \mathbf{G}_S)\mathbf{G}_S^{-1}$ is the *growth velocity gradient.* Since the growth tensor, $\mathbf{G}_S$, has to be regarded as an independent constitutive variable, it must be assigned by prescribing an appropriate growth law consistent with the Clausius-Duhem inequality (cfr. Ref [6] for details), i.e.,

$$\mathbf{L}_S^G = \mathcal{L}_S^G(t, \mathbf{X}, C_1, ..., C_{N-1}, \Phi_S, p, \mathbf{F}_S^{el}). \tag{60}$$

In Eq. (60), tensor $\mathbf{F}_S^{el}$ can alternatively be replaced by a suitable stress measure $\mathcal{S}_S$ (for example, $\mathcal{S}_S$ can be identified with the second Piola-Kirchhoff stress tensor [21][22], or the Eshelby stress tensor [11]). In some cases [21][22], Eq. (60) can be also written as

$$\frac{\partial \mathbf{G}_S}{\partial t} = \mathcal{F}_S(t, \mathbf{X}, C_1, ..., C_{N-1}, \Phi_S, p, \mathcal{S}_S, \mathbf{G}_S). \tag{61}$$

We remark that, by virtue of Eq. (59), the functional $\mathcal{F}_S$ has to account for both the mass uptake due to growth and the mass exchange between the solid and the fluid phase.

The elasto-growth decomposition enables us to reformulate the constitutive law for $\mathbf{P}_S^{el}$ in terms of $\mathbf{F}_S^{el} = \mathbf{F}_S \mathbf{G}_S^{-1}$. Indeed, by expressing the solid phase Helmholtz free energy density as $A_S(\mathbf{F}_S, \Theta_0, \mathbf{X}) = A_S(\mathbf{F}_S \mathbf{G}_S^{-1}, \Theta_0)$ [11] (i.e., the explicit dependence of A_S on $\mathbf{X}$ is accounted for by the growth tensor, $\mathbf{G}_S$), Eq. (24) can be rewritten as

$$\mathbf{P}_S^{el} = J_S \phi_S \rho_S \frac{\partial A_S}{\partial \mathbf{F}_S} = J_S \phi_S \rho_S \frac{\partial A_S}{\partial \mathbf{F}_S^{el}} \mathbf{G}_S^{-T}. \tag{62}$$

Substituting this constitutive relation into Eq. (55) implies that the tensor fields $\mathbf{F}_S$ and $\mathbf{G}_S$, although being independent, are coupled with each other. This means that, since different growth laws (61) lead to different deformation fields inside the tissue, it is possible to construct a functional relation between $\mathbf{F}_S$ and $\mathbf{G}_S$ based on the fact that the solution to Eq. (55) depends on the solution to Eq. (61) and thus on the initial condition applied to it.

Equations (53)-(60), supplemented with suitable initial and boundary conditions, constitute a set of coupled nonlinear equations whose solution describes the macroscopic mechano-chemical behaviour of a tissue in the presence of growth. To the best of our knowledge, determining a solution to this problem is not an easy task. However, since the purpose of this paper is to speculate on the possible influence of growth on transport processes, we find it interesting to seek for a formal solution to Eq. (56), and discuss the interaction with growth by substituting this result into the set of equations mentioned above. Apart from particular cases of exactly solvable nonlinear transport equations, our procedure is possible if Eq. (56) is assumed to be linear (i.e., the effective diffusivity tensor, Δ_β, and the mass exchange rate, $\hat{R}_\beta$, are independent on concentration of chemical substances), and its formal solution is found by employing the Green's function formalism associated to the boundary value problem

$$\begin{cases} \dfrac{\partial C}{\partial t} = \nabla_{\mathbf{X}} \cdot [\Delta . \nabla_{\mathbf{X}} C - C\mathcal{V} + C(\mathbf{F}_S^{-1}\mathbf{K}_F\mathbf{F}_S^{-T}).\nabla_{\mathbf{X}} p] + C\hat{R}, \\ \\ C(0, \mathbf{X}) = \mathcal{C}(\mathbf{X}), \quad \forall \mathbf{X} \in \mathcal{B}_R, \\ \\ \alpha C(t, \mathbf{X}_b) + \gamma[\Delta(t, \mathbf{X}_b).\nabla_{\mathbf{X}} C(t, \mathbf{X}_b)] \cdot \mathbf{N}(t, \mathbf{X}_b) = f(t, \mathbf{X}_b), \quad \forall \mathbf{X}_b \in \partial\mathcal{B}_R \end{cases} . \tag{63}$$

Here, the index β has been dropt because, in the following, we shall assume that only one species of chemical substances is present in water.

5 Influence of growth on transport processes

An example of biological interest that may be suitable for our purposes is the transport of chemical agents in a solid tumour at the avascular growth stage. During this stage, the tumour cells are fed by nutrients diffusing throughout the growing tissue, while mitosis is inhibited or promoted depending on whether the concentration of a chemical agent, called *growth inhibitory factor* (GIF), is greater or smaller than a given threshold value, respectively [23][24]. The transport processes undergone by the GIF and nutrients are usually studied by solving a boundary value problem, regarding the tumour as a spheroid, the cellular phase as an isotropic material, and assuming spherical growth [21][22][25][26]. In some cases, the solution of the advection-diffusion-reaction equation is found in the stationary limit.

Here, we assume that growth is anisotropic, and characterized by a time-scale, t_G, largely separated from the time-scales t_{adv}, t_D, and t_R associated with advection, diffusion, and reaction, respectively. Moreover, by referring to diffusion as to the fastest process that is accounted for in our study, we express the separation of scales by introducing a positive smallness parameter ε such that $t_D/t_G = \varepsilon \ll 1$. We motivate this assertion by saying that chemical substances diffusing throughout rapidly growing tumours attain steady state on a time-scale much faster than the time-scale associated with growth [22]-[24]. Indeed, according to some data reported in the literature (cfr., for example, [24]), we can assume that the radius of a tumour spheroid is of order $L_{sph} \sim 10^{-1} mm$, the characteristic value of diffusivity is $D_c \sim 10^{-5} mm^2 s^{-1}$, the time-scales associated with growth and diffusion are $t_G \sim 10^6 s$, and $t_D \sim 10^3 s$, respectively, and the smallness parameter ε is thus $\varepsilon \sim 10^{-3}$. Under these hypotheses, we propose a picture in which growth is able to interact with the evolution of the chemical substances (i.e., the GIF or the nutrients) by varying very slowly in time the transport properties $\mathbf{V}_{FS}$, Δ, and $\mathcal{V}$ featuring in Eq. (56).

A process in which the parameters driving the evolution of a given physical quantity change very slowly in time is sometimes said to be an *adiabatic process* [27], whereas the set of approximations involved to solve the equations governing the process constitutes the *adiabatic approximation*. Although this approximation may fail in the case of other biological tissues, e.g., articular cartilage (in this case, the time-scale of diffusion processes is not largely separated from the time-scale associated with growth [6]), we believe that it can give physical insight to study the problem stated in Eqs. (53)-(60).

In order to apply the adiabatic approximation, we have to define all the time-scales involved in Eqs. (53)-(60), and relate them to the time-scales t_D, t_{adv}, t_R, and t_G. We identify t_G with the time-scale associated with the production of material inhomogeneities. Thus, by accounting for the definition of the growth velocity gradient, $\mathbf{L}_S^G$, we rewrite Eq. (59) as

$$\hat{R}_S = \frac{1}{t_G} \bar{R}_S = tr(\mathbf{L}_S^G), \tag{64}$$

where $\bar{R}_S$ represents the nondimensional overall source of mass for the solid phase. Substitution of Eq. (64) into Eqs. (53) and (54) implies that t_G also coincides with the time-scale associated with deformation, and the evolution of Φ_S, respectively. Moreover, by referring to $t_{R_F^{tr}}$ as to the time-scale characterizing the mass transfer rate $\hat{R}_F^{tr}$, we assume that it is of the same order of magnitude of t_G (i.e., $t_{R_F^{tr}} \sim t_G$). This implies that $\hat{R}_F^{tr}$ rescales as

$$\hat{R}_F^{tr} = \frac{1}{t_{R_F^{tr}}} \bar{R}_F^{tr} = \frac{1}{t_G} \bar{R}_F^{tr}. \tag{65}$$

Finally, we identify t_R with the time-scale characterizing the production rate of chemical substances, $\hat{R}$, and define t_D and t_{adv} by introducing the notation

$$\begin{aligned} t_D &= \frac{L^2}{D_c}, \\ t_{adv} &= \frac{L}{W_c} = \frac{L^2}{K_c p_c} = \frac{t_D}{Pe}, \end{aligned} \tag{66}$$

where L is a characteristic length of the tissue (e.g., the radius of the tumour spheroid, L_{sph}), W_c, K_c, and p_c are the characteristic values of Darcy velocity, $\mathbf{V}_{FS}$, permeability, $\mathbf{K}_F$, and pressure, p, respectively, and $Pe = W_c L/D_c$ is Péclet number.

In the following, we perform a perturbative analysis of the field equations (53)-(60). For this purpose, we introduce the nondimensional variables $\vartheta = t/t_D$, $\tau = t/t_G$, and $\mathbf{Z} = \mathbf{X}/L$, and express a given physical quantity Ψ as a two-scale function [28], i.e.,

$$\Psi(t, \mathbf{X}) = \Psi_c \bar{\Psi}(\vartheta, \tau, \mathbf{Z}), \tag{67}$$

where Ψ_c and $\bar{\Psi}$ represent the characteristic and nondimensional part of Ψ, respectively [29]. Equation (67) means that, even though ϑ and τ are related by the identity $\tau = \varepsilon\vartheta$, they are regarded as formally independent because they measure the "rapidly" and "slowly" varying part of Ψ, respectively [28]. The nondimensional derivatives of Ψ are given by

$$\begin{aligned} \nabla_{\mathbf{X}} \Psi(t, \mathbf{X}) &= \tfrac{\Psi_c}{L} \nabla_{\mathbf{Z}} \bar{\Psi}(\vartheta, \tau, \mathbf{Z}), \\ \frac{\partial \Psi}{\partial t}(t, \mathbf{X}) &= \frac{\Psi_c}{t_G} \left[\frac{\partial \bar{\Psi}}{\partial \tau}(\vartheta, \tau, \mathbf{Z}) + \frac{1}{\varepsilon} \frac{\partial \bar{\Psi}}{\partial \vartheta}(\vartheta, \tau, \mathbf{Z}) \right]. \end{aligned} \tag{68}$$

By virtue of Eqs. (66)-(68), the nondimensional form of the field equations (53)-(56) reads

$$\frac{\partial \Phi_S}{\partial \tau} + \frac{1}{\varepsilon} \frac{\partial \Phi_S}{\partial \vartheta} = \Phi_S \bar{R}_S, \tag{69}$$

$$J_S tr(\bar{\mathbf{L}}_S) - \frac{1}{\varepsilon} Pe \nabla_{\mathbf{Z}} \cdot [(J_S - \Phi_S)(\mathbf{F}_S^{-1} \bar{\mathbf{K}}_F \mathbf{F}_S^{-T}).\nabla_{\mathbf{Z}} \bar{p}] = \Phi_S \bar{R}_S + (J_S - \Phi_S) \bar{R}_F^{tr}, \tag{70}$$

$$\frac{1}{\varepsilon}\nabla_{\mathbf{Z}}\cdot\left[\bar{\mathbf{P}}_S^{el} - \frac{p_c}{\rho_S A_{Sc}} J_S \bar{p}\mathbf{F}_S^{-T}\right] = -\frac{\rho_F W_c^2}{\rho_S A_{Sc}}\frac{1}{Pe}(J_S-\Phi_S)\bar{R}_F^{tr}(\mathbf{F}_S^{-1}\bar{\mathbf{K}}_F\mathbf{F}_S^{-T}).\nabla_{\mathbf{Z}}\bar{p}, \tag{71}$$

$$\frac{\partial C}{\partial \tau} + \frac{1}{\varepsilon}\frac{\partial C}{\partial \vartheta} = \frac{1}{\varepsilon}\nabla_{\mathbf{Z}}\cdot\left[\bar{\Delta}.\nabla_{\mathbf{Z}}C - C\bar{\mathcal{V}} + PeC(\mathbf{F}_S^{-1}\bar{\mathbf{K}}_F\mathbf{F}_S^{-T}).\nabla_{\mathbf{Z}}\bar{p}\right] + \frac{1}{\varepsilon}\frac{t_D}{t_R}C\bar{R}. \tag{72}$$

The perturbative analysis is carried out by expanding the generic nondimensional field $\bar{\Psi}$ in asymptotic series, i.e.,

$$\bar{\Psi}(\vartheta, \tau, \mathbf{Z}) = \sum_{k=0}^{\infty} \varepsilon^k \bar{\Psi}_{(k)}(\vartheta, \tau, \mathbf{Z}). \tag{73}$$

The expansion (73) has to be used both for the independent unknown fields Φ_S, p, $\mathbf{F}_S$, and C, and the quantities $\bar{R}_S$, $\bar{\mathbf{P}}_S^{el}$, $\bar{\Delta}$, $\bar{\mathcal{V}}$, and $\bar{R}$. The asymptotic series are assumed to exist and converge to their asymptotic solutions in the limit $\varepsilon \ll 1$. By inserting Eq. (73) into Eqs. (69)-(72), and regrouping the terms of the same power of ε, we obtain a set of equations which have to be satisfied asymptotically for any infinitely small ε. Since the coefficients of each power of ε are independent of the parameter itself, each coefficient has to be identically zero in order to satisfy the equation for any arbitrary small ε. By arresting the expansion (73) up to the first order in ε, Eqs. (69)-(72) generate three sets of equations found by equating the coefficients of ε^{-1}, ε^0, and ε^1, respectively. The first set involves only the zeroth-order terms of the fields expanded according to Eq. (73), while the second and the third set contain both the zeroth- and the first-order term of the same physical quantities (terms of order higher than the zeroth are sometimes referred to as *correctors*). The fields, obtained by solving the first set of equations, must be inserted into the second set in order to determine the general form of the first-order correctors. Finally, the third set provides the consistency conditions that complete the determination of the first-order correctors. By following this procedure, it is possible to describe how the effect of growth is “felt” by each physical quantity, for each order of the asymptotic expansion (73). For example, it can be proven [12] that the zeroth-order material volume fractions, $\Phi_{S(0)}$ and $\Phi_{F(0)}$, are only functions of the slowly varying time coordinate, τ, i.e.,

$$\frac{\partial \Phi_{S(0)}}{\partial \vartheta} = 0. \tag{74}$$

This result means that the time variation of $\Phi_{S(0)}$ is significant only if observed over a time-scale comparable with the time-scale dictated by growth, t_G.

Here, for the sake of conciseness, we focus only on the zeroth-order approximation of the boundary value problem (63). Moreover, by assuming negligible drift velocity $\mathbf{V}_{FS}$ (this is equivalent to assume $Pe \sim \varepsilon$ in Eq. (72)), we obtain

$$\begin{cases} \frac{\partial C_{(0)}}{\partial \vartheta} = \nabla_{\mathbf{Z}} \cdot [\bar{\Delta}_{(0)}.\nabla_{\mathbf{Z}} C_{(0)} - C_{(0)} \bar{\mathcal{V}}_{(0)}] + \frac{t_D}{t_R} C_{(0)} \bar{R}_{(0)}, \\ C_{(0)}(0,0,\mathbf{Z}) = \mathcal{C}(\mathbf{Z}), \quad \tau = \varepsilon\vartheta = 0, \forall \mathbf{Z} \in \mathcal{B}_R \\ \bar{\alpha} C_{(0)} + \xi \bar{\gamma} [\bar{\Delta}_{(0)}.\nabla_{\mathbf{Z}} C_{(0)}] \cdot \mathbf{N} = \kappa \bar{f}, \quad \forall \mathbf{Z}_b \in \partial \mathcal{B}_R \ , \end{cases} \tag{75}$$

where we introduced the notation

$$\xi = \frac{\gamma_c D_c}{\alpha_c L} = \frac{\gamma_c L}{\alpha_c t_D}, \quad \kappa = \frac{f_c}{\alpha_c} \ , \tag{76}$$

the ratio t_D/t_R is treated as a parameter, and the zeroth-order transport coefficients $\bar{\Delta}_{(0)}$ and $\bar{\mathcal{V}}_{(0)}$ are given by

$$\begin{aligned} \Delta_{(0)} &= J_{S(0)} \mathbf{F}^{-1}_{S(0)} \tfrac{\mathbf{D}_\beta}{\rho_F \Phi_{F(0)}} \mathbf{F}^{-T}_{S(0)}, \\ \mathcal{V}_{(0)} &= \Delta_{(0)}.\nabla_{\mathbf{Z}} \ln(\Phi_{F(0)}). \end{aligned} \tag{77}$$

By virtue of Eq. (74), it can be proven that $\bar{\Delta}_{(0)}$, $\bar{\mathcal{V}}_{(0)}$, and $\bar{R}_{(0)}$ depend only on space coordinates $\mathbf{Z}$, and the slowly varying time variable τ, but are independent on ϑ. This conclusion allows for studying Eq. (75) as an initial boundary value problem with separable variables.

Since we are interested in the behaviour of concentration $C_{(0)}$ for sufficiently long time, we have to look for the asymptotic solution to Eq. (75) (i.e., the solution obtained in the limit $\vartheta \sim \varepsilon^{-1}$). This solution is expected to be independent on the rapidly varying time coordinate, ϑ. Rather, it can be identified with the function of τ and $\mathbf{Z}$ that satisfies the boundary value problem

$$\left\{\begin{array}{l} \nabla_{\mathbf{Z}} \cdot [\bar{\Delta}_{(0)}.\nabla_{\mathbf{Z}} C_{(0)} - C_{(0)}\bar{\mathcal{V}}_{(0)}] + \frac{t_D}{t_R} C_{(0)}\bar{R}_{(0)} = 0, \\ \\ \bar{\alpha} C_{(0)} + \xi\bar{\gamma}[\bar{\Delta}_{(0)}.\nabla_{\mathbf{Z}} C_{(0)}] \cdot \mathbf{N} = \kappa \bar{f}, \quad \forall \mathbf{Z}_b \in \partial\mathcal{B}_R \ . \end{array}\right. \tag{78}$$

In order to rewrite Eq. (78) in a more concise form, and account for the term $\bar{\mathcal{V}}_{(0)}$ ($\bar{\mathcal{V}}_{(0)}$ represents the zeroth-order drift contribution due to the material inhomogeneity of the field $\Phi_{F(0)}$), we apply the commonly used transformation

$$C_{(0)}(\tau, \mathbf{Z}) = C^*_{(0)}(\tau, \mathbf{Z}) e^{\Lambda(\tau,\mathbf{Z})}, \tag{79}$$

with calculated value $\Lambda(\tau, \mathbf{Z}) = \frac{1}{2}\ln(\Phi_F(0))$. By substituting Eq. (79) into Eq. (78), we obtain

$$\left\{\begin{array}{l} \nabla_{\mathbf{Z}} \cdot [\bar{\Delta}_{(0)}.\nabla_{\mathbf{Z}} C^*_{(0)}] + \dfrac{t_D}{t_R} C^*_{(0)}\bar{R}^*_{(0)} = 0, \\ \\ \{\bar{\alpha} + \xi\bar{\gamma}[\mathbf{N} \cdot \bar{\Delta}_{(0)}.\nabla_{\mathbf{Z}}\Lambda]\} C^*_{(0)} + \xi\bar{\gamma}[\mathbf{N} \cdot \bar{\Delta}_{(0)}.\nabla_{\mathbf{Z}} C^*_{(0)}] = \kappa \bar{f}_e^{-\Lambda}, \quad \forall \mathbf{Z}_b \in \partial\mathcal{B}_R \ , \end{array}\right. \tag{80}$$

where $\bar{R}^*_{(0)} = \bar{R}_{(0)} - \frac{1}{2}\nabla_{\mathbf{Z}} \cdot \bar{\mathcal{V}}_{(0)} - \frac{1}{4}\bar{\mathcal{V}}_{(0)} \cdot \bar{\Delta}^{-1}_{(0)}.\bar{\mathcal{V}}_{(0)}$.

By denoting by $\mathcal{G}^*_{(0)}(\tau, \mathbf{Z}, \mathbf{Z}')$ the Green's function associated with Eq. (80), the formal solution can be written as

$$\begin{aligned} C_{(0)}(\tau, \mathbf{Z}) = {} & \int_{\partial\mathcal{B}_R} \frac{e^{\Lambda(\tau,\mathbf{Z})}\mathcal{G}^*_{(0)}(\tau,\mathbf{Z},\mathbf{Z}_b)e^{-\Lambda(\tau,\mathbf{Z}_b)}}{1+\{\bar{\alpha}+\xi\bar{\gamma}[\mathbf{N}(\tau,\mathbf{Z}_b)\cdot\bar{\Delta}_{(0)}(\tau,\mathbf{Z}_b).\nabla_{\mathbf{Z}_b}\Lambda(\tau,\mathbf{Z}_b)]\}} \kappa\bar{f}(\tau, \mathbf{Z}_b) dA_b \\ & - \int_{\partial\mathcal{B}_R} \frac{e^{\Lambda(\tau,\mathbf{Z})}[\bar{\Delta}_{(0)}(\tau,\mathbf{Z}_b).\nabla_{\mathbf{Z}_b}\mathcal{G}^*_{(0)}(\tau,\mathbf{Z},\mathbf{Z}_b)\cdot\mathbf{N}(\tau,\mathbf{Z}_b)]e^{-\Lambda(\tau,\mathbf{Z}_b)}}{1+\{\bar{\alpha}+\xi\bar{\gamma}[\mathbf{N}(\tau,\mathbf{Z}_b)\cdot\bar{\Delta}_{(0)}(\tau,\mathbf{Z}_b).\nabla_{\mathbf{Z}_b}\Lambda(\tau,\mathbf{Z}_b)]\}} \kappa\bar{f}(\tau, \mathbf{Z}_b) dA_b, \end{aligned} \tag{81}$$

where $\mathbf{Z}_b \in \partial\mathcal{B}_R$, and dA_b denotes the surface measure on $\partial\mathcal{B}_R$.

An analogous procedure can be followed to determine the first-order concentration $C_{(1)}(\tau, \mathbf{Z})$. In this case, the differential equation in the corresponding boundary value problem contains terms depending explicitly on $C_{(0)}(\tau, \mathbf{Z})$ and its space and time derivatives. Since these terms are all defined by means of Eq. (81), they can be regarded as a source. Thus, the differential equation determining $C_{(1)}(\tau, \mathbf{Z})$ has to be treated as inhomogeneous.

Since the transport coefficients $\bar{\Delta}_{(0)}$ and $\bar{\mathcal{V}}_{(0)}$ are related to $\mathbf{G}_S$ through $\mathbf{F}_S$, and the Green's function $\mathcal{G}^*_{(0)}(\tau, \mathbf{Z}, \mathbf{Z}')$ depends on $\bar{\Delta}_{(0)}$ and $\bar{\mathcal{V}}_{(0)}$, we can conclude that $\mathcal{G}^{*}_{(0)}(\tau, \mathbf{Z}, \mathbf{Z}')$ is influenced by the growth tensor, $\mathbf{G}_S$. If we assume that growth is anisotropic, we can write $\mathbf{G}_S$ as a sum of a spherical and a deviatoric part, i.e., $(\mathbf{G}_S)^{\alpha}_{A} = g\delta^{\alpha}_{A} + (\mathbf{G}^{D}_{S})^{\alpha}_{A}$ (here, the Greek index α refers to the coordinates in the intermediate configuration $\mathcal{B}_G$), and we can perform a formal Taylor expansion of the Green's function around the spherical tensor $g\delta^{\alpha}_{A}$, so that $\mathcal{G}^{*}_{(0)}(\tau, \mathbf{Z}, \mathbf{Z}')$ can be split as

$$\mathcal{G}^{*}_{(0)}(\tau, \mathbf{Z}, \mathbf{Z}') = \mathcal{G}^{*sph}_{(0)}(\tau, \mathbf{Z}, \mathbf{Z}') + \mathcal{G}^{*dev}_{(0)}(\tau, \mathbf{Z}, \mathbf{Z}'), \tag{82}$$

where $\mathcal{G}^{*sph}_{(0)}(\tau, \mathbf{Z}, \mathbf{Z}')$ refers to the Green's function evaluated in the case of purely spherical growth, while $\mathcal{G}^{*dev}_{(0)}(\tau, \mathbf{Z}, \mathbf{Z}')$ accounts for the deviatoric part of $\mathbf{G}_S$. Analogously, by expanding the effective diffusivity tensor, $\bar{\Delta}_{(0)}$, around $g\delta^{\alpha}_{A}$, we find

$$\bar{\Delta}_{(0)}(\tau, \mathbf{Z}) = \bar{\Delta}^{sph}_{(0)}(\tau, \mathbf{Z}) + \bar{\Delta}^{dev}_{(0)}(\tau, \mathbf{Z}). \tag{83}$$

By substituting Eqs. (82) and (83) into Eq. (81), and restricting for the sake of conciseness to the case $\bar{\gamma} = 0$, we can write the concentration $C_{(0)}(\tau, \mathbf{Z})$ as

$$C_{(0)}(\tau, \mathbf{Z}) = C^{sph}_{(0)}(\tau, \mathbf{Z}) + C^{dev}_{(0)}(\tau, \mathbf{Z}), \tag{84}$$

where the terms $C^{sph}_{(0)}(\tau, \mathbf{Z})$ and $C^{dev}_{(0)}(\tau, \mathbf{Z})$ are defined by the formulae

$$\begin{aligned} C^{sph}_{(0)}(\tau, \mathbf{Z}) = {} & \int_{\partial\mathcal{B}_R} \tfrac{e^{\Lambda(\tau,\mathbf{Z})}\mathcal{G}^{*sph}_{(0)}(\tau,\mathbf{Z},\mathbf{Z}_b)e^{-\Lambda(\tau,\mathbf{Z}_b)}}{1+\bar{\alpha}} \kappa\bar{f}(\tau, \mathbf{Z}_b)dA_b \\ & - \int_{\partial\mathcal{B}_R} \tfrac{e^{\Lambda(\tau,\mathbf{Z})}[\bar{\Delta}^{sph}_{(0)}(\tau,\mathbf{Z}_b).\nabla_{\mathbf{Z}_b}\mathcal{G}^{*sph}_{(0)}(\tau,\mathbf{Z},\mathbf{Z}_b)\cdot\mathbf{N}(\tau,\mathbf{Z}_b)]e^{-\Lambda(\tau,\mathbf{Z}_b)}}{1+\bar{\alpha}} \kappa\bar{f}(\tau, \mathbf{Z}_b)dA_b, \end{aligned} \tag{85}$$

$$\begin{aligned} C^{dev}_{(0)}(\tau, \mathbf{Z}) = {} & \int_{\partial\mathcal{B}_R} \tfrac{e^{\Lambda(\tau,\mathbf{Z})}\mathcal{G}^{*dev}_{(0)}(\tau,\mathbf{Z},\mathbf{Z}_b)e^{-\Lambda(\tau,\mathbf{Z}_b)}}{1+\bar{\alpha}} \kappa\bar{f}(\tau, \mathbf{Z}_b)dA_b \\ & - \int_{\partial\mathcal{B}_R} \tfrac{e^{\Lambda(\tau,\mathbf{Z})}[\bar{\Delta}^{sph}_{(0)}(\tau,\mathbf{Z}_b).\nabla_{\mathbf{Z}_b}\mathcal{G}^{*dev}_{(0)}(\tau,\mathbf{Z},\mathbf{Z}_b)\cdot\mathbf{N}(\tau,\mathbf{Z}_b)]e^{-\Lambda(\tau,\mathbf{Z}_b)}}{1+\bar{\alpha}} \kappa\bar{f}(\tau, \mathbf{Z}_b)dA_b \\ & - \int_{\partial\mathcal{B}_R} \tfrac{e^{\Lambda(\tau,\mathbf{Z})}[\bar{\Delta}^{dev}_{(0)}(\tau,\mathbf{Z}_b).\nabla_{\mathbf{Z}_b}\mathcal{G}^{*sph}_{(0)}(\tau,\mathbf{Z},\mathbf{Z}_b)\cdot\mathbf{N}(\tau,\mathbf{Z}_b)]e^{-\Lambda(\tau,\mathbf{Z}_b)}}{1+\bar{\alpha}} \kappa\bar{f}(\tau, \mathbf{Z}_b)dA_b \\ & - \int_{\partial\mathcal{B}_R} \tfrac{e^{\Lambda(\tau,\mathbf{Z})}[\bar{\Delta}^{dev}_{(0)}(\tau,\mathbf{Z}_b).\nabla_{\mathbf{Z}_b}\mathcal{G}^{*dev}_{(0)}(\tau,\mathbf{Z},\mathbf{Z}_b)\cdot\mathbf{N}(\tau,\mathbf{Z}_b)]e^{-\Lambda(\tau,\mathbf{Z}_b)}}{1+\bar{\alpha}} \kappa\bar{f}(\tau, \mathbf{Z}_b)dA_b. \end{aligned} \tag{86}$$

6 Summary and discussion

We expressed the macroscopic transport equation (44) in material form (cfr. Eq. (50) or (56)), and showed how material transport properties are influenced by the growth tensor. Under the hypothesis of largely separated time-scales, we studied the transport of a given chemical substance (e.g., GIF or nutrients) in a growing tissue as a process in which the mechanical state and material symmetries vary *adiabatically* in time. This approximation enabled us to perform an asymptotic analysis of the boundary value problem (63). In particular, we determined the zeroth-order formal solution of the transport equation in terms of its associated Green's function, and we showed how the concentration can be "modulated" by the time evolution of the growth tensor (cfr. Eq. (84)). Equation (84) implies that, for a given growth tensor, $\mathbf{G}_S$, the concentration of a chemical substance, $C(t, \mathbf{X})$, can be split into the sum of the concentration computed as if the growth tensor were spherical, i.e., $C^{sph}(t, \mathbf{X})$, and the concentration due to the deviatoric part of the growth tensor, i.e., $C^{dev}(t, \mathbf{X})$. Since the growth tensor changes in time, and yields a continuous variation of the transport coefficients, the term $C^{dev}(t, \mathbf{X})$ can be interpreted as a modulation of the concentration $C^{sph}(t, \mathbf{X})$ due to the continuous rearrangement of the transport coefficients induced by anisotropic growth. The assumption of anisotropic growth is made in order to account for some effects (probably ascribable to genetic information, chemical interactions, etc.) that may establish preferential directions in the mechanisms that govern the evolution of the tissue. From the mathematical point of view, anisotropic growth can be considered by choosing appropriate initial conditions to the growth law (61). For example, this can be done by imposing that, at $t = 0$, the growth tensor $\mathbf{G}_S(0, \mathbf{X})$ has a non-vanishing deviatoric part. The result commented above was obtained as a possible application of the Theory of Upscaling [8][13]-[15], briefly exposed in sections 2 and 3, to the biological problem explained in section 5.

We used the Theory of Upscaling for two reasons: *i*) we needed to find an upscaled advection-diffusion-reaction equation in which the Fick-type current was consistent with the constitutive framework established at the macroscopic scale; *ii*) we had in mind to relate the pore scale concentration of chemical substances with their average concentration in order to investigate the possible repercussions of growth on the mesoscopic dynamics of the tissue. Indeed, by expressing the macroscopic density of chemical substances as

$$\rho = \langle \rho_m \rangle_F^F = \frac{C}{\Phi_F} = \frac{c}{\phi_F}, \tag{87}$$

and assuming that mesoscopic density can be written as

$$\rho_m(t, \mathbf{r}) = \rho(t, \mathbf{x}) + \mathbf{b}(t, \mathbf{r}) \cdot \nabla_{\mathbf{x}} \rho(t, \mathbf{x}) \tag{88}$$

(where $\mathbf{b}(t, \mathbf{r})$ has to be e zero-mean field over the subset $\Omega_F(t, \mathbf{x}) \subset \Omega(\mathbf{x})$), the modulation felt by ρ through the material concentration C is reflected on ρ_m.

Acknowledgements

The Authors are grateful to Prof. Sabine Attinger, Prof. Jean-Louis Auriault, Prof. Majid Hassanizadeh and Prof. Shoji Imatani for useful discussions and providing references. This work was supported by CNISM - Consorzio Nazionale Interuniversitario per lo Studio delle Scienze Fisiche della Materia (National Inter-university Consortium of Study of the Physical Sciences of the Matter).

References

[1] Taber L. A., *Biomechanics of growth, remodelling and morphogenesis.* Appl. Mech. Rev., Vol. 48, 487-545, 1995.

[2] Garikipati K., Arruda E. M., Grosh K., Narayanan H., Calve S., *A continuum treatment of growth in biological tissues: the coupling of mass transport and mechanics.* J. Mech. Phys. Solids, Vol. 52, 1595-1625, 2004.

[3] Mow V. C., Lai., M., *Biorheology of swelling tissue.* Biorheology, Vol. 27 (1), 110-119, 1990.

[4] Humphrey J. D., and Rajagopal K. R., *A constrained mixture model for arterial adaptations to a sustained step change in blood flow.* Biomechan. Model. Mechanobiol., Vol. 2 (2), 109-126, 2003.

[5] Ateshian G. A., *On the theory of reactive mixture for modeling biological growth.* Biomechan. Model Mechanobiol., in press, DOI 10.1007/s10237-006-0070-x, 2007.

[6] Loret B., and Simes F. M. F., *A framework for deformation, generalized diffusion, mass transfer and growth in multi-species multi-phases biological tissue.* Eur. J. Mech. A - Solids, Vol. 24, 757-781, 2005.

[7] Biot M. A., *Variational Lagrangian-thermodynamics of non-isothermal finite strain mechanics of porous solids and thermo-molecular diffusion.* Int. J. Solids Structures, Vol., 13, 579-597, 1977.

[8] Hassanizadeh S. M., *Derivation of basic equations of mass transport in porous media, Part 1. Macroscopic balance laws*, Adv. Water Resour., Vol. 9, 196-206, 1986.

[9] Rajagopal K., R., *Diffusion through polymeric solids undergoing large deformations*, Material Science and Technology, Vol. 19, 1175-1180, 2003.

[10] Thiffeault J.-L., *Advection-Diffusion in Lagrangian Coordinates*, Physics Letters A, Vol. 309 (5-6), 415-422, 2003.

[11] Epstein M. and Maugin G. A., *Thermomechanics of volumetric growth in uniform bodies.* Int. J. Plasticity, Vol. 16, 951-978, 2000.

[12] Grillo A., Zingali G., Borrello D., Federico S., Herzog W., Giaquinta G., *Interaction between growth and transport phenomena in living mixtures.* Journal of Physics: Conference Series, 62, 43–71, 2007.

[13] Hassanizadeh S. M., and Gray W. G., *General conservation equations for multi-phase systems: 1. Averaging procedure*, Adv. Water Resour., Vol. 2, 131-144, 1979.

[14] Hassanizadeh S. M., and Gray W. G., *General conservation equations for multi-phase systems: 2. Mass, momenta, energy and entropy equations*, Adv. Water Resour., Vol. 2, 191-203, 1979.

[15] Hassanizadeh S. M., and Gray W. G., *General conservation equations for multi-phase systems: 3. Constitutive theory for porous media flow*, Adv. Water Resour., Vol. 3, 25-40, 1980.

[16] Dormieux L., Kondo D., and Ulm F.-J., *Microporomechanics*, John Wiley & Sons Ltd, England, 2006.

[17] Lubarda V. A., and Hoger A., *On the mechanics of solids with a growing mass*, Int. J. Solids Structures, Vol. 39, 4627-4664, 2002.

[18] Ruggeri T., *Galilean invariance and entropy principles for systems of balance laws-The structure of extended thermodynamics*, Continuum Mech. Thermodyn., Vol. 1, 3-20, 1989.

[19] Ruggeri T., and Simić S., *On the hyperbolic system of a mixture of a Eulerian fluids: A comparison between single- and multi-temperature models*, Math. Meth. Appl. Sci., Vol. 30, 827-849, 2007.

[20] Quiligotti S., Maugin G. A., Dell'Isola F., *An Eshelbian approach to the nonlinear mechanics of constrained solid-fluid mixtures.* Acta Mech., Vol. 160 (1-2), 45-60, 2003.

[21] Ambrosi D., and Mollica F., *On the mechanics of a growing tumour*, Int. J. Eng. Science., Vol. 40, 1297-1316, 2002.

[22] Ambrosi D., and Mollica F., *The role of stress in the growth of a multicell spheroid*, J. Math. Biol., Vol. 48, 477-499, 2004.

[23] Chaplain M. A. J., Benson D. L., and Maini P. K., *Nonlinear diffusion of a growth inhibitory factor* Mathematical Biosciences, Vol. 121, 1-13, 1994.

[24] Chaplain M. A. J., *Avascular Growth, Angiogenesis and Vascular Growth in Solid Tumours: The Mathematical Modelling of the Stages of Tumour Development*, Mathl. Comput. Modelling, Vol. 23, 6, 47-87, 1996.

[25] Ambrosi D., and Preziosi L., *On the closure for mass balance models for tumor growth*, Mathematical Models and Methods in Applied Sciences, Vol. 12, 5, 737-754, 2002.

[26] Byrne H., and Preziosi L., *Modelling Solid Tumour Growth Using Theory of Mixtures*, Math. Medicine and Biol., Vol. 20, 341-366, 2003.

[27] Shashikanth B. N., and Newton P. K., *Vortex Motion and the Geometric Phase. Part I. Basic Configurations and Asymptotics*, J. Nonlinear Sci., Vol. 8, 183-214, 1997.

[28] Lunati I., Attinger S., and Kinzelbach W., *Macrodipersivity for Transport in Arbitrary Nonuniform Flow fields Asymptotic and preasymptotic results*, Water Resour. Res., Vol. 30, 10, 1187-1198, 2002.

[29] Auriault J. L., and Adler P. M., *Taylor dispersion in porous media: Analysis by multiple scale expansions*, Adv. Water. Resources, Vol. 18, 4, 217-226, 1995.

Appendix A.

The macroscopic fluxes $\mathbf{J}_\alpha$ and $\mathbf{J}_S$ featuring in Eqs. (10) and (11) are given by

$$\mathbf{J}_\alpha \cdot \mathbf{N} = \frac{1}{|A|} \int_A [\Im_{m,\alpha} - \rho_{m,\alpha} \widetilde{\psi_{m,\alpha}}^{\alpha} \widetilde{\mathbf{v}_{m,\alpha}}^{\alpha}] \cdot \mathbf{n}\gamma_F dA_{\mathbf{r}}, \tag{89}$$

$$\mathbf{J}_S \cdot \mathbf{N} = \frac{1}{|A|} \int_A [\Im_{m,S} - \rho_{m,S} \widetilde{\psi_{m,S}}^{S} \widetilde{\mathbf{v}_{m,S}}^{S}] \cdot \mathbf{n}\gamma_S dA_{\mathbf{r}}, \tag{90}$$

where $\boldsymbol{N}$ is the unit vector normal to the Representative Elementary Area (REA), and the fields $\widetilde{\psi_{m,\alpha}}^{\alpha} = \psi_{m,\alpha} - \overline{\psi_{m,\alpha}}^{\alpha}$ and $\widetilde{\mathbf{v}_{m,\alpha}}^{\alpha} = \mathbf{v}_{m,\alpha} - \overline{\mathbf{v}_{m,\alpha}}^{\alpha}$ represent the fluctuations of $\psi_{m,\alpha}$ and $\mathbf{v}_{m,\alpha}$, respectively, with respect to mass averages operators defined in Eqs. (8) and (9). The quantities $\mathcal{E}_S(\rho_{m,S}\psi_{m,S})$, $\mathcal{E}_\alpha(\rho_{m,\alpha}\psi_{m,\alpha})$, $\Re_S$, and $\Re_\alpha$ are given by

$$\mathcal{E}_\alpha(\rho_{m,\alpha}\psi_{m,\alpha}) = \frac{1}{\phi_F \langle \rho_{m,\alpha} \rangle_F^F} \frac{1}{|\Omega|} \int_{A_{FS}} [\rho_{m,\alpha}\psi_{m,\alpha}(\mathbf{u} - \mathbf{v}_{m,\alpha})]|_F \cdot \mathbf{n}_{FS} dA_{\mathbf{r}}, \tag{91}$$

$$\mathcal{E}_S(\rho_{m,S}\psi_{m,S}) = \frac{1}{\phi_S \langle \rho_{m,S} \rangle_S^S} \frac{1}{|\Omega|} \int_{A_{SF}} [\rho_{m,S}\psi_{m,S}(\mathbf{u} - \mathbf{v}_{m,S})]|_S \cdot \mathbf{n}_{SF} dA_{\mathbf{r}} \tag{92}$$

$$\Re_\alpha = \frac{1}{\phi_F \langle \rho_{m,\alpha} \rangle_F^F} \frac{1}{|\Omega|} \int_{\Omega_\alpha} [\Im_{m,\alpha}]|_F \cdot \mathbf{n}_{FS} dA_{\mathbf{r}}, \tag{93}$$

$$\Re_S = \frac{1}{\phi_S \langle \rho_{m,S} \rangle_S^S} \frac{1}{|\Omega|} \int_{\Omega_S} [\Im_{m,S}]|_S \cdot \mathbf{n}_{SF} dA_{\mathbf{r}}. \tag{94}$$

The first pair of equations accounts for the transfer of $\psi_{m,\alpha}$ and $\psi_{m,S}$ due to the relative motion between the interface and the α-th constituent, and between the interface and the solid phase, respectively, while the second pair describes the transfer due to the presence of the mesoscopic currents $\Im_{m,\alpha}$ and $\Im_{m,S}$, respectively.

Appendix B.

The thermodynamic quantities given in Table 3 represent the macroscopic fields obtained by averaging their mesoscopic counterparts (cfr. Table 1).

Mass density:

$$\rho_\alpha = \langle \rho_{m,\alpha} \rangle_F^F, \tag{95}$$

Mass production rate due to chemical reactions:

$$\hat{r}_{\alpha}^{ch} = \overline{\hat{r}_{m,\alpha}^{ch}}^{\alpha}, \tag{96}$$

Mass production rate due to transfer of mass across the fluid-solid interface:

$$\hat{r}_{\alpha}^{tr} = \frac{1}{\phi_F \rho_\alpha} \frac{1}{|\Omega|} \int_{A_{FS}} \rho_{m,\alpha} (\mathbf{u} - \mathbf{v}_{m,\alpha}) \cdot \mathbf{n}_{FS} dA_{\mathbf{r}}, \tag{97}$$

Velocity

$$\mathbf{v}_\alpha = \overline{\mathbf{v}_{m,\alpha}}^{\alpha}, \tag{98}$$

Stress tensor, σ_α, defined by

$$\sigma_\alpha \cdot \mathbf{N} = \frac{1}{|A|} \int_A \gamma_F (\sigma_{m,\alpha} - \rho_{m,\alpha} \widetilde{\mathbf{v}_{m,\alpha}}^{\alpha} \otimes \widetilde{\mathbf{v}_{m,\alpha}}^{\alpha}) \cdot \mathbf{n} dA_{\mathbf{r}}, \tag{99}$$

Velocity associated to the mass uptake, $\hat{\mathbf{v}}_\alpha$:

$$\hat{\mathbf{v}}_\alpha = \overline{\hat{\mathbf{v}}_{m,\alpha}}^{\alpha}. \tag{100}$$

Exchange of momentum production due to chemical reaction, $\hat{\lambda}_{\alpha}^{ch}$:

$$\hat{\lambda}_{\alpha}^{ch} = \overline{\hat{\lambda}_{m,\alpha}}^{\alpha} + \overline{\widetilde{\hat{r}_{m,\alpha}^{ch}}^{\alpha} \widetilde{\hat{\mathbf{v}}_{m,\alpha}}^{\alpha}}^{\alpha} \tag{101}$$

Momentum exchange rate, $\hat{\mathbf{m}}_\alpha$, between the α-th chemical substance and the solid matrix as a result of physio-chemical and mechanical interactions:

$$\hat{\mathbf{m}}_\alpha = \frac{1}{\phi_F \rho_\alpha} \frac{1}{|\Omega|} \int_{A_{FS}} [\rho_{m,\alpha} \widetilde{\mathbf{v}_{m,\alpha}}^{\alpha} \otimes (\mathbf{u} - \mathbf{v}_{m,\alpha}) + \sigma_{m,\alpha}]|_F . \mathbf{n}_{FS} dA_{\mathbf{r}}. \tag{102}$$

Macroscopic internal energy density of the α-th chemical substance, U_α:

$$U_\alpha = \overline{U_\alpha}^{\alpha} + \overline{\tfrac{1}{2} (\widetilde{v_{m,\alpha}}^{\alpha})^2}^{\alpha}. \tag{103}$$

Macroscopic heat flux, $\mathbf{q}_\alpha$:

$$\begin{aligned} \mathbf{q}_\alpha \cdot \mathbf{N} \;=\; & \frac{1}{|A|} \int_A \gamma_F \{ \mathbf{q}_{m,\alpha} + \sigma_{m,\alpha} . \widetilde{\mathbf{v}_{m,\alpha}}^{\alpha} - \rho_{m,\alpha} [U_{m,\alpha} + \\ & \frac{1}{2} (\widetilde{v_{m,\alpha}}^{\alpha})^2] \widetilde{\mathbf{v}_{m,\alpha}}^{\alpha} \} \cdot \mathbf{n} dA_{\mathbf{r}}. \end{aligned} \tag{104}$$

Macroscopic source of internal energy density, $\hat{U}_\alpha$:

$$\hat{U}_\alpha = \overline{\hat{U}_{m,\alpha}}^{\alpha} + \overline{\tfrac{1}{2}(\widetilde{\hat{v}_{m,\alpha}}^{\alpha})^2}^{\alpha}. \tag{105}$$

Macroscopic effect of molecular exchange of energy between the α-th chemical substance and all other substances, $\hat{\theta}_\alpha$:

$$\hat{\theta}_\alpha = \overline{\hat{\theta}_{m,\alpha}}^{\alpha} + \overline{\hat{\lambda}^{ch}_{m,\alpha} \cdot \widetilde{\mathbf{v}_{m,\alpha}}^{\alpha}}^{\alpha} + \overline{\widetilde{\hat{r}^{ch}_{m,\alpha}}^{\alpha} \left[\widetilde{\hat{U}_{m,\alpha}}^{\alpha} + \tfrac{1}{2}(\widetilde{\hat{v}_{m,\alpha}}^{\alpha})^2 \right]}^{\alpha}, \tag{106}$$

where $\widetilde{\hat{U}_{m,\alpha}}^{\alpha} = \hat{U}_{m,\alpha} - \hat{U}_\alpha$.

Exchange of energy between the α-th chemical substance and the solid matrix as a result of physio-chemical, mechanical, and thermal interactions, $\hat{e}_\alpha$:

$$\begin{aligned} \hat{e}_\alpha \;\; = \;\; & \frac{1}{\phi_F \rho_\alpha} \frac{1}{|\Omega|} \int_{A_{FS}} \left\{ \rho_{m,\alpha} \left[\widetilde{U_{m,\alpha}}^{\alpha} + \frac{1}{2}(\widetilde{v_{m,\alpha}}^{\alpha})^2 \right] (\mathbf{u} - \mathbf{v}_{m,\alpha}) + \right. \\ & \left. \sigma_{m,\alpha} . \widetilde{\mathbf{v}_{m,\alpha}}^{\alpha} + \mathbf{q}_{m,\alpha} \right\}_F \Big| \cdot \mathbf{n}_{FS} dA_{\mathbf{r}} \end{aligned} \tag{107}$$

Macroscopic entropy density, S_α:

$$S_\alpha = \overline{S_{m,\alpha}}^{\alpha}. \tag{108}$$

Macroscopic entropy density flux vector, φ_α:

$$\varphi_\alpha \cdot \mathbf{N} = \frac{1}{|A|} \int_A \gamma_F [\varphi_{m,\alpha} - \rho_{m,\alpha} S_{m,\alpha} \widetilde{\mathbf{v}_{m,\alpha}}^{\alpha}] \cdot \mathbf{n} dA_{\mathbf{r}}. \tag{109}$$

Macroscopic source of entropy density, $\hat{S}_\alpha$:

$$\hat{S}_\alpha = \overline{\hat{S}_{m,\alpha}}^{\alpha}. \tag{110}$$

Macroscopic effect of molecular exchange of entropy between the α-th chemical substance and all other substances, $\hat{\zeta}_\alpha$:

$$\hat{\zeta}_\alpha = \overline{\hat{\zeta}_{m,\alpha}}^{\alpha} + \overline{\widetilde{\hat{r}^{ch}_{m,\alpha}}^{\alpha} \widetilde{\hat{S}_{m,\alpha}}^{\alpha}}^{\alpha}. \tag{111}$$

Macroscopic entropy production rate, Γ_α:

$$\Gamma_\alpha = \overline{\Gamma_{m,\alpha}}^{\alpha}. \tag{112}$$

Macroscopic supply of entropy to the α-th chemical substance as a result of thermodynamic interactions with the solid matrix, η_α:

$$\hat{\eta}_\alpha = \frac{1}{\phi_F \rho_\alpha} \frac{1}{|\Omega|} \int_{A_{FS}} \left[\rho_{m,\alpha} \widetilde{S_{m,\alpha}}^{\alpha} (\mathbf{u} - \mathbf{v}_{m,\alpha}) + \varphi_{m,\alpha}\right]\Big|_F \cdot \mathbf{n}_{FS} dA_{\mathbf{r}}. \tag{113}$$

In order to summarise in a single term, for each balance law, the combination of molecular effects and interface interactions, we define the quantities

$$\hat{R}_\alpha = \hat{r}^{ch}_\alpha + \hat{r}^{tr}_\alpha, \tag{114}$$

$$\hat{\mathbf{T}}_\alpha = \hat{\lambda}^{ch}_\alpha + \hat{\mathbf{m}}_\alpha, \tag{115}$$

$$\hat{Q}_\alpha = \hat{\theta}_\alpha + \hat{e}_\alpha, \tag{116}$$

$$\hat{\Phi}_\alpha = \hat{\zeta}_\alpha + \hat{\eta}_\alpha. \tag{117}$$

The macroscopic thermodynamic quantities referred to the solid phase (cfr. Table 5) are obtained by following an analogous procedure, substituting in Eqs. (95)-(113) the quantities defined in Table 1, and replacing the index F by the index S in the intrinsic volume averaging operators.

The thermodynamic quantities given in Table 4 represent the macroscopic fields associated to the fluid phase as a whole.

Mass density, ρ_F:

$$\rho_F = \sum\nolimits_{\alpha=1}^{N} \rho_\alpha. \tag{118}$$

Overall mass production rate, $\hat{R}^{tr}_F$:

$$\rho_F \hat{R}^{tr}_F = \sum\nolimits_{\alpha=1}^{N} \rho_\alpha \hat{r}^{tr}_\alpha. \tag{119}$$

Velocity, $\mathbf{v}_F$:

$$\rho_F \mathbf{v}_F = \sum\nolimits_{\alpha=1}^{N} \rho_\alpha \mathbf{v}_\alpha. \tag{120}$$

Cauchy stress tensor, σ_F:

$$\sigma_F = \sum\nolimits_{\alpha=1}^{N} [\sigma_\alpha - \phi_F \rho_\alpha \mathbf{v}_{\alpha F} \otimes \mathbf{v}_{\alpha F}], \tag{121}$$

where $\mathbf{v}_{\alpha F} = \mathbf{v}_\alpha - \mathbf{v}_F$ is the diffusive velocity of the α-th chemical substance with respect to the fluid phase.

Exchange of momentum between the fluid and the solid phase, $\hat{\mathrm{T}}_F$:

$$\rho_F \hat{\mathbf{T}}_F = \sum\nolimits_{\alpha=1}^{N} \rho_\alpha(\hat{r}_\alpha^{tr}\mathbf{v}_{\alpha F} + \hat{\mathbf{m}}_\alpha). \tag{122}$$

Energy density, U_F:

$$\rho_F U_F = \sum\nolimits_{\alpha=1}^{N} \rho_\alpha(U_\alpha + \tfrac{1}{2}v_{\alpha F}^2). \tag{123}$$

Energy density flux vector, $\mathbf{q}_F$:

$$\mathbf{q}_F = \sum\nolimits_{\alpha=1}^{N} [\mathbf{q}_\alpha - \sigma_\alpha.\mathbf{v}_{\alpha F} - \phi_F\rho_\alpha(U_\alpha + \tfrac{1}{2}v_{\alpha F}^2)\mathbf{v}_{\alpha F}]. \tag{124}$$

Exchange of energy between the fluid and the solid phase, $\hat{Q}_F$:

$$\rho_F \hat{Q}_F = \sum\nolimits_{\alpha=1}^{N} \rho_\alpha\{\hat{e}_\alpha + \hat{\mathbf{m}}_\alpha \cdot \mathbf{v}_{\alpha F} + \hat{r}_\alpha^{tr}[(U_\alpha - U_F) + \tfrac{1}{2}v_{\alpha F}^2]\}. \tag{125}$$

Entropy density, S_F:

$$\rho_F S_F = \sum\nolimits_{\alpha=1}^{N} \rho_\alpha S_\alpha. \tag{126}$$

Entropy flux vector, φ_F:

$$\varphi_F = \sum\nolimits_{\alpha=1}^{N} [\varphi_\alpha - \phi_F\rho_\alpha S_\alpha \mathbf{v}_{\alpha F}]. \tag{127}$$

Entropy production rate, Γ_F:

$$\rho_F \Gamma_F = \sum\nolimits_{\alpha=1}^{N} \rho_\alpha \Gamma_\alpha. \tag{128}$$

Supply of entropy to the fluid phase as a result of thermodynamic interactions of all fluid components, $\hat{\Phi}_F$:

$$\rho_F \hat{\Phi}_F = \sum\nolimits_{\alpha=1}^{N} \rho_\alpha[\hat{\eta}_\alpha + \hat{r}_\alpha^{tr}(S_\alpha - S_F)]. \tag{129}$$

Submitted on April 2007.

Opis rasta i transporta bioloških tkiva sa više skala

Proučavamo rastuća biološka tkiva kao otvorenu dvofaznu mešavinu sa razmenom mase izmedju faza. Čvrsta faza je identifikovana sa matricom poroznog medijuma, dok je fluidna faza uključuje vodu zajedno sa svim rstvorenim hemijskim supstancama koje se nalaze u prostoru pora. Pretpostavljamo da hemijske supstance evoluiraju saglasno transportnim mehanizmima odredjenim kinematskim i konstitutivnim jednačinama i predlažemo da se rast posmatra kao proces sposoban da utiče na transport neprekidnim variranjem termomehaničkog stanja tkiva. Usmeravanjem pažnje na slučaj anizotropnog rasta pokazujemo da takav uticaj postoji neprekidnim ponovnim rasporedjivanjem materijalnih simetrija tkiva. U cilju ilustracije ovog medjudejstva ograničavamo razmatranje na transport diktiran difuzijom i pretpostavljamo da su vremenske skale pridružene rastu i transportnom procesu različitog reda veličine. Ovo nam dozvoljava da izvršimo asimptotsku analizu “jednačina polja” sistema. U ovom okviru, dajemo formalno rešenje transportne jednačine pridruženom Grinovom funkcijom i pokazujemo kako je makroskopska koncentracija date hemijske supstance “modulirana” anizotropnim rastom.

doi:10.2298/TAM0701051G Math.Subj.Class.: 37N25, 45N60, 92C37, 74F25