Interaction between growth and transport phenomena in living mixtures

A Grillo $^{1,2}$, G Zingali $^3$, D Borrello $^3$, S Federico $^4$, W Herzog $^4$, G Giaquinta $^{1,2}$

$^1$ DMFCl, Facoltà di Ingegneria, Università di Catania
Viale Andrea Doria 6, 95125 Catania, Italy

$^2$ CNISM - Unità di Ricerca di Catania
Viale Andrea Doria 6, 95125 Catania, Italy

$^3$ Dottorato di Ricerca in Ingegneria Fisica. Università di Catania
Viale Andrea Doria 6, 95125 Catania, Italy

$^4$ HPL - Faculty of Kinesiology, The University of Calgary
2500 University Drive NW, Calgary, Alberta, T2N 1N4, Canada

E-mail: agrillo@dmfci.unict.it

Abstract. Biological growth is regulated by the presence of several chemical substances, and is modulated by thermo-mechanical stimuli. The evolution of chemical substances is described by the advection-diffusion-reaction process of solutes dissolved in the fluid-phase of a biphasic mixture with mass exchange between phases. We present a picture in which growth, by changing material symmetries, modifies the environment in which transport processes take place, and we outline a possible interaction between growth and chemical agents. In order to study this interaction, we use averaging methods to determine the macroscopic counterparts of the transport properties defined at the microscale, and, by writing the macroscopic transport equation in material form, we illustrate how these properties are modulated by growth. In the case of anisotropic growth, such a modulation has a geometric meaning, and is related to both the change of material symmetries, and the development of material inhomogeneities. By regarding growth as a process characterized by a time-scale much slower than that of the transport process of interest, we provide an asymptotic analysis of transport in a growing porous medium based on the adiabatic approximation. We prove that the macroscopic concentration of chemical substances is “renormalized” by the anisotropy of growth.

1. Introduction
A living tissue is said to experience growth when it undergoes a variation of mass [1]. This variation can be either positive (mass production) or negative (mass resorption), and is the product of a variety of phenomena occurring at different scales of observation. At the molecular scale, growth is regulated by the presence of several chemical substances [2] [3], while at the macroscale (i.e., the scale at which the tissue is regarded as a macroscopic complex continuum system), growth is modulated by environmental factors [2]. When growth is studied within a purely thermo-mechanical context, these factors are identified with thermo-mechanical stimuli.
The presence of a given chemical substance in a tissue is measured by its local concentration, and its evolution is described by the change of concentration due to the occurrence of various transport phenomena. In this paper, we assume that transport takes place in the interstitial fluid filtrating biological tissues [2] [3], and occurs through advection, diffusion and reaction. These processes are governed by transport properties which, although being intrinsic in origin, must be determined within a thermo-mechanical analysis of the tissue as a whole.

In response to growth, the geometry, internal structure, thermo-mechanic state, and material properties of a tissue change in time. On the other hand, externally applied thermo-mechanical stimuli contribute to these variations, and concur to the macroscopic evolution of the tissue. The resulting picture is that chemical substances evolve in a continuously varying environment.

Although a tissue “feels” the influence of growth and thermo-mechanical stimuli at the macroscale, we believe that there may exist an effective interaction between transport of chemical substances and the thermo-mechanical environment. In order to describe this interaction, it is necessary to “upscale” transport processes from the molecular to the continuum scale. By following the upscaling procedures introduced by Gray and Hassanizadeh in [4], we first study the behaviour of chemical agents at the pore scale (this study is based on the analysis of transport of uncharged substances in porous media [5]), and then we show how to obtain a macroscopic advection-diffusion-reaction equation, which is consistent with the microscopic description.

We model a growing biological tissue as a biphasic mixture made of a fluid phase filtrating a porous solid matrix, and undergoing mass exchange between phases [6]-[9]. This approach is based on the formulation of Mixture Theory as proposed in [10] [11].

We assume that the mixture is closed, i.e., strict mass balance holds true for the mixture as a whole, and saturated, i.e., the sum of fluid- and solid-phase volume fractions equals unity. These hypotheses imply that the mass variation of the solid-phase is compensated for by that of the fluid-phase. We focus only on the case of mass accretion (positive growth) of the solid matrix, and, in accordance with the picture proposed by Epstein and Maugin [12], we regard growth as a source of material inhomogeneities.

In our opinion, growth is also responsible for modulating the transport properties which determine the macroscopic evolution of chemical substances. In order to prove this, we write the macroscopic advection-diffusion-reaction equation in material form [3] [13], and we show that, in the peculiar case of anisotropic growth, this modulation has a geometric meaning, and occurs through the evolution of material symmetries, and the development of material inhomogeneities.

Finally, by regarding growth as a process characterized by a time-scale much slower than that of the transport process of interest, we provide an asymptotic analysis of transport in a growing porous medium (this method is extensively used within the theory of Homogenization [14] [15]). In this framework, we show how the macroscopic concentration of a given chemical substance is continuously modulated by anisotropic growth.

This paper has two scopes. The first scope is to compare the description of a biological tissue obtained by employing the theory of upscaling with other models present in the literature which are not – at least explicitly – based on this method (this aspect was studied in sections 2 to 6, and required the presentation of the theory of upscaling, the development of a macroscopic constitutive framework, and the adaptation of results to the description of a biological system). The second scope is to investigate a possible repercussion of the evolution of material symmetries on the physical quantities which characterize transport processes both at the macroscale and the microscale.

A class of biological systems which may lend themselves to the above given description is provided by solid tumours during their avascular growth stage [16]. The specialization of the theory presented in our paper to this case will be given in section 7, and the results will be discussed in section 8.

2. Microscopic Formulation of Balance Laws

We consider a system made of a solid- and a fluid-phase. The former constitutes the porous solid matrix (or skeleton) of the system, while the latter fills the pore space. In general, the fluid phase is a
subsystem made up by $N+1$ chemical substances co-existing in the pore space. Among these substances, the presence of water is taken for granted in the biological context.

The pore scale corresponds to what we mean in this paper by microscopic description of the tissue. In general, a given physical quantity, $\psi$, can be defined at any point $r$ of the system. When this quantity is evaluated at a point $r$ occupied by the $j$-th constituent of the fluid-phase, it will be denoted by $\psi_j$. Analogously, $\psi_F$ and $\psi_S$ will denote the restriction of $\psi$ to the subset of the body occupied by the fluid-phase and solid-phase, respectively.

In order to study the balance laws at the pore scale, we attach a given physical quantity, $\psi$, and a velocity field, $u$, to any point $r$ of the tissue. These quantities are assumed to vary continuously within each component of the system, and to experience jump conditions at the solid-fluid interface. In the pore space, mass density, $\mu$, equals the mass density of the fluid-phase, i.e.,

$$
\mu_F = \sum_{j=0}^{N} \rho_j = \mu_0 + \sum_{j=1}^{N} \rho_j,
$$

where $\rho_j = \omega_j \rho_j^{(i)}$ ( $j = 0,...,N$ ) is the mass density of the $j$-th constituent (the index 0 refers to water), $\omega_j$ and $\rho_j^{(i)}$ being the volume fractions (referred to the volume of the pore space) and intrinsic mass densities of the $N+1$ chemical substances, respectively.

The spatial (Eulerian) form of the balance equation of a given thermodynamic quantity $\psi_j$, referred to the $j$-th species of the fluid-phase, having flux vector $\mathbf{J}_\psi_j$, external supply $f_\psi_j$, and net production rate $g_\psi_j$, is given by [4] [5] [17]-[20]

$$
\frac{\partial (\rho_j \psi_j)}{\partial t} + \nabla \cdot (\rho_j \psi_j \mathbf{u}_j) + \nabla \cdot \mathbf{J}_\psi_j - \mu_j f_\psi_j = \mu_j g_\psi_j,
$$

where $\nabla$ denotes differentiation with respect to the microscopic space variable, $r$. Analogously, the balance law of a physical quantity, $\psi_S$, associated with the solid-phase reads

$$
\frac{\partial (\rho_S \psi_S)}{\partial t} + \nabla \cdot (\rho_S \psi_S \mathbf{u}_S) + \nabla \cdot \mathbf{J}_\psi_S - \mu_S f_\psi_S = \mu_S g_\psi_S,
$$

where $\rho_S$ and $\mathbf{u}_S$ are the mass density and velocity of the solid-phase, respectively. In Equations (2.2) and (2.3), the thermodynamic quantities, $\psi_j$ and $\psi_S$, are expressed per unit mass.

Microscopic balance of mass, momentum, energy and entropy are found by specifying, for each case, the appropriate quantity $\psi$, flux vector, external supply, and net production rate which must be substituted into Equations (2.2) and (2.3). By referring to Table 1 for the fluid-phase, and to Table 2 for the solid-phase, we obtain:

**Mass Balance Law**

$$
\frac{\partial \mu_j}{\partial t} + \nabla \cdot (\mu_j \mathbf{u}_j) = \mu_j \pi_j,
$$

$$
\frac{\partial \mu_S}{\partial t} + \nabla \cdot (\mu_S \mathbf{u}_S) = 0.
$$

**Momentum Balance Law**

$$
\frac{\partial (\mu_j \mathbf{u}_j)}{\partial t} + \nabla \cdot (\mu_j \mathbf{u}_j \otimes \mathbf{u}_j) + \nabla \cdot \mathbf{J}_\mathbf{u}_j - \mu_j \mathbf{g}_j = \mu_j (\pi_j \mathbf{u}_j + \lambda_j),
$$

$$
\frac{\partial (\mu_S \mathbf{u}_S)}{\partial t} + \nabla \cdot (\mu_S \mathbf{u}_S \otimes \mathbf{u}_S) - \mu_S \mathbf{g}_S = 0.
$$

**Energy Balance Law**
\[
\frac{\partial}{\partial t} \left[ \mu_j \left( E_j + \frac{1}{2} u_j^2 \right) \right] + \nabla \cdot \left[ \mu_j \left( E_j + \frac{1}{2} u_j^2 \right) u_j \right] + \nabla \cdot \left[ \Sigma_j u_j + q_j \right] - \mu_j [g_j \cdot u_j + h_j] = 0.
\]

(2.8)

In Equations (2.4)-(2.11), \( \pi_j \) is the mass production rate of substance \( j \) due to homogeneous chemical reactions and/or decay or production processes, \( \Sigma_j \) is the microscopic “partial stress” tensor for the species \( j \), \( g_j \) are body forces per unit mass (due to gravity, or ionic or molecular forces), \( \lambda_j \) are the internal body forces per unit mass exerted upon the substance \( j \) by all other substances, \( E_j \) is the microscopic internal energy per unit mass, \( q_j \) is the heat flux within the \( j \)-th species, \( h_j \) is an external supply of energy, \( e_j \) is the energy exchange between the substance \( j \) and all other substances, \( \eta_j \) is the entropy density per unit mass, \( \phi_j \) is the entropy flux, \( b_j \) is the entropy external supply, \( \zeta_j \) is the entropy exchange between the substance \( j \) and all other substances, and \( \Upsilon_j \) is the rate of net production of entropy of the \( j \)-th species.

Since the exchanges of mass, momentum, energy, and entropy involving the individual balance equations of chemical species take place within the fluid-phase, they cannot give rise to net production or decay of the corresponding properties as referred to the fluid-phase as a whole. This implies that exchange terms must satisfy the constraints [5]

\[
\sum_{j=0}^{N} \mu_j \pi_j = 0, \quad \sum_{j=0}^{N} \mu_j (\pi_j u_j + \lambda_j) = 0,
\]

\[
\sum_{j=0}^{N} \mu_j \left[ \pi_j \left( E_j + \frac{1}{2} u_j^2 \right) + \lambda_j u_j + e_j \right] = 0, \quad \sum_{j=0}^{N} \mu_j (\pi_j \eta_j + \zeta_j) = 0.
\]

(2.12)

At the fluid-solid interface, balance laws are expressed by the jump condition

\[
\sum_{j=0}^{N} \mu_j [\psi_j (v - u_j) - \mathcal{S}_{\psi_j}]_F \cdot n_{FS} + [\mu_j \psi_S (v - u_S) - \mathcal{S}_{\psi_S}]_S \cdot n_{SF} = 0.
\]

(2.13)

This equation holds true for mass, momentum and energy, but, in the case of entropy, it is replaced by the inequality

\[
\sum_{j=0}^{N} \mu_j [\eta_j (v - u_j) - \phi_j]_F \cdot n_{FS} + [\mu_j \eta_S (v - u_S) - \phi_S]_S \cdot n_{SF} \geq 0.
\]

(2.14)

In Equations (2.13) and (2.14), \( v \) is the velocity of the fluid-solid interface, \( n_{FS} = -n_{SF} \) is the unit normal vector pointing out of the fluid-phase and into the solid-phase, and the symbols \([...]_F\) and \([...]_S\) indicate that, at the interface, the limit of the expression within brackets is to be evaluated from the fluid- and solid-phase side, respectively.

3. Averaging Techniques and Upscaling of Microscopic Balance Equations

In this section, we outline the procedure we used to “bring” the problem presented in section 2 to the scale at which transport in porous materials can be studied within a thermo-mechanic framework of growth in deformable media. This procedure is the basis on which the theory of upscaling is built.
The theory of upscaling requires the existence of a Representative Elementary Volume (REV), $\Omega_{[20]-[21]}$. 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 microscopic heterogeneities, and much smaller than the length-scale of the macroscopic inhomogeneities. If a porous material admits an REV, a given microscopic field can be upscaled by defining a suitable average operator on the REV. In order for the average of a microscopic quantity to be physically meaningful, it is necessary to use the appropriate average operator for that particular quantity. This requirement has to be fulfilled by following criteria based on thermodynamic considerations. An extensive exploitation of these criteria can be found in [18].

3.1. Averaging Operators

The average of microscopic quantities should be evaluated at any point $x$ of the portion of space, $B$, occupied by the system. If $x$ is far enough from the boundary of $B$, this is done by attaching the REV to $x$, and expressing microscopic quantities as a function of the relative variable $\xi = r - x$, where $r$ is a point lying in the intersection between the REV and $B$. However, as point $x$ approaches the boundary of $B$ the average is no longer physically meaningful because, in this case, the REV contains points which do not belong to $B$. Therefore, the portion of $B$ over which averages can be safely evaluated must be restricted to the subset of $B$, which is spanned by smoothly “dragging” the REV along $B$. Although this is an approximation, the error is acceptable by virtue of the smallness of the REV as compared to the entire body.

Among the various operators defined in the literature to average a given physical quantity, $\psi$, in this paper we use [17]-[20]:

- The **global volume average**

$$
\langle \psi \rangle_{\Omega}(t,x) = \frac{1}{|\Omega(x)|} \int_{\Omega(x)} \psi(t,x+\xi)d\sigma_\xi = \frac{1}{|\Omega(x)|} \int_{B(t)} \psi(t,x+\xi)\gamma_\Omega(\xi)d\sigma_\xi, \tag{3.1}
$$

where $B(t)$ is the configuration of the system at time $t$, and $\gamma_\Omega$ is the characteristic function of the REV, i.e.,

$$
\gamma_\Omega(\xi) = \begin{cases} 
1 & \forall \xi \in \Omega(x) \cap B(t) \\
0 & \text{elsewhere.}
\end{cases} \tag{3.2}
$$

It should be noted that, although the point $x$ can be made to vary continuously within the space occupied by the system, the size of the REV does not depend on time and physical coordinates.

- The **apparent volume average**

$$
\langle \psi \rangle_n(t,x) = \frac{1}{|\Omega(x)|} \int_{\Omega_n(t,x)} \psi(t,x+\xi)d\sigma_\xi = \frac{1}{|\Omega(x)|} \int_{\Omega(t,x)} \psi(t,x+\xi)\gamma_n(t,x+\xi)d\sigma_\xi = \langle \psi \rangle_{\Omega_n}(t,x), \tag{3.3}
$$

where $n$ is a phase index (i.e., $n = F$ for the fluid phase, and $n = S$ for the solid phase), $\langle \cdot \rangle_n$ means that the average is calculated over the domain $\Omega_n(t,x)$, i.e., the portion of the REV centred at $x$ and occupied by the $n$-th phase at time $t$, and $\gamma_n$ is the characteristic function associated with $\Omega_n(t,x)$, i.e.,

$$
\gamma_n(t,x+\xi) = \begin{cases} 
1 & \forall r = x+\xi \in \Omega_n(t,x) \\
0 & \text{elsewhere.}
\end{cases} \tag{3.4}
$$

- The **intrinsic volume average**
where the macroscopic field $\phi_n$ represents the volume fraction of the $n$-th phase, and is defined by

$$
\phi_n(t, x) = \frac{1}{|\Omega_n(t, x)|} \int_{\Omega_n(t, x)} \phi_n(t, x) d\Omega \quad \text{and} \quad \phi_n(t, x) = \frac{1}{|\Omega_n(t, x)|} \int_{\Omega_n(t, x)} \phi_n(t, x) d\Omega,
$$

where (3.5)

The mass average with respect to the $n$-th phase

$$
\psi_n(t, x) = \frac{1}{\phi_n(t, x)} \int_{\Omega_n(t, x)} \psi_n(t, x + \xi)d\sigma = \frac{1}{\phi_n(t, x)} \int_{\Omega_n(t, x)} \psi_n(t, x + \xi)d\sigma = \frac{\Omega_n(t, x)}{|\Omega(t, x)|}
$$

(3.6)

The mass average for fluid species

$$
\psi_j(t, x) = \frac{1}{\phi_f(t, x)} \int_{\Omega_f(t, x)} \psi_j(t, x + \xi)d\sigma = \frac{1}{\phi_f(t, x)} \int_{\Omega_f(t, x)} \psi_j(t, x + \xi)d\sigma = \frac{\Omega_f(t, x)}{|\Omega(t, x)|}
$$

(3.7)

(3.8)

If the mass density of the $n$-th phase, $\mu_n$, is constant, the mass average operator (3.7) and the intrinsic volume average operator (3.5) coincide. This situation occurs when the concentration of chemical constituents in water is very low, and the fluid-phase mass density can be approximated by the constant mass density of water.

### 3.2. Upscaling of Microscopic Balance Equations

The macroscopic balance equations of chemical substances (i.e., the constituents of the fluid-phase) and the solid-phase can be obtained by upscaling the microscopic balance laws given in Equations (2.2) and (2.3), respectively. We undertake the upscaling procedure by appealing for two theorems which provide the result of the application of the apparent volume average operator to the time and space derivative of a given microscopic field, respectively [17] [20] [21]. Although these theorems are valid for scalar, vector and tensor fields, for the sake of conciseness we only show here how they apply to the cases we are interested in.

Let $\psi$ and $\Psi$ denote a scalar and a vector field, respectively. The first theorem states that the apparent volume average of the time derivative of $\psi$ is given by

$$
\frac{1}{|\Omega(x)|} \int_{\Omega(x)} \frac{\partial \psi(t, r)}{\partial t} d\sigma_r = \frac{\partial}{\partial t} \left[ \frac{1}{|\Omega(x)|} \int_{\Omega(x)} \psi(t, r) d\sigma_r \right] - \frac{1}{|\Omega(x)|} \int_{\Lambda_{nm}(t, x)} [\psi(t, r) u(t, r)]_n \cdot n_{nm}(t, r) dA_r,
$$

(3.9)

where $\Lambda_{nm}(t, x)$ is the portion of the solid-fluid interface enclosed by the REV.

The second theorem states that the apparent volume average of the divergence of $\Psi$ is given by

$$
\nabla \cdot \Psi(t, r) d\sigma_r = \nabla \cdot \left[ \frac{1}{|\Omega(x)|} \int_{\Omega(x)} \Psi(t, r) d\sigma_r \right] + \frac{1}{|\Omega(x)|} \int_{\Lambda_{nm}(t, x)} \Psi(t, r) dA_r,
$$

(3.10)

This result can be alternatively stated by introducing the Representative Elementary Area (REA) $A$, i.e., the boundary of the REV. In this case, Equation (3.10) becomes
\[
\frac{1}{|\Omega(x)|} \int_{\Omega_x(t,x)} \nabla_r \cdot \mathbf{\Psi}(t,r) d\sigma_r = \frac{1}{|\Omega(x)|} \int_{\Omega_F(x)} [\nabla_r \cdot \mathbf{\Psi}(t,r)] \gamma_F(t,r) d\sigma_r \\
= \frac{1}{|\Lambda(x)|} \int_{\Lambda_F(x)} \mathbf{\Psi}(t,r) \gamma_F(t,r) \cdot n(t,r) dA_r \\
+ \frac{1}{|\Omega(x)|} \int_{\Omega_{mF}(t,x)} \mathbf{\Psi}(t,r) \cdot n_{nm}(t,r) dA_r. \tag{3.11}
\]

The proofs of Equations (3.9), (3.10) and (3.11) can be found in [17] [21].

By using theorems (3.9)-(3.11) to upscale Equations (2.2) and (2.3), we obtain

\[
\frac{\partial}{\partial t} \left[ \frac{1}{|\Omega_F|} \int_{\Omega_F} \mu_j \psi_j d\sigma_r \right] + \nabla_x \cdot \left[ \frac{1}{|\Omega_F|} \int_{\Omega_F} \mu_j \psi_j \mu_j d\sigma_r \right] + \left[ \frac{1}{|\Lambda_F|} \int_{\Lambda_F} \gamma_F \mathbf{3}_j \cdot n dA_r \right] \\
= \frac{1}{|\Omega_F|} \int_{\Omega_F} \mu_j (f_j + g_j) d\sigma_r + \frac{1}{|\Lambda_{FS}|} \int_{\Lambda_{FS}} [\mu_j \psi_j (v - u_j) - \mathbf{3}_j] dA_r, \tag{3.12}
\]

and

\[
\frac{\partial}{\partial t} \left[ \frac{1}{|\Omega_S|} \int_{\Omega_S} \mu_S \psi_S d\sigma_r \right] + \nabla_x \cdot \left[ \frac{1}{|\Omega_S|} \int_{\Omega_S} \mu_S \psi_S u_S d\sigma_r \right] + \left[ \frac{1}{|\Lambda_S|} \int_{\Lambda_S} \gamma_S \mathbf{3}_s \cdot n dA_r \right] \\
= \frac{1}{|\Omega_S|} \int_{\Omega_S} \mu_S (f_s + g_s) d\sigma_r + \frac{1}{|\Lambda_{SF}|} \int_{\Lambda_{SF}} [\mu_S \psi_S (v - u_S) - \mathbf{3}_s] dA_r. \tag{3.13}
\]

Here, the dependence of \( \Omega, \Omega_F, \Omega_S, \Lambda_{FS} \) and \( \Lambda_{SF} \) on time, \( t \), and space coordinate \( x \), and the dependence of all the other quantities on time and space coordinate \( r \) have been omitted for the sake of conciseness. By employing the average operators, Equations (3.12) and (3.13) can be written as

\[
\frac{\partial}{\partial t} \left[ \phi_F \left\{ \mu_j \right\}_F^F \psi_j \right] + \nabla_x \cdot \left[ \phi_F \left\{ \mu_j \right\}_F^F \psi_j \tilde{u}_j \right] + \nabla_x \cdot \mathbf{J}_{\psi_j} \\
= \phi_F \left\{ \mu_j \right\}_F^F \left[ f_j \psi_j + \bar{f}_j \psi_j + E_j (\mu_j \psi_j) + \mathbf{R}_j \psi_j \right], \tag{3.14}
\]

and

\[
\frac{\partial}{\partial t} \left[ \phi_S \left\{ \mu_S \right\}_S^S \psi_S \right] + \nabla_x \cdot \left[ \phi_S \left\{ \mu_S \right\}_S^S \psi_S \tilde{u}_S \right] + \nabla_x \cdot \mathbf{J}_{\psi_S} \\
= \phi_S \left\{ \mu_S \right\}_S^S \left[ f_S \psi_S + \bar{f}_S \psi_S + E_S (\mu_S \psi_S) + \mathbf{R}_S \psi_S \right], \tag{3.15}
\]

respectively. In these equations, the vectors \( \mathbf{J}_{\psi_j} \) and \( \mathbf{J}_{\psi_S} \) are macroscopic fluxes, and are defined by the relations

\[
\mathbf{J}_{\psi_j} \cdot \mathbf{N} = \frac{1}{|\Lambda|} \int_{\Lambda} [\mathbf{3}_{\psi_j} - \mu_j \tilde{u}_j] \cdot n \gamma_F dA_r, \tag{3.16}
\]

\[
\mathbf{J}_{\psi_S} \cdot \mathbf{N} = \frac{1}{|\Lambda|} \int_{\Lambda} [\mathbf{3}_{\psi_S} - \mu_S \psi_S \tilde{u}_S] \cdot n \gamma_S dA_r,
\]

where \( \mathbf{N} \) is a unit vector normal to the REA, and the fields \( \tilde{u}_j = u - \bar{u}_j \), \( \tilde{u}_S = u_S - \bar{u}_S \), \( \psi_S = \psi - \bar{\psi}_S \), and \( \bar{\psi}_j = \psi_j - \bar{\psi}_j \) are the fluctuations of \( u_j \), \( u_S \), \( \psi_j \), and \( \psi_S \), respectively, relative to the mass average operators defined in Equations (3.8) and (3.7). Moreover, quantities \( E_j (\mu_j \psi_j) \), \( E_S (\mu_S \psi_S) \), \( \mathbf{R}_j \), and \( \mathbf{R}_S \) are exchange terms describing the transfer of the properties \( \psi_j \) and \( \psi_S \) across the solid-fluid interface, and are given by
\[ E_j (\mu_j \psi_j) = \frac{1}{\phi_F} \frac{1}{\Omega} \int_{\Lambda_{FS}} \left[ \mu_j \psi_j (v - u_j) \right]_{FS} \cdot n_{FS} d \Lambda_r, \]
\[ E_S (\mu_S \psi_S) = \frac{1}{\phi_S} \frac{1}{\Omega} \int_{\Lambda_{SF}} \left[ \mu_S \psi_S (v - u_S) \right]_{SF} \cdot n_{SF} d \Lambda_r, \]

and
\[ R_{\psi_j} = \frac{1}{\phi_F} \frac{1}{\Omega} \int_{\Lambda_{FS}} \left[ \mathcal{F}_{\psi_j} \right]_{FS} \cdot n_{FS} d \Lambda_r, \]
\[ R_{\psi_S} = \frac{1}{\phi_S} \frac{1}{\Omega} \int_{\Lambda_{SF}} \left[ \mathcal{F}_{\psi_S} \right]_{SF} \cdot n_{SF} d \Lambda_r. \]

The first pair of equations accounts for the transfer of \( \psi_j \) and \( \psi_S \) due to the relative motion between the interface and the \( j \)-th constituent, and between the interface and the solid-phase, respectively, while the second pair describes the transfer due to the presence of the microscopic currents \( \mathcal{F}_{\psi_j} \) and \( \mathcal{F}_{\psi_S} \), respectively.

4. Macroscopic Formulation of Balance Laws

In this section, we show the balance laws which characterize the macroscopic thermodynamic behaviour of porous materials, and we outline the thermodynamic considerations on which the Constitutive Framework is established. Only the results which are crucial for our purposes will be discussed. The complete derivation of the theory on which this section is based can be found in [5] [20] [21].

The average operators given in Equations (3.1)-(3.8), the definition of volume fraction (cfr. Equation (3.6)), and the theorems (3.9)-(3.11) allow for determining the upscaled counterparts of the balance laws of mass, momentum, energy, and entropy, which are employed for the thermodynamic description of chemical substances and solid-phase at the pore scale (cfr. Equations (2.4)-(2.11)). Each macroscopic balance law has to be written both for the solid-phase and the \( N+1 \) chemical constituents of the fluid-phase, and is obtained by substituting the appropriate thermodynamic variables (selected from Table 2 and Table 1, respectively) into Equations (3.14) and (3.15), respectively. However, since our concern is the interaction between the chemical substances and the mixture, we find it convenient to replace the \( N+1 \) equations, which characterize the balance of a given physical quantity associated with chemical agents, by a set consisting of \( N \) equations referring to chemical agents, and an equation involving the mean thermodynamic properties of the fluid-phase as a whole. This equation is found by summing the \( N+1 \) upscaled balance laws of chemical species, and introducing appropriate definitions for bulk properties of the fluid-phase.

The macroscopic balance equations have to be determined by accounting for some constraints on the quantities describing the exchange processes occurring both inside the fluid-phase and between the fluid- and solid-phase.

4.1. Constraints on Exchange Terms

For the macroscopic description of the porous material to be consistent with the pore scale formulation, upscaled balance equations must be accompanied by two set of restrictions. The first set provides the constraints on the macroscopic quantities describing the exchange terms among chemical species \textit{inside} the fluid-phase, and is obtained by averaging Equations (2.12), i.e.,
\[ \sum_{j=0}^{N} \phi_F \rho_j \pi_j = 0, \quad \sum_{j=0}^{N} \left[ \phi_F \rho_j \pi_j v_j + \phi_F \rho_j A_j \right] = 0, \]
\[ \sum_{j=0}^{N} \phi_F \rho_j \left[ \pi_j \left( U_j + \frac{1}{2} v_j \cdot v_j \right) + A_j \cdot v_j + Q_j \right] = 0, \quad \sum_{j=0}^{N} \phi_F \rho_j (\pi_j S_j + \Xi_j) = 0. \]
Here, we denoted the averaged quantities by the familiar notation
\[ \rho_j = \langle \mu_j \rangle_F, \quad \rho_S = \langle \mu_S \rangle_S, \quad v_j = \bar{u}_j, \quad S_j = \bar{\eta}_j, \]
and we introduced the macroscopic internal energy of the \( j \)-th constituent, \( U_j \), and the exchange terms of momentum, \( A_j \), energy, \( Q_j \), and entropy, \( \Xi_j \). These quantities are given by
\[ A_j = \bar{a}_j + \bar{\eta}_j \bar{u}_j, \quad U_j = \bar{E}_j + \frac{1}{2} \bar{u}_j \cdot \bar{u}_j, \]
\[ Q_j = \bar{e}_j + \bar{\eta}_j \bar{u}_j + \bar{\eta}_j \left( \bar{E}_j + \frac{1}{2} \bar{u}_j \cdot \bar{u}_j \right), \quad \Xi_j = \bar{\xi}_j + \bar{\eta}_j \bar{u}_j. \]

The second set of constraints comes from the average of the interfacial equations (2.13) and (2.14), and imposes restrictions on the exchange terms between the fluid- and the solid-phase, i.e.,
\[ \sum_{j=0}^{N} (\phi_F \rho_j M_j) + \phi_S \rho_S \Pi_S = 0, \]
\[ \sum_{j=0}^{N} \phi_F \rho_j (M_j v_j + p_j) + \phi_S \rho_S (\Pi_S v_S + m_S) = 0, \]
\[ \sum_{j=0}^{N} \left[ \phi_F \rho_j \left( M_j \left( U_j + \frac{1}{2} v_j^2 \right) + p_j \cdot v_j + p_j \right) + \phi_S \rho_S \left( \Pi_S \left( U_S + \frac{1}{2} v_S^2 \right) + m_S \cdot v_S + W_S \right) \right] = 0, \]
\[ \sum_{j=0}^{N} \phi_F \rho_j (M_j S_j + H_j) + \phi_S \rho_S (\Pi_S S_S + \Phi_S) \geq 0. \]

The quantities \( M_j, p_j, P_j, \) and \( H_j \) are given by
\[ M_j = \frac{1}{\phi_F \rho_j} \left[ \int_{\partial S} \mu_j [v - u_j] \cdot n_{FS} dA \right], \]
\[ p_j = \frac{1}{\phi_F \rho_j} \left[ \int_{\partial S} \mu_j \bar{u}_j \otimes (v - u_j) + \Sigma_j \right] \cdot n_{FS} dA, \]
\[ P_j = \frac{1}{\phi_F \rho_j} \left[ \int_{\partial S} \mu_j \bar{E}_j + \frac{1}{2} \bar{u}_j \cdot \bar{u}_j (v - u_j) + \Sigma_j \cdot \bar{u}_j + q_j \right] \cdot n_{FS} dA, \]
\[ H_j = \frac{1}{\phi_F \rho_j} \left[ \int_{\partial S} \mu_j \bar{\xi}_j (v - u_j) + \varphi_j \right] \cdot n_{FS} dA, \]
and represent the rate of mass, momentum, energy, and entropy, respectively, transferred by the fluid to the solid at the fluid-solid interface. These terms are compensated for by the uptake of mass, \( \Pi_S \), momentum, \( m_S \), energy, \( W_S \), and entropy, \( \Phi_S \), experienced by the solid phase, i.e.,
\[ \Pi_S = M_S = \frac{1}{\phi_S \rho_S} \left[ \int_{\partial S} \mu_S [v - u_S] \right] \cdot n_{SF} dA, \]
\[ m_S = p_S = \frac{1}{\phi_S \rho_S} \left[ \int_{\partial S} \mu_S \bar{u}_S \otimes (v - u_S) + \Sigma_S \right] \cdot n_{SF} dA, \]
\[ W_S = P_S = \frac{1}{\phi_S \rho_S} \left[ \int_{\partial S} \mu_S \left( \bar{E}_S + \frac{1}{2} \bar{u}_S \cdot \bar{u}_S \right) (v - u_S) + \Sigma_S \cdot \bar{u}_S + q_S \right] \cdot n_{SF} dA, \]
\[ \Phi_S = \Pi_S = \frac{1}{\phi_S \rho_S} \left[ \int_{\partial S} \mu_S \bar{\xi}_S (v - u_S) + \varphi_S \right] \cdot n_{SF} dA. \]

The conditions (4.4)-(4.7) must be respected because the mixture is assumed to be closed, i.e., no net production or annihilation of total mass, momentum, and energy is present in the mixture. Moreover,
the saturation condition, $\phi_F + \phi_S = 1$, is assumed to hold true in deriving these relations as well as in the rest of the paper.

4.2. Macroscopic Balance Equations of the Mixture

The quantities defined in Equations (4.3) and (4.8)-(4.11) represent the production or decay terms having intrinsic origin, and the contributions due to the interfacial transfer, respectively. Therefore, the global exchange terms of mass, momentum, energy, and entropy which concern the $j$-th constituent of the fluid-phase, can be written as $\Pi_j = \Pi_j^f + M_j$, $m_j = A_j + p_j$, $W_j = Q_j + P_j$, and $\Phi_j = \Xi_j + H_j$, respectively. This consideration and the constraints given in Equations (4.1) allow for introducing the exchange terms associated with the fluid-phase as a whole, i.e.,

- **Exchange of mass, $\Pi_F$**
  \[ \Pi_F = \sum_{j=0}^{N} c_j \Pi_j = \sum_{j=0}^{N} c_j M_j, \]  (4.16)

- **Exchange of momentum, $m_F$**
  \[ m_F = \sum_{j=0}^{N} c_j (p_j + M_j v_{jF}) = -\Pi_F v_F + \sum_{j=0}^{N} c_j (\Pi_j v_{jS} + m_j), \]  (4.17)

- **Exchange of energy, $W_F$**
  \[ W_F = \sum_{j=0}^{N} c_j \left[ p_j + p_j \cdot v_{jF} + M_j \left( U_j - U_{PF} \right) + \frac{1}{2} v_{jF} \cdot v_{jF} \right] \]
  \[ = -m_F \cdot w - \Pi_F \left( U_F + \frac{1}{2} w^2 \right) + \sum_{j=0}^{N} c_j \left[ W_j + M_j \cdot v_{jS} + \Pi_j \left( U_j + \frac{1}{2} v_{jS}^2 \right) \right], \]  (4.18)

- **Exchange of entropy, $\Phi_F$, and entropy net production, $\Gamma_F$**
  \[ \Phi_F = \sum_{j=0}^{N} c_j \left[ H_j + M_j (S_j - S_F) \right], \]  (4.19)
  \[ \Gamma_F = \sum_{j=0}^{N} c_j \Gamma_j. \]  (4.20)

In Equations (4.16)-(4.20), $c_j = \rho_j / \rho_F$ denotes the mass fraction of the $j$-th chemical substance, $\rho_F = \sum_{j=0}^{N} \rho_j$ and $v_F = \sum_{j=0}^{N} c_j v_j$ are the overall mass density and velocity of the fluid-phase, $v_{jF} = v_j - v_F$ and $v_{jS} = v_j - v_S$ are the velocities of the $j$-th constituent relative to the fluid- and solid-phase, respectively, $U_F = \sum_{j=0}^{N} c_j (U_j + \frac{1}{2} v_{jF}^2)$ and $S_F = \sum_{j=0}^{N} c_j S_j$ are the overall internal energy and entropy of the fluid-phase, respectively, and $w = v_F - v_S$ is the velocity of the fluid relative to the solid. Moreover, we note that the $v_{jF}$’s must respect the constraint $\sum_{j=0}^{N} c_j v_{jF} = 0$.

By using the exchange terms given in Equations (4.16) and (4.17), assuming that the microscopic external supplies of momentum, $g_j$ and $g_S$, are only due to gravity (i.e., $g_j = g_S = g$), and regarding these contributions as negligible, the macroscopic balance equations of mass and momentum of the system can be written as

**Mass Balance Law**

- **Solid-phase**
  \[ \frac{\partial}{\partial t} (\phi_S \rho_S) + \nabla \cdot (\phi_S \rho_S v_S) = \phi_S \rho_S \Pi_S, \]  (4.21)

- **Fluid-phase**
  \[ \frac{\partial}{\partial t} (\phi_F \rho_F) + \nabla \cdot (\phi_F \rho_F v_F) = \phi_F \rho_F \Pi_F, \]  (4.22)

**Chemical Constituents**
\[
\frac{\partial}{\partial t}(\phi_F \rho_F c_k) + \nabla \cdot (\phi_F \rho_F c_k v_k) = \phi_F \rho_F c_k \Pi_k, \quad k = 1, \ldots, N, \tag{4.23}
\]

**Momentum Balance Law**

- **Solid-phase**
  \[\phi_S \rho_S \frac{D_S v_S}{Dt} = \nabla \cdot \sigma_S + \phi_S \rho_S \mathbf{m}_S, \tag{4.24}\]

- **Fluid-phase**
  \[\phi_F \rho_F \frac{D_F v_F}{Dt} = \nabla \cdot \sigma_F + \phi_F \rho_F \mathbf{m}_F, \tag{4.25}\]

- **Chemical Constituents**
  \[\phi_F \rho_F c_k \left( \frac{D_k v_k}{Dt} - \frac{D_0 v_0}{Dt} \right) = \left( \nabla \cdot \sigma_k - \frac{c_k}{c_0} \nabla \cdot \sigma_0 \right) + \phi_F \rho_F c_k (\mathbf{m}_k - \mathbf{m}_0), \quad k = 1, \ldots, N, \tag{4.26}\]

In Equations (4.24)-(4.26), we introduced the “phase” substantial derivative operators
\[\frac{D_S}{Dt} = \frac{\partial}{\partial t} + \mathbf{v}_S \cdot \nabla, \quad \frac{D_F}{Dt} = \frac{\partial}{\partial t} + \mathbf{v}_F \cdot \nabla, \quad \frac{D_j}{Dt} = \frac{\partial}{\partial t} + \mathbf{v}_j \cdot \nabla, \tag{4.27}\]
and we denoted by \(\sigma_j\), \(\sigma_F\), and \(\sigma_S\) the Cauchy stress tensors of the \(j\)-th chemical constituent, and the fluid- and solid-phase, respectively. Tensors \(\sigma_j\) and \(\sigma_S\) are found through the upscaling procedure, and are defined by
\[\sigma_j : \mathbf{N} = \frac{1}{|A|} \int_A \gamma_F (\Sigma_j - \mu_j \mathbf{u}_j \otimes \mathbf{u}_j) \, dA, \quad \sigma_S : \mathbf{N} = \frac{1}{|A|} \int_A \gamma_S (\Sigma_S - \mu_S \mathbf{u}_S \otimes \mathbf{u}_S) \, dA, \tag{4.28}\]
while tensor \(\sigma_F\) is given by
\[\sigma_F = \sum_{j=0}^N (\sigma_j - \phi_F \rho_F c_j \mathbf{v}_{jF} \otimes \mathbf{v}_{jF}). \tag{4.29}\]

**Energy Balance Law and Clausius-Duhem Inequality**

Before going through energy balance laws, we note that, if all chemical substances are at the same temperature, \(\theta_F\), the energy balance of the fluid-phase can be expressed by considering the overall balance law of the fluid-phase energy only. Moreover, since the solid may be at a temperature \(\theta_S\), different from \(\theta_F\), the solid-phase energy balance equation has to be considered in order to accomplish the study of the overall energy balance of the mixture. However, if the solid and the fluid can be assumed to be in thermal equilibrium (i.e., \(\theta_S = \theta_F = \theta\)), the treatment becomes simpler. Under this hypothesis, it suffices to study only one energy equation for the mixture as a whole. In the absence of microscopic external supplies of energy, \(h_j\) and \(h_S\), and entropy, \(s_j\) and \(s_S\), this equation reads
\[\rho \frac{D_u}{Dt} + \nabla \cdot (\phi_F \rho_F U \mathbf{w}) - \sigma_F : \nabla v_F - \sigma_S : \nabla v_S - \nabla \cdot \mathbf{Q} + \phi_F \rho_F \left( \mathbf{m}_F \cdot \mathbf{w} + \frac{1}{2} \Pi_F \mathbf{w}^2 \right) = 0, \tag{4.30}\]
where \(\rho = \phi_F \rho_F + \phi_S \rho_S\), \(U = \rho^{-1} [\phi_F \rho_F U_F + \phi_S \rho_S U_S]\), and \(\mathbf{Q} = \mathbf{Q}_F + \mathbf{Q}_S\) denote the mixture overall mass density, internal energy, and heat flux vector, respectively, and \(\mathbf{Q}_F\) is given by
\[\mathbf{Q}_F = \sum_{j=0}^N \left[ \mathbf{Q}_j + \sigma_j \mathbf{v}_{jF} - \phi_F \rho_F \left( U_j + \frac{1}{2} v_{jF} \cdot v_{jF} \right) v_{jF} \right]. \tag{4.31}\]

In order to show that the theory exposed so far is consistent with the Second Law of Thermodynamics, we invoke the Clausius-Duhem inequality, and require that the net entropy
production of the mixture as a whole, \( \rho \Gamma = \phi_F \rho_F \Gamma_F + \phi_S \rho_S \Gamma_S \), is greater than or equal to zero, i.e., \( \rho \Gamma \geq 0 \). It can be proved that the Clausius-Duhem inequality can be written as

\[
0 \leq \rho \Gamma \geq 0 \quad \text{(4.32)}
\]

where \( I \) is the identity tensor, and \( A_j = U_j - \theta S_j \), \( A_F = U_F - \theta S_F = \sum_{j=0}^{N} c_j A_j \), and \( A_S = U_S - \theta S_S \) are the Helmholtz free energy densities of chemical constituents, fluid-phase and solid-phase, respectively. We note that the last term in the Clausius-Duhem inequality (4.32) implies that the overall entropy flux does not reduce to the Coleman-Noll definition.

Eventually, we remark that in order to obtain the Clausius-Duhem inequality as in Equation (4.32), we need to introduce the macroscopic fluxes of entropy

\[
\Phi_j = \frac{D_j}{Dt} + \sigma_S : \nabla \Phi_S - \phi_F \rho_F m_F \cdot \omega - \phi_F \rho_F \left[ (A_F - A_S) + \frac{1}{2} \omega^2 \right] \Pi_F
\]

and assume that they are related to the heat flux vectors \( Q_j \) and \( Q_S \) through the relations \( \theta F_j = Q_j \) and \( \theta F_S = Q_S \), respectively.

### 4.3. Constitutive Framework

Since the balance equations presented so far are not sufficient for the macroscopic thermodynamic characterization of the porous material, we need to establish a constitutive framework, which has to be consistent with the Second Law of Thermodynamics and in accordance with the continuum theory of Mixtures [10, 11]. In order to do that, we exploit the Clausius-Duhem inequality (4.32), and select the appropriate independent constitutive variables on the basis of specific hypotheses about the behaviour of the fluid components, the fluid-phase, and the solid-phase.

Our first hypothesis is that the solid-phase behaves as a thermo-elastic material. The elastic deformation of the solid is described by means of the solid-phase motion \( \chi_S \) (also called \( S \)-motion [9, 22]). This field maps each material point \( X \) in the reference configuration of the mixture, \( B_R \), onto the portion of space occupied by the mixture at time \( t \), \( B(t) \), i.e., there exists a point \( x \in B(t) \), such that \( x = \chi_S(t, X) \), for every \( X \in B_R \). The \( S \)-motion is such that its time derivative equals the solid-phase velocity, i.e., \( \nu(t,x) = \frac{\partial \chi_S}{\partial t}(t,X) \). We also assume that the solid-phase is incompressible, i.e., its mass density, \( \rho_S \), is constant throughout the motion \( (D_S \rho_S /Dt = 0) \). This assumption is acceptable as long as we deal with a saturated biological porous material [23]. 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 [23, 24].

By virtue of the hypotheses stated above, the variables to be treated as unknowns are the fluid-phase mass density, \( \rho_F \), and volume fraction, \( \phi_F \), temperature, \( \theta \), the \( S \)-motion, \( \chi_S \), the relative
velocity, $w$, the mass fractions of constituents, $c_k$, and velocities of constituents relative to the fluid-phase, $v_{kF}$. In these last two terms, the index $k$ runs from 1 to $N$.

It is possible to prove [5] that, by accounting for the restrictions imposed by the principles of material frame indifference and admissibility, the exploitation of the Clausius-Duhem inequality (4.32), and the choice of the above mentioned unknowns enable us to express the Helmholtz free energy densities as

$$A_F = A_S \left( \rho_F , c, \theta \right), \quad A_S = A_S \left( E_S , \theta, X \right), \quad A_k - A_0 = A_{k0} \left( \rho_F, c_k, \theta \right),$$

where $E_S = \frac{1}{2} \left( F_S F_S^T - I_R \right)$ is the Green-Lagrange strain tensor of the solid-phase, $I_R$ is the identity tensor in the reference configuration, $B_R$, and $F_S = \nabla_X \chi_S$ is the solid-phase deformation tensor. By virtue of these relations, the entropy of the mixture is given by

$$\rho_S = -\phi_F \rho_F \frac{\partial A_F}{\partial \theta} - \phi_S \rho_S \frac{\partial A_S}{\partial \theta},$$

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

$$\sigma_F = -\phi_F \rho_F I - \phi_F \rho_F \sum_{j=0}^{N} c_j v_{jF} \otimes v_{jF}, \quad \sigma_S = -\phi_S \rho_F I + \sigma_S^el.$$  

where the thermodynamic pressure, $p_F$, is given by

$$p_F = \rho_F \frac{\partial A_F}{\partial \rho_F},$$

and the tensor $\sigma_S^el$ represents the elastic part of $\sigma_S$. By expressing the solid-phase Helmholtz free energy density as a function of $F_S$, and introducing the first Piola-Kirchhoff stress tensor,

$$P_S^el = J_S \phi_S \frac{\partial A_S}{\partial F_S},$$

where $J_S = \det(F_S)$, tensor $P_S^el$ can be written as

$$\sigma_S^el = \frac{1}{J_S} P_S^el F_S^{-T}.$$  

We note that the term $-\phi_F \rho_F \sum_{j=0}^{N} c_j v_{jF} \otimes v_{jF}$ represents the non-equilibrium part of the fluid-phase stress tensor, $\sigma_F$.

Equations (4.34) enable us to define the “relative” chemical potentials

$$Y_{k0} = Y_k - Y_0 = \frac{\partial A_F}{\partial c_k}, \quad k = 1, ..., N,$$

$Y_k$ and $Y_0$ being the chemical potentials of the $k$-th chemical constituent and water, respectively, and the Cauchy stress tensors

$$\sigma_{k0} = \sigma_k - \begin{pmatrix} \frac{c_k}{c_0} \end{pmatrix}_0 \sigma_0 = -\phi_F \rho_F c_k (Y_{k0} - A_{k0}) I, \quad k = 1, ..., N.$$  

Finally, the momentum exchange terms, $\phi_F \rho_F m_F$ and $\phi_F \rho_F c_k (m_k - m_0)$, can be written as

$$\phi_F \rho_F m_F = \phi_F \rho_F f_F + p_F \nabla_x \phi_F,$$

$$\phi_F \rho_F c_k (m_k - m_0) = \phi_F \rho_F c_k \tilde{f}_k + \nabla_x [\phi_F \rho_F c_k (Y_{k0} - A_{k0})] - \phi_F \rho_F c_k \nabla_x Y_{k0} - \sigma_0 \nabla_x \begin{pmatrix} \frac{c_k}{c_0} \end{pmatrix},$$

where $\phi_F \rho_F f_F$ and $\phi_F \rho_F c_k \tilde{f}_k$ represent dissipative terms describing the drag forces exerted on the fluid-phase and the $k$-th chemical substance, respectively.
By appealing for the constitutive relations written so far, and introducing the relative velocity $v_{kF}$, and the diffusive current $\mathbf{J}_k = \phi_F \rho_F c_k v_{kF}$, we can finally recast the mass and momentum balance laws reported in Equations (4.21)-(4.26) in the form [5]

**Mass Balance Laws**

\[
\frac{\partial}{\partial t}(\phi_S \rho_S) + \nabla \cdot (\phi_S \rho_S \mathbf{v}_S) = \phi_S \rho_S \Pi_S, \quad (4.44)
\]

\[
\frac{\partial}{\partial t}(\phi_F \rho_F) + \nabla \cdot (\phi_F \rho_F \mathbf{v}_F) = \phi_F \rho_F \Pi_F, \quad (4.45)
\]

\[
\frac{\partial}{\partial t}(\phi_F \rho_F c_k) + \nabla \cdot (\phi_F \rho_F c_k \mathbf{v}_F) + \nabla \cdot \mathbf{J}_k = \phi_F \rho_F c_k \Pi_k, \quad k=1,...,N. \quad (4.46)
\]

**Momentum Balance Law**

\[
\phi_S \rho_S \frac{D_S \mathbf{v}_S}{Dt} = -\phi_S \nabla \cdot \mathbf{p}_F + \nabla \cdot \mathbf{\sigma}_{SL} \phi_S - \phi_F \rho_F \mathbf{f}_F - \phi_F \rho_F \Pi_F \mathbf{w}, \quad (4.47)
\]

\[
\phi_F \rho_F \frac{D_F \mathbf{v}_F}{Dt} + \nabla \cdot \left[ \sum_{j=0}^{N} c_j \mathbf{v}_{jF} \otimes \mathbf{v}_{jF} \right] = -\nabla \cdot \mathbf{p}_F + \mathbf{\rho}_F \mathbf{f}_F, \quad (4.48)
\]

\[
\phi_F \rho_F \frac{D_k \mathbf{v}_k}{Dt} - \phi_F \rho_F \frac{D_F \mathbf{v}_0}{Dt} + \nabla \cdot \mathbf{Y}_0 = \mathbf{f}_k, \quad k=1,...,N. \quad (4.49)
\]

For the complete thermodynamic picture of the system to be stated in closed form, Equations (4.44)-(4.49) must be studied together with the energy balance law given in Equation (4.30). However, a further simplification can be achieved by regarding temperature, $\theta$, as constant. By assuming that this is the case, the energy balance law can be disregarded, temperature can be treated as a parameter, and Equations (4.44)-(4.49) become necessary and sufficient conditions for describing the behaviour of the mixture and chemical substances, and the interaction between these substances and the mechanical environment in which the system evolves.

### 5. Determination of the Macroscopic Transport Properties of Chemical Substances

In this section we specialize Equations (4.44)-(4.49) to the macroscopic description of the chemical substances evolving in the interstitial fluid of a porous material of biological interest.

#### 5.1. Determination of the Advection-Diffusion-Reaction Equation

Our aim is to show that, under suitable hypotheses, the macroscale evolution of chemical substances can be treated as an advection-diffusion-reaction process described by the mass balance law (4.46). For this purpose, we start by expressing the dissipative terms $f_F$ and $f_k$ as [5]

\[
f_F = -\mathbf{R}_F \cdot \mathbf{w} + \sum_{i=1}^{N} \mathbf{T}_{FI} \mathbf{v}_{IF}, \quad f_k = \mathbf{R}_k \cdot \mathbf{w} - \sum_{i=1}^{N} \mathbf{T}_{ki} \mathbf{v}_{IF}, \quad (5.1)
\]

where the second-order tensors $\mathbf{R}_F$, $\mathbf{T}_{FI}$, $\mathbf{R}_k$, and $\mathbf{T}_{ki}$ are called material coefficients, and depend on $\rho_F$, $\phi_F$, $c_k$, and $\theta$. Since inertial contributions can be neglected for the biological system of interest, substitution of Equations (5.1) into the momentum balance laws (4.48) and (4.49) leads to

\[
-\mathbf{R}_F \cdot \mathbf{w} + \sum_{i=1}^{N} \mathbf{T}_{FI} \mathbf{v}_{IF} = \frac{1}{\rho_F} \nabla \cdot \mathbf{p}_F + \frac{1}{\rho_F} \nabla \cdot \left( \sum_{j=0}^{N} c_j \mathbf{v}_{jF} \otimes \mathbf{v}_{jF} \right), \quad (5.2)
\]

\[
\mathbf{R}_k \cdot \mathbf{w} - \sum_{i=1}^{N} \mathbf{T}_{ki} \mathbf{v}_{IF} = \nabla \cdot \mathbf{Y}_0, \quad k=1,...,N. \quad (5.3)
\]

Moreover, if the relative velocities $v_{jF}$ are assumed to be small, the non-equilibrium part of the fluid-phase Cauchy stress tensor, $\mathbf{\sigma}_F$, can be disregarded, and the balance laws (5.2) and (5.3) can be treated as a set of $3(N+1)$ linear equations in the $3(N+1)$ unknowns $\mathbf{w}$ and $v_{IF}$. Therefore, after some algebraic manipulations, it is possible to prove that the formal solution of Equations (5.2) and (5.3) is given by
$w = -K_F \nabla x p_F - \left[ B_F \nabla x p_F + \sum_{i=0}^{N} D_{Fi} \nabla x c_i \right], \quad (5.4)$

$J_k = \phi_F \rho_F c_k v_{Fk} = -K_k \nabla x p_F - \left[ B_k \nabla x p_F + \sum_{i=0}^{N} D_{ki} \nabla x c_i \right], \quad (5.5)$

where tensors $B_F$, $B_k$, $D_{Fi}$, and $D_{ki}$ are expressed by the relations

$B_F = \sum_{i=1}^{N} \mathbf{L}_{Fi} \frac{\partial Y_{0i}}{\partial \rho_F}$,  

$B_k = \sum_{i=1}^{N} \mathbf{L}_{ki} \frac{\partial Y_{0i}}{\partial \rho_F}$,  

$D_{Fi} = \sum_{i=1}^{N} \mathbf{L}_{Fi} \frac{\partial Y_{0i}}{\partial c_i}$,  

$D_{ki} = \sum_{i=1}^{N} \mathbf{L}_{ki} \frac{\partial Y_{0i}}{\partial c_i}$,  

and tensors $\mathbf{L}_{Fi}$ and $\mathbf{L}_{ki}$ are related to the material coefficients [5]. We remark that Equations (5.4) and (5.5) represent the generalized macroscopic forms of Darcy’s and Fick’s Law, respectively, and tensors $K_F$, $K_k$, and $D_{Fi}$, $D_{ki}$ can be identified with the permeability, and diffusivity-dispersivity tensors of the fluid-phase and the chemical substances dissolved in interstitial water, respectively. We remark that the definition of the macroscopic diffusivity-dispersivity tensor $D_{ki}$ contains the derivatives of chemical potentials $Y_{0i}$ with respect to the mass fraction $c_i$ of the $i$-th fluid constituent.

This is consistent with the fact that the fluid-phase Helmholtz free energy density, $A_F$, changes when the concentration of a given chemical substance is varied.

We hypothesise that, at the pore scale, all chemical substances are present in the interstitial water at very low concentrations. 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., $\rho_F = \rho_0$. Consequently, Equations (5.4) and (5.5) can be rewritten as

$w = -K_F \nabla x p_F - \sum_{i=0}^{N} D_{Fi} \nabla x c_i$, \hspace{1cm} (5.7)

$J_k = -K_k \nabla x p_F - \sum_{i=0}^{N} D_{ki} \nabla x c_i$, \hspace{1cm} (5.8)

and the fluid can be considered as incompressible, i.e., $D_F \rho_F / Dt = 0$. Moreover, by assuming that the fluid is macroscopically inviscid, its mass density, $\rho_F$, can be replaced by the thermodynamic pressure, $p_F$, in the list of unknowns treated as independent constitutive variables.

Equations (5.7) and (5.8) can be further simplified by requiring that, in the limit of very low concentrations of chemical substances, tensors $D_{Fi}$ tend towards the null tensor, tensors $D_{ki}$ vanish when indices $k$ and $i$ are different, and pressure effects on the diffusive current, $J_k$, are negligible. By employing these approximations, we re-obtain the “classical” expressions of Darcy’s and Fick’s Laws, i.e.,

$w = -K_F \nabla x p_F$, \hspace{1cm} (5.9)

$J_k = -D_k \nabla x c_k$. \hspace{1cm} (5.10)

Here, tensors $D_k$ replace the tensors $D_{ki}$ featuring in Equation (5.8).

Equations (5.9) and (5.10) establish a “constitutive” relation between the relative velocity $w$, and pressure $p_F$, and between the diffusive current, $J_k$, and the mass fraction $c_k$ of the $k$-th chemical constituent. Vice versa, this result, the unknowns are the volume fraction $\phi_F$ (or $\phi_F = 1 - \phi_F$), pressure, $p_F$, the $S$-motion, $\chi_S$, and the mass fractions of fluid constituents, $c_j$ ($j = 0, \ldots, N$). These fields are to be determined by solving Equations (4.44), (4.45), (4.46), and (4.47), which can now be rearranged as

$\frac{\partial}{\partial t} (\phi_F \rho_F) + \nabla \cdot (\phi_F \rho_F v_F) = \phi_F \rho_F \Pi_F$, \hspace{1cm} (5.11)

$\frac{\partial}{\partial t} (\phi_F \rho_F) + \nabla \cdot (\phi_F \rho_F v_F) = \phi_F \rho_F \Pi_F$, \hspace{1cm} (5.12)
\[
\frac{\partial}{\partial t}(\phi_F \rho_F c_k) + \nabla \cdot (\phi_F \rho_F c_k \mathbf{v}_F) = \nabla \cdot \left[D_k \nabla c_k\right] + \phi_F \rho_F c_k \Pi_k, \quad k = 1, \ldots, N, \tag{5.13}
\]
\[
\nabla \cdot \mathbf{j}_F^d = [I - \phi_F \rho_F \Pi_F \mathbf{K}_F] \nabla \cdot \mathbf{j}_F. \tag{5.14}
\]

These are the “equations of motion” which completely govern the dynamic of the system. We remark that, although \(N+1\) mass fractions have to be determined, it suffices to have \(N\) mass balance equations of the kind (5.13) because of the constraint \(\sum_{j=0}^{N} c_j = 1\).

Equation (5.13) 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, \(\phi_F \rho_F c_k \mathbf{v}_F\), the Fick-type diffusive current, \(-D_k \nabla c_k\), and the reaction term, \(\phi_F \rho_F c_k \Pi_k\), we refer to Equation (5.13) as to an advection-diffusion-reaction equation.

5.2. An Alternative Formulation of Macroscopic Transport

Although in this paper we determine the transport coefficients, \(\mathbf{v}_F\), \(D_k\), and \(\Pi_k\), on the basis of a constitutive characterization of the tissue valid at the macroscale (i.e., at the scale at which measurements are made), we remark that these quantities can also be evaluated by following other “philosophies”. While the procedure shown in the previous sections does not give, or need, any information about the microscopic evolution of chemical agents, other Authors prefer to make a constitutive “guess” at the pore scale, and obtain the macroscopic description of transport by upscaling the microscopic balance equations and the constitutive relations simultaneously. This approach is widely employed for upscaling advective-diffusive-reactive processes in periodic porous materials [14] [15] [25]-[27] (in this case macroscopic equations are obtained through the Theory of Homogenization), and is also used in biological tissues with constant porosity [28]. These methods are based on the assumption that, at the pore scale, the particles of a given solute behave as a Brownian system.

Under this hypothesis, the microscopic mass balance law of the solute, having mass fraction \(\kappa\), is allowed to contain the divergence of the Fick-type current \(\mathbf{\zeta} = -\mu_0 D_m \nabla \kappa\), where \(\mu_0\) is the mass density of water and \(D_m\) is molecular diffusivity (assumed to be a scalar quantity by virtue of the isotropy of the hosting fluid). Then, by enforcing the upscaling procedure, it is possible to obtain an advection-diffusion-reaction equation representing the macroscopic description of a Brownian process. In this case, the reaction term describes the exchange of the solute between the fluid- and the solid-phase, and consists of two contributions: i) the contribution \(\kappa (\mathbf{v} - \mathbf{u})\) accounts for the drift given by the relative motion of the fluid and the fluid-solid interface; and ii) the contribution \(\mu_0^{-1} \mathbf{\Sigma}^\ell \cdot \mathbf{n}_F\) is the component of the diffusive current across the fluid-solid interface. In some cases, this term can be expressed through the boundary condition [28]

\[
\mu_0^{-1} \mathbf{\Sigma}^\ell \cdot \mathbf{n}_F = \hat{\lambda} (\kappa - \kappa^{(in)}), \tag{5.15}
\]

where \(\kappa^{(in)}\) is the mass fraction of the solute inside the solid phase, and \(\hat{\lambda}\) is a quantity called mass transfer coefficient, and also the physical dimension of a velocity.

It can also be proven that upscaling the Fick-type current, \(\mathbf{\zeta} = -\mu_0 D_m \nabla \kappa\), leads to

\[
\langle \mu_0^{-1} \mathbf{\Sigma}^\ell \rangle_F = -D_m \langle \nabla \kappa \rangle_F = -D_m \nabla_x \langle \kappa \rangle_F - D_m \left[\frac{1}{|A_F|} \int_{A_F} \kappa^\ell \cdot \mathbf{n}_F dA_r\right]. \tag{5.16}
\]

Moreover, since the surface integral on the right-hand-side can be rewritten by introducing a tensor \(\mathbf{T}\) [28] [29] such that

\[
D_m \left[\frac{1}{|A_F|} \int_{A_F} \kappa^\ell \cdot \mathbf{n}_F dA_r\right] = D_m (\mathbf{T} - \mathbf{I}) \nabla_x \langle \kappa \rangle_F, \tag{5.17}
\]

substitution of Equation (5.17) into Equation (5.16) yields
According to Equation (5.18), the macroscopic version of the Fick-type current features the diffusivity tensor, $D_mT$. The tensor $T$ is called tortuosity tensor, and describes the fact that, in general, the path lines of molecules diffusing throughout a porous material are not parallel to the Fickian diffusive flux, even in the case of an isotropic molecular diffusivity at the microscale [21][28]. This behaviour is due to the presence of the solid-fluid interface, which acts as a barrier to the motion of particles. In principle, the tortuosity tensor obtained in Equation (5.17) is not predicted to be a priori symmetric because its symmetry (or asymmetry) is determined by the microscopic geometry of the pore space only. Therefore, if the overall diffusivity tensor is required to be symmetric, the porous medium has to possess suitable material properties. It can be proven that, for a second order tensor to be symmetric, the porous medium has to be orthotropic (a symmetric second order tensor can always be diagonalized, and a diagonal tensor represents an orthotropic material). When the Theory of Homogenisation is applicable, it is possible to give an explicit form to the tortuosity tensor [25].

Finally, upscaling of the drift term, $\kappa u_F$ ($u_F$ is the fluid-phase velocity at the microscale), yields

$$\left\langle \kappa u_F \right\rangle_F = \left\langle \kappa \right\rangle_F v_F + \left\langle \kappa u_F^F \right\rangle_F,$$

where the first term on the right-hand side represents the macroscopic drift given by the average fluid-phase velocity, $v_F$, and the second term accounts for the microscale fluctuations, $\kappa$ and $u_F^F$, of the mass fraction, $\kappa$, and velocity field, $u_F$, respectively. Although the quantity $\left\langle \kappa u_F^F \right\rangle_F$ can usually be disregarded in biological systems, it may play a non negligible role in other contexts. Indeed, it can be shown that, under certain hypotheses, this term leads to the determination of the eddy diffusivity tensor [21][30][31].

To the best of our knowledge, the theory on which this paper is based (i.e., the theory exposed in sections 2 to 4) and the procedure briefly sketched here do not lead to equivalent results in general. Whereas the former approach does not provide direct insight on the relationship between macroscopic tensor quantities, such as permeability and diffusivity, and the microstructure of the porous material, the latter may turn out to be inconsistent with the macroscopic thermodynamic description of the tissue as a whole. Nevertheless, we believe that the assignment of a constitutive law at the microscale may be useful to enrich the physical insight on the intrinsic nature of the macroscopic transport coefficients featuring in Equation (5.13). For example, the determination of Fick’s Law given in section 5.1. prescribes the quantity $D_k$ to be a symmetric tensor, but does not explicitly take tortuosity into account. On the other hand, Equations (5.17) and (5.18) suggest that, although the tensor $D_k$ featuring in Equation (5.13) is symmetric, it must somehow account for the tortuosity tensor (which is not symmetric in general) in order to reflect how microscopic geometry plays a role on the material symmetries of the porous medium.

In the absence of a microstructural description of the tissue, the tensors defined in Equation (5.6) can only be found through experiments or empirical methods, and no explicit relation between transport properties and the microscopic geometry can be given. The problem of the macroscopic characterization of a tissue on the basis of microstructural considerations is of great interest in Biomechanics. For instance, for the case of articular cartilage, this problem arises when the overall elasticity is described by considerations on the internal morphology of the tissue (e.g., [33]-[34]).

6. Material Form of the “Equations of Motion”
In order to study growth from the point of view of Continuum Physics, it is convenient to write the “equations of motion” (5.11)-(5.14) in material form. This is done by employing the formalism presented in [9][22]. 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 Equation (5.13). In the literature, the study of the transport equation in material form can be found, for example, in [3][13].
6.1. Material Form of Mass and Momentum Balance Laws

In Mixture Theory, the material field $\Psi$ associated with a given physical quantity $\psi$, defined on the domain $B(t) \subset \mathbb{E}$ ($\mathbb{E}$ being the three-dimensional Euclidean space) occupied by the mixture at time $t$, is determined by performing the Piola transformation of $\psi$ with respect to the S-motion, $\chi_S$ [9] [22].

By virtue of the S-motion, for every material point $X \in B_R$, there exists a point $x \in B(t)$, such that $\psi(t, x) = \hat{\psi}(t, X)$. This identity implies that the substantial derivative of $\psi$ with respect to the solid-phase motion, $D_S \psi / Dt$, and the gradient $\nabla_x \psi$ can be written as

$$
\frac{D_S \psi(t, X)}{Dt}(t, x) = \frac{\partial \hat{\psi}(t, X)}{\partial t}, \quad \nabla_x \hat{\psi}(t, X) = F_S^{-T}(t, X) \nabla_x \psi(t, X).
$$

(6.1)

By rearranging Equations (5.11) and (5.12) as

$$
\frac{D_S (\phi_S \rho_S)}{Dt} + \phi_S \rho_S \nabla_x \cdot v_S = \phi_S \rho_S \Pi_S,
$$

(6.2)

$$
\frac{D_S (\phi_F \rho_F)}{Dt} + \phi_F \rho_F \nabla_x \cdot v_F + \nabla_x \cdot (\phi_F \rho_F w) = \phi_F \rho_F \Pi_F,
$$

(6.3)

using the identity

$$
\nabla_x \cdot v_S(t, X) = \frac{1}{J_S(t, X)} \frac{\partial J_S}{\partial t}(t, X),
$$

(6.4)

and accounting for Equation (6.1), the material form of the solid- and fluid-phase mass balance laws is given by

$$
\frac{\partial (\hat{\rho}_S \phi_S^{(R)})}{\partial t} = \hat{\rho}_S \phi_S^{(R)} \hat{\Pi}_S,
$$

(6.5)

$$
\frac{\partial (\hat{\rho}_F \phi_F^{(R)})}{\partial t} + \nabla_x \cdot (\hat{\rho}_F \phi_F^{(R)} W) = \hat{\rho}_F \phi_F^{(R)} \hat{\Pi}_F,
$$

(6.6)

where $\phi_S^{(R)} = J_S \phi_S$ and $\phi_F^{(R)} = J_S \phi_F$ represent the Piola-transform of the volume fractions $\phi_S$ and $\phi_F$, respectively, and vector $W = F_S^{-1} \dot{w}$ is the material form of the relative velocity $w = v_F - v_S$.

By rewriting Equation (5.14) as

$$
\nabla_x \cdot \sigma_{\text{el}} = \nabla_x \rho_F + \phi_F \rho_F \Pi_F \dot{w},
$$

(6.7)

and invoking the definition of the first Piola-Kirchhoff stress tensor given in Equations (4.38) and (4.39), the material form of the solid-phase momentum balance law reads

$$
\nabla_x \cdot P_{\text{el}} = J_S F_S^{-T} \nabla_x \hat{\rho}_F + \hat{\rho}_F \phi_F^{(R)} \hat{\Pi}_F W.
$$

(6.8)

We note that substituting Equation (6.5) into Equation (6.6) yields

$$
J_S \text{tr}[L_S] + \nabla_x \cdot (\phi_F^{(R)} W) = \left(1 - \frac{\hat{\rho}_S}{\hat{\rho}_F}\right) \phi_S^{(R)} \hat{\Pi}_S,
$$

(6.9)

where the tensor $L_S$ is the solid-phase velocity gradient. Equation (6.9) imposes a kinematical constraint on the solid-phase motion, the fluid material filtration velocity, $\phi_F^{(R)} W$, and the mass exchange between phases. This result can also be found, for example, in [7] [35]. In order for Equation (6.9) to hold true it is necessary to require $i)$ the mixture to be closed, i.e., $\phi_S \rho_S \Pi_S + \phi_F \rho_F \Pi_F = 0$, $ii)$ the saturation condition to be fulfilled, i.e., $\phi_S + \phi_F = 1$, and $iii)$ the fluid- and solid-phase to be incompressible. In our opinion, the strongest of these three hypotheses is that the mixture is closed.

Recently, Loret and Simões [23] have presented a model in which a growing biological tissue was described by a thermodynamically open mixture. In a forthcoming paper, we would like to generalize the picture of growth we have given in this work by allowing for a net production of mass for the mixture as whole.
6.2. Material Form of the Advection-Diffusion-Reaction Equation

In order to write the advection-diffusion-reaction equation of chemical substances in material form, we introduce the notation \( k_F F_k C_C \phi \rho = \), and rearrange Equation (5.13) as

\[
\frac{D}{D} C_k \nabla_x v_S + \nabla_x \cdot (C_k W) = \nabla_x \left[ D_k \nabla_x \left( \frac{C_k}{\phi_F \rho_F} \right) \right] + C_k \Pi_k .
\]  

(6.10)

We note that, because of the change of variables \( c_k \mapsto C_k \), the Fick-type current, \( J_k \), becomes

\[
J_k = -\left[ D_k \nabla_x \left( \frac{C_k}{\phi_F \rho_F} \right) \right] = -\left[ D_k \nabla_x C_k - C_k \frac{D_k}{\phi_F \rho_F} \nabla_x (\phi_F \rho_F) \right].
\]  

(6.11)

By performing the Piola-transformation of Equation (6.11), we find that the material counterpart of \( J_k \) is given by

\[
I_k = J_S F_S^{-1} \hat{J}_k = -\left[ D_k \nabla_x \left( \frac{C_k}{\hat{\rho}_F \phi_F^{(R)}} \right) \right] = -\left[ D_k \nabla_x C_k - C_k \frac{D_k}{\hat{\rho}_F \phi_F^{(R)}} \nabla_x (\hat{\rho}_F \phi_F^{(R)}) \right],
\]  

(6.12)

where \( C_k = J_S C_k \) represents the material form of concentration \( C_k \), and tensor \( D_k \) is defined by

\[
D_k = J_S F_S^{-1} \hat{D}_k F_S^{-T} .
\]  

(6.13)

Finally, by substituting Equations (6.12) into Equation (6.10), and regarding the fluid-phase mass density, \( \hat{\rho}_F \), as a constant, we obtain

\[
\frac{\partial C_k}{\partial t} + \nabla_x \cdot (C_k W) = \nabla_x \cdot [A_k \nabla_x C_k - C_k V_k] + C_k \Pi_k ,
\]  

(6.14)

where

\[
A_k = \frac{D_k}{\hat{\rho}_F \phi_F^{(R)}} , \quad V_k = A_k \nabla_x \ln(\phi_F^{(R)}) .
\]  

(6.15)

Equation (6.14) provides the material description of the advective, diffusive and reactive processes undergone by the chemical substances present in the mixture.

By comparing Equation (6.14) with Equation (5.13), we note that, while the advective current \( C_k W \) is simply the material counterpart of \( \phi_F \rho_F c_k \) (this result is prescribed by the kinematical formulation of Mixture Theory based on inverse-motion description [9] [22]), the Piola-transform of the Fick-type current, \( I_k \), requires the introduction of the effective diffusivity tensor, \( A_k \), and the additional drift term, \( V_k \). The presence of these terms is due to the change of variables \( c_k \mapsto C_k \). The term \( V_k \) vanishes identically if, and only if, the Piola transform of the fluid-phase volume fraction, \( \phi_F^{(R)} \), does not depend on material points, \( X \). Since \( \nabla_x \phi_F^{(R)} = \nabla_X J_S - \nabla_X \phi_S^{(R)} \), we conclude that, when growth is considered, this can be true only in the following two special cases: i) neither volume fractions \( \phi_F \) and \( \phi_R \) depend on material points, nor does the determinant of \( F_S \), \( J_S \); ii) the “packing” of material points, ascribable to \( \nabla_X J_S \), is entirely compensated for by the spatial variation of \( \phi_S^{(R)} \).

When these conditions are not respected, the term \( V_k \) 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 between the fluid- and the solid-phase.

The material drift velocity, \( W \), and the effective diffusivity tensor, \( A_k \), depend explicitly on deformation. In the presence of growth, the global mechanical deformation accounts for both the external stimuli and the internal rearrangement of body inhomogeneities and material symmetries [2] [12]. We investigate the role played by the latter contributions on the transport coefficients \( W \) and \( A_k \).

If the solid-phase of the tissue is a thermo-elastic body, the anelastic deformation induced by the development of material inhomogeneities is entirely ascribable to growth, and can be treated by
introducing a growth tensor, \( G \), such that the deformation gradient tensor, \( F_s \), can be multiplicatively decomposed as

\[
F_s = F_{el}G
\]  

(6.16)

where \( F_{el} \) is a purely elastic deformation tensor. Other Authors, in analogy with the Theory of Plasticity, give an alternative decomposition of \( F_s \) based on the definition of a transplant operator, \( K \), i.e.,

\[
F_s = F_{el}K^{-1}
\]  

(6.17)

By virtue of Equation (6.16), the drift velocity, \( W \), and the effective diffusivity tensor, \( A_k \), can be written as

\[
W = F_s^{-1} \hat{w} = G^{-1}W_G
\]  

(6.18)

and

\[
A_k = \frac{D_k}{\hat{\rho}_F} = J_GF_s^{-1} \frac{J_{el} \hat{D}_k}{\hat{\rho}_F} F_s^{-T} = J_GG^{-1} \frac{D_k^{(G)}}{\hat{\rho}_F} G^{-T}
\]  

(6.19)

where \( J_{el} = \det(F_{el}) \), \( J_G = \det(G) \), and the quantities \( W_G = (F_{el}^{-1} \hat{w}) \), and \( D_k^{(G)} = J_{el}F_{el}^{-1} \hat{D}_{el}F_{el}^{-T} \) are relative to an elastically released configuration, \( B_G \), which is obtained by applying the linear map \( G \) to the tangent space, \( T_XB_R \), of \( B_R \), for any \( X \in B_R \). Since the growth tensor, \( G \), varies continuously in time, Equation (6.19) shows how growth may induce the variation in time of the symmetry of the tensor \( D_k \). For instance, if \( D_k \) is isotropic, or transversely isotropic, in the spatial description, it may become fully anisotropic in the reference configuration. This essentially depends on whether the body material symmetries are preserved or destroyed by the global deformation field inside the tissue.

We conclude this section by noting that Equation (6.14) can be made formally equivalent to the transport equation (5.13) by means of the change of variables

\[
C(t, X) \mapsto C(t, X) = \Theta(t, X)e^{\Lambda(t, X)}, \quad \Lambda(t, X) = \frac{1}{2} \ln[\phi_F^{(R)}(t, X)].
\]  

(6.20)

By performing the transformation (6.20), we obtain

\[
\frac{\partial \Theta_k}{\partial t} + \nabla_X \cdot (\Theta_k W) = \nabla_X \cdot [A_k \nabla_X \Theta_k] + \Theta_k A_k.
\]  

(6.21)

where

\[
A_k = \hat{\Pi}_k + \left( \frac{\partial \Lambda}{\partial t} + (V_k + W) \cdot \nabla_X \Lambda \right) - (\nabla_X \cdot A_k) \cdot \nabla_X \Lambda - A_k \cdot \nabla_X \otimes \nabla_X \Lambda - \frac{1}{2} V_k \cdot \nabla_X \Lambda.
\]  

(6.22)

The transformation (6.20) is widely employed in the Physics literature [43]-[45], and represents the Classical Mechanics analogue of a gauge transformation.

7. Interaction between Growth and Transport Phenomena

A possible biomechanical application of the theory presented so far is given by the study of transport of chemical agents (such as growth inhibitory factors) in a solid tumour at the avascular growth stage [16]. Solid tumours progress through two distinct stages of growth: i) the avascular stage, and ii) the vascular stage. The former one consists of a diffusion-limited, dormant state in which mitosis is controlled by the presence of growth inhibitory factors (GIF’s), which are produced by the tumour cells and diffuse throughout the tissue. The latter one is characterized by the ability of the tumour to invade surrounding tissues and metastasize [46]. The transition from one stage to the other is due to angiogenesis, i.e., the appearance and enlargement of the vascular system feeding the tumour, controlled by the diffusion of nutrients and other chemical signals. During the avascular growth stage, the regulation of mitosis is the result of a negative feed-back mechanism such that, if the concentration of the GIF in a certain region of the tissue is less than a certain threshold value, mitosis occurs in this region, whereas if the concentration is greater than the threshold value, mitosis is inhibited [16] [46].
Transport of GIF’s is typically studied by considering the nonlinear version of the advection-diffusion-reaction equation (5.13), and solving a boundary value problem [16] [6] [8] [47]. Nonlinearity is introduced by prescribing that both the reaction term and diffusivity (assumed to be a scalar) depend on the macroscopic concentration of the GIF (the functional dependence of these quantities on concentration is usually obtained on the basis of phenomenological observations). In some cases, the study is restricted to the stationary case [16] [8], i.e., the partial time derivative of the GIF concentration is set equal to zero, and transport coefficients are given by some prescribed spatially dependent functions [16]. When transport processes are investigated within the framework of Mixture Theory, the advection-diffusion-reaction equation is generally written in spatial (Eulerian) form, and the evolution of material symmetries due to growth is not considered. This approach is justified because the tumour is studied as a spheroid, the cellular phase is treated as an isotropic material, and growth is assumed to be isotropic.

In this section, we explicitly assume that growth is anisotropic, and, rather than considering the case of a stationary advection-diffusion-reaction equation, we propose an asymptotic analysis of the equations of motion (6.5), (6.8), (6.9), and (6.14). Our aim is to show how growth is able to interact with transport processes by inducing an adiabatic variation of the environment in which the GIF evolves. We motivate our approach by claiming that growth is a very slow process as compared to the advective, diffusive, and reactive phenomena experienced by the GIF. This statement can be equivalently formulated by postulating that the time-scale associated with growth is very well separated from the time-scales characterizing advection, diffusion and reaction of the GIF. We remark that separation of time-scales holds true if, and only if, the slowest and the fastest process occurring in the system are characterized by two parameters, denoted by \( t_s \) and \( t_f \), respectively, such that \( t_f / t_s = \varepsilon \ll 1 \). In our case, by denoting by \( t_g \), \( \tau_{\text{adv}} \), \( \tau_D \), and \( \tau_{\Pi} \) the time scales of growth, advection, diffusion, and reaction, respectively, the condition of separation of scales is obtained by setting \( t_s = t_g \) and \( t_f = \tau_D \) (i.e., we assume the fastest process in the system is represented by diffusion of the GIF). This guess is justified by virtue of the fact that rapidly growing tumours enlarge at a rate of the order 0.4 – 0.7 mm/day [48], while chemical substances, characterized by diffusion coefficients of order \( 10^{-8} \text{mm}^2\text{s}^{-1} \), attain steady state on a time-scale of the order of a few minutes [16].

7.1. Nondimensionalisation of the Equations of Motion

In the following, for the sake of simplicity we assume that the only fluid constituents are water and the GIF. Then, for our convenience, we carry out a nondimensional analysis of the equations of motion. For this purpose, we introduce the nondimensional variables \( \tau = t / \tau_D \), \( \tau = t / t_g \), and \( Z = X / L \) (\( L \) is a characteristic length of the system), and express a given physical quantity \( \Psi \) as a two-scale function [26], i.e.,

\[
\Psi(t, X) = \Psi(\vartheta, \tau, Z). \tag{7.1}
\]

This way of writing means that, even though \( \vartheta \) and \( \tau \) are related by the identity \( \tau = \varepsilon \vartheta \), they are regarded as formally independent because they measure the “rapidly” and “slowly” varying part of \( \Psi \), respectively [26].

In order to obtain the nondimensional derivatives of \( \Psi \), we decompose \( \Psi \) as \( \Psi = \Psi_c \overline{\Psi} \) (\( \Psi_c \) and \( \overline{\Psi} \) denote the characteristic and nondimensional part of \( \Psi \), respectively [25]), and we differentiate Equation (7.1) with respect to space and time, i.e.

\[
\nabla_X \Psi(t, X) = \frac{\Psi_c}{L} \nabla_Z \overline{\Psi}(\vartheta, \tau, Z), \quad \frac{\partial \Psi}{\partial t}(t, X) = \Psi_c \left[ \frac{1}{t_g} \frac{\partial \overline{\Psi}}{\partial \vartheta}(\vartheta, \tau, Z) + \frac{\partial \overline{\Psi}}{\partial \tau}(\vartheta, \tau, Z) \right]. \tag{7.2}
\]

By rescaling the mass production rates, \( \hat{\Pi}_S \) and \( \hat{\Pi}_F \), as

\[
\hat{\Pi}_S(\vartheta, \tau, Z) = \frac{1}{t_g} \Pi_S(\vartheta, \tau, Z), \quad \hat{\Pi}_F(\vartheta, \tau, Z) = \frac{1}{t_g} \Pi_F(\vartheta, \tau, Z), \tag{7.3}
\]
rerearranging the elastic-growth decomposition (6.16) as

\[ F_S(t, X) = F_{ed}(\partial, r, Z)G(r, Z), \]  

and accounting for Equations (7.2), the equations of motion can be rewritten as

- **Solid-phase Mass Balance Law**

\[ \frac{1}{\varepsilon} \partial \phi_S^{(R)} + \partial \phi_F^{(R)} = \phi_S^{(R)} \Pi_S, \]  

- **Solid-phase Momentum Balance Law**

\[ \nabla \cdot F_S^{ed} = \frac{P_c}{\rho_s A_c} (J_S F_S^{-T} \nabla Z + \tilde{P}_F) + \varepsilon \frac{1}{\rho_s A_c} \phi_F^{(R)} \Pi_F \tilde{W}, \]  

- **Kinematical Constraint**

\[ J_S \left[ \frac{\partial F_{ed}}{\partial \phi} F_{ed}^{-1} \right] + \frac{1}{\varepsilon} J_S \left[ \frac{\partial F_{ed}}{\partial \phi} F_{ed}^{-1} \right] + J_S \left[ F_{ed} \frac{\partial G}{\partial \phi} G^{-1} F_{ed}^{-1} \right] + \frac{1}{\varepsilon} P_e \nabla Z \cdot (\phi_F^{(R)} \tilde{W}) = \left( 1 - \frac{\rho_S}{\rho_F} \right) \phi_S^{(R)} \Pi_S, \]  

- **Transport Equation of the GIF**

\[ \frac{1}{\varepsilon} \frac{\partial C_{GIF}}{\partial \phi} + \frac{\partial C_{GIF}}{\partial \phi} + \frac{1}{\varepsilon} P_e \nabla Z \cdot (C_{GIF} \tilde{W}) = \frac{1}{\varepsilon} \nabla Z \cdot \left[ A_{GIF} \nabla Z C_{GIF} - \bar{C}_{GIF} V_{GIF} \right] + \bar{C}_{GIF} \frac{t_c}{\tau_{GIF}} \Pi_{GIF}. \]  

In Equations (7.5)-(7.8), we denoted by \( p_c, W_c, \) and \( \Lambda_c \), the characteristic values of pressure, \( \hat{p}_F \), relative velocity, \( W \), and solid-phase Helmholtz free energy density, \( A_S \), respectively, and we introduced the Péclet number

\[ Pe = \frac{t_D}{t_{adv}} = \frac{W_c t_D}{L} = \frac{\hat{P}_F W_c L}{D_c} < 1, \]  

where the characteristic time for diffusion, \( t_D \), is defined by the relation

\[ \frac{D_c t_D}{L^2 \hat{P}_F} = 1. \]  

We note that, by virtue of Darcy’s Law, the parameters \( \rho_c \) and \( W_c \) are related by the condition

\[ W_c = \frac{K_c \rho_c}{L} = \frac{L}{t_{adv}}, \]  

where \( K_c \) is the characteristic permeability of the tissue.

### 7.2. Asymptotic Analysis of the Equations of Motion

In order to analyse the equations of motion, we expand \( \phi_S^{(R)}, \phi_F^{(R)}, \bar{W}, \bar{P}_F, P_S^{ed}, \bar{A}_{GIF}, \) and \( \bar{C}_{GIF} \) in asymptotic series, i.e.,

\[ \phi_S^{(R)} = \sum_{\alpha=0}^{\infty} \varepsilon^\alpha \Phi_S^{(\alpha)}, \quad \bar{W} = \sum_{\alpha=0}^{\infty} \varepsilon^\alpha \bar{W}^{(\alpha)}, \quad \bar{P}_F = \sum_{\alpha=0}^{\infty} \varepsilon^\alpha \bar{P}_F^{(\alpha)}, \]

\[ P_S^{ed} = \sum_{\alpha=0}^{\infty} \varepsilon^\alpha P_S^{ed(\alpha)}, \quad \bar{A}_{GIF} = \sum_{\alpha=0}^{\infty} \varepsilon^\alpha \bar{A}_{GIF}^{(\alpha)}, \quad \bar{C}_{GIF} = \sum_{\alpha=0}^{\infty} \varepsilon^\alpha \bar{C}_{GIF}^{(\alpha)}. \]  

Expansions (7.12) are assumed to exist and converge to their asymptotic solutions in the limit \( \varepsilon \rightarrow 0 \). By inserting Equations (7.12) into Equations (7.5)-(7.8), and regrouping the terms of the same power of \( \varepsilon \), we obtain a set of equations which have to be satisfied asymptotically for any infinitely small \( \varepsilon \). Since the coefficients of each power of \( \varepsilon \) are independent of the parameter itself, each coefficient must be identically zero in order to satisfy the equation for any arbitrary small \( \varepsilon \).

By arresting the expansions (7.12) up to the first order in \( \varepsilon \), and dropping the index “GIF”, we obtain the homogenized equations of motion (7.13)-(7.22) written below.
Solid-phase Mass Balance Law

\[
\frac{\partial \Phi_S^{(0)}}{\partial \vartheta} = 0, \quad (7.13)
\]

\[
\frac{\partial \Phi_S^{(1)}}{\partial \vartheta} + \frac{\partial \Phi_S^{(0)}}{\partial \tau} = \Phi_S^{(0)} \overline{\Pi}_S. \quad (7.14)
\]

From Equation (7.13), we notice that the zeroth-order volume fraction, \(\Phi_S^{(0)}\), is independent of the rapidly varying time coordinate \(\vartheta\). This implies that the variation of \(\Phi_S^{(0)}\) is appreciable only over the slow time-scale dictated by growth. Moreover, if we assume that \(\Phi_S^{(1)}\) does not depend on \(\vartheta\), Equation (7.14) gives the evolution of \(\Phi_S^{(0)}\) as a function of \(\tau\). The evolution of \(\Phi_S^{(1)}\) can be evaluated by solving the higher order mass balance equation

\[
\frac{\partial \Phi_S^{(1)}}{\partial \tau} = \Phi_S^{(1)} \overline{\Pi}_S. \quad (7.15)
\]

Solid-phase Momentum Balance Law

\[
\nabla_Z \cdot \mathbf{P}_S^{el(0)} = \frac{p_c}{\tilde{\rho}_S \Lambda_c} J_S F_S^{-T} \nabla_Z \overline{p}^{(0)}, \quad (7.16)
\]

\[
\nabla_Z \cdot \mathbf{P}_S^{el(1)} = \frac{p_c}{\tilde{\rho}_S \Lambda_c} J_S F_S^{-T} \nabla_Z \overline{p}^{(1)} + \frac{1}{\text{Pe}} \frac{\hat{\rho}_c W_c^2}{\tilde{\rho}_S \Lambda_c} \Phi_S^{(0)} \overline{\Pi}_F F_S \overline{W}^{(0)}. \quad (7.17)
\]

The nondimensional coefficients \(\frac{p_c}{\tilde{\rho}_S \Lambda_c}\) and \(\frac{\hat{\rho}_c W_c^2}{\tilde{\rho}_S \Lambda_c}\) compare the “static” pressure, \(p_c\), and “dynamic” pressure, \(\hat{\rho}_c W_c^2\), to the solid-phase Helmholtz free energy density, \(\tilde{\rho}_S \Lambda_c\), respectively. We note that the exchange of momentum due to mass transfer between phases features only in the first-order equilibrium condition (7.17), while no exchange term contributes to the zeroth-order equation (7.16).

Kinematical Constraint

\[
J_S \left[ \frac{\partial \mathbf{F}_{el}}{\partial \vartheta} F_{el}^{-1} \right] + \text{Pe} \nabla_Z \cdot (\Phi_F^{(0)} \overline{W}^{(0)}) = 0, \quad (7.18)
\]

\[
\left( 1 - \frac{\hat{\rho}_S}{\hat{\rho}_F} \right) \Phi_S^{(0)} \overline{\Pi}_S = J_S \left[ \frac{\partial \mathbf{F}_{el}}{\partial \tau} F_{el}^{-1} \right] + J_S \left[ \mathbf{F}_{el} \frac{\partial \mathbf{G}}{\partial \tau} F_{el}^{-1} \right] + \text{Pe} \nabla_Z \cdot (\Phi_F^{(0)} \overline{W}^{(1)} + \Phi_F^{(1)} \overline{W}^{(0)}). \quad (7.19)
\]

From Equations (7.18) and (7.19), it follows that mass exchange terms are taken into account only in the first-order term of the asymptotic expansion of the kinematical constraint. In particular, it is worth to mention that, if the tensor \(\mathbf{F}_{el}\) does not depend on \(\vartheta\), Equation (7.18) reduces to

\[
\nabla_Z \cdot (\Phi_F^{(0)} \overline{W}^{(0)}) = 0, \quad (7.20)
\]

i.e., the zeroth-order term of the Piola transform of filtration velocity, \(\Phi_F^{(0)} \overline{W}^{(0)}\), is a divergence-free field.

Transport Equation of the GIF

\[
\frac{\partial \overline{\mathbf{C}}^{(0)}}{\partial \vartheta} + \text{Pe} \nabla_Z \cdot (\overline{\mathbf{C}}^{(0)} \overline{W}^{(0)}) = \nabla_Z \cdot \left[ \overline{\mathbf{D}}^{(0)} \nabla \overline{\mathbf{C}}^{(0)} - \overline{\mathbf{C}}^{(0)} \overline{\mathbf{W}}^{(0)} \right] + \frac{t_S}{t_{\Pi}} \overline{\mathbf{C}}^{(0)} \overline{\Pi}, \quad (7.21)
\]
\[
\frac{\partial \overline{C}^{(1)}}{\partial \theta} + \frac{\partial \overline{C}^{(0)}}{\partial \tau} + \text{Pe} \nabla_Z \cdot (\overline{C}^{(1)} \overline{W}^{(0)} + \overline{C}^{(0)} \overline{W}^{(1)}) = \nabla_Z \cdot \left[ \overline{A}^{(0)} \nabla_Z \overline{C}^{(1)} + \overline{A}^{(1)} \nabla_Z \overline{C}^{(0)} - \overline{C}^{(1)} \overline{V}^{(0)} - \overline{C}^{(0)} \overline{V}^{(1)} \right] + \frac{t_f}{t_{\Pi}} \overline{C}^{(1)} \Pi,
\]

where the terms \( \overline{V}^{(0)} \) and \( \overline{V}^{(1)} \) are given by

\[
\overline{V}^{(0)} = \overline{A}^{(0)} \nabla_Z \Phi_F^{(0)} / \Phi_F^{(0)}, \quad \overline{V}^{(1)} = \overline{A}^{(1)} \nabla_Z \Phi_F^{(0)} / \Phi_F^{(0)}.
\]

In the case of small Péclet number (e.g., \( \text{Pe} \ll \epsilon \)), the contribution of the advective current to the transport of the GIF can be neglected, and Equations (7.21) and (7.22) can be approximated by

\[
\frac{\partial \overline{C}^{(0)}}{\partial \theta} - \nabla_Z \cdot [\overline{A}^{(0)} \nabla_Z \overline{C}^{(0)} - \overline{C}^{(0)} \overline{V}^{(0)}] - \frac{t_f}{t_{\Pi}} \overline{C}^{(0)} \Pi = 0,
\]

\[
\frac{\partial \overline{C}^{(1)}}{\partial \theta} - \nabla_Z \cdot \left[ \overline{A}^{(1)} \overline{C}^{(1)} - \overline{C}^{(1)} \overline{V}^{(1)} \right] - \frac{t_f}{t_{\Pi}} \overline{C}^{(0)} \Pi = -\frac{\partial \overline{C}^{(0)}}{\partial \tau} + \nabla_Z \cdot \left[ \overline{A}^{(1)} \nabla_Z \overline{C}^{(0)} - \overline{C}^{(0)} \overline{V}^{(1)} \right].
\]

Equations (7.24) and (7.25) are linear. Moreover, since the transport coefficients \( \overline{A}^{(0)}, \overline{V}^{(0)}, \) and \( \Pi \) do not depend on \( \theta \), a formal solution can be found in terms of their Green’s function, \( G \). In particular, it can be proven that the solution to the first equation is given by

\[
\overline{C}^{(0)} (\epsilon^{-1} \tau, \tau, Z) = \int_{B_{\text{g}}} G(G | \epsilon^{-1} \tau, \tau, Z | \epsilon^{-1} \tau_0, \tau_0, Z ') \overline{C}^{(0)} (\epsilon^{-1} \tau_0, \tau_0, Z ') d^3 Z '.
\]

Here, the dependence of \( G \) and the zeroth-order concentration, \( \overline{C}^{(0)} \), on the growth tensor, \( g \), has been put in evidence because the Green’s function depends on the transport coefficients, \( \overline{A}^{(0)} \) and \( \overline{V}^{(0)} \), which, in turn, depend on the growth tensor, \( g \) (cfr. Equation (6.19)).

On account of Equation (7.26), the right-hand-side of Equation (7.25) can be regarded as known. Hence, by introducing the notation

\[
\overline{C}^{(1)}_{G} (\epsilon^{-1} \tau, \tau, Z) = \int_{B_{\text{g}}} G(G | \epsilon^{-1} \tau, \tau, Z | \epsilon^{-1} \tau_0, \tau_0, Z ') \overline{C}^{(1)}_{G} (\epsilon^{-1} \tau_0, \tau_0, Z ') d^3 Z '.
\]

we can express the first-order concentration, \( \overline{C}^{(1)} \), as

\[
\overline{C}^{(1)} (\epsilon^{-1} \tau, \tau, Z) = \int_{B_{\text{g}}} G(G | \epsilon^{-1} \tau, \tau, Z | \epsilon^{-1} \tau_0, \tau_0, Z ') \overline{C}^{(1)} (\epsilon^{-1} \tau_0, \tau_0, Z ') d^3 Z ' + \int_{t_{\tau}}^{t} \int_{B_{\text{g}}} G(G | \epsilon^{-1} \tau, \tau, Z | \epsilon^{-1} \tau_0, \tau_0, Z ') \overline{C}^{(1)} (\epsilon^{-1} \tau, \tau, Z ') d^3 Z ' d \tau '.
\]

According to Equations (7.26), for a given initial concentration \( \overline{C}^{(0)} (\epsilon^{-1} \tau_0, \tau_0, Z ') \), the growth tensor, \( G \), contributes to determine the concentration \( \overline{C}^{(0)}_{G} \), and, by virtue of Equation (7.28), this implies that also the first-order concentration, \( \overline{C}^{(1)}_{G} \), depends on \( G \).

Since we assume that growth is anisotropic, we can write the growth tensor as the sum of a spherical and a deviatoric contribution, i.e.,

\[
G = g I + G_d,
\]

and we can perform a formal Taylor expansion of the Green’s function, \( G \), around the isotropic tensor \( g I \), i.e.,

\[
G(G | \epsilon^{-1} \tau, \tau, Z | \epsilon^{-1} \tau', \tau', Z ') = G_{\text{iso}} (\epsilon^{-1} \tau, \tau, Z | \epsilon^{-1} \tau', \tau', Z ') + G_{\text{aniso}} (\epsilon^{-1} \tau, \tau, Z | \epsilon^{-1} \tau', \tau', Z '),
\]

where
By substituting Equation (7.30) into Equation (7.26), we obtain that the zeroth-order concentration, \( \overline{C}_G^{(0)} \), is given by

\[
\overline{C}_G^{(0)} = C_{iso}^{(0)} + C_{aniso}^{(0)},
\]

(7.32)

where

\[
C_{iso}^{(0)}(e^{-1}\tau, \tau, Z) = \int_{Br} G_{iso}(e^{-1}\tau, \tau, Z | e^{-1}\tau_0, \tau_0, Z') \overline{C}_G^{(0)}(e^{-1}\tau_0, \tau_0, Z') d^3 Z',
\]

(7.33)

\[
C_{aniso}^{(0)}(e^{-1}\tau, \tau, Z) = \int_{Br} G_{aniso}(e^{-1}\tau, \tau, Z | e^{-1}\tau_0, \tau_0, Z') \overline{C}_G^{(0)}(e^{-1}\tau_0, \tau_0, Z') d^3 Z'.
\]

(7.33)

Analogously, by substituting Equation (7.31) into Equations (7.27) and (7.28), and writing \( \overline{Y}_G^{(0)} \) as the superposition of an isotropic and an anisotropic part, i.e., \( \overline{Y}_G^{(0)} = \overline{Y}_{iso}^{(0)} + \overline{Y}_{aniso}^{(0)} \), we find that the first-order concentration, \( \overline{C}_G^{(1)} \), is given by

\[
\overline{C}_G^{(1)} = \overline{C}_{iso}^{(1)} + \overline{C}_{aniso}^{(1)},
\]

(7.34)

where

\[
\overline{C}_{iso}^{(1)}(e^{-1}\tau, \tau, Z) = \int_{Br} G_{iso}(G | e^{-1}\tau, \tau, Z | e^{-1}\tau_0, \tau_0, Z') \overline{C}_G^{(1)}(e^{-1}\tau_0, \tau_0, Z') d^3 Z' + \int_{\tau_0}^{\tau} \int_{Br} G_{iso}(G | e^{-1}\tau, \tau, Z | e^{-1}\tau_0, \tau_0, Z') \overline{Y}_{iso}^{(0)}(e^{-1}\tau', \tau', Z') d^3 Z' d\tau',
\]

(7.35)

\[
\overline{C}_{aniso}^{(1)}(e^{-1}\tau, \tau, Z) = \int_{\tau_0}^{\tau} \int_{Br} G_{aniso}(e^{-1}\tau, \tau, Z | e^{-1}\tau_0, \tau_0, Z') \overline{C}_G^{(1)}(e^{-1}\tau_0, \tau_0, Z') d^3 Z' + \int_{\tau_0}^{\tau} \int_{Br} G_{aniso}(G | e^{-1}\tau, \tau, Z | e^{-1}\tau_0, \tau_0, Z') \overline{Y}_{aniso}^{(0)}(e^{-1}\tau', \tau', Z') d^3 Z' d\tau'.
\]

(7.36)

By virtue of Equations (7.32) and (7.34), the material macroscopic concentration of the GIF, \( C \), is approximated by

\[
C = C_{C}(C^{(0)} + \varepsilon C^{(1)})
\]

\[
= C_{C}[C_{iso}^{(0)} + C_{aniso}^{(0)} + \varepsilon(C_{iso}^{(1)} + C_{aniso}^{(1)})] = C_{C}[C_{iso}^{(0)} + \varepsilon C_{iso}^{(1)} + C_{aniso}^{(0)} + \varepsilon C_{aniso}^{(1)}].
\]

(7.37)

Equation (7.37) shows how anisotropic growth “modulates” the macroscopic concentration of the GIF as the growth tensor, \( G \), evolves in time. This result and its possible implications are commented in section 8.

8. Conclusions

In this paper, we started from a microscopic thermo-mechanic description of a porous material in order to determine the advection-diffusion-reaction equation that has to be used for modelling the macroscopic transport of chemical substances in a biological tissue. The motivation of this work was to extend a previous paper of ours [49] in which we pointed out the possibility for the existence of a self-interaction of the mass source in a living tissue undergoing anisotropic growth.

We based our procedure on the theory of upscaling and the averaging techniques introduced by Hassanizadeh and Gray [17]-[20] and Hassanizadeh [5]. We had recourse to these methods for two reasons: i) we wanted to relate the pore scale concentration of chemical substances with their average concentration (i.e., the concentration evaluated at the scale at which measurements are made) in order to investigate the possible repercussions of the thermo-mechanical environment surrounding the tissue on the microscopic dynamics of the tissue itself, and ii) we needed to find a macroscopic description...
of diffusion (i.e., a valid expression for the Fick-type current) on the basis of suitable constitutive assumptions.

We discussed a possible application of the general theory presented in sections 2 to 4 by specializing the advection-diffusion-reaction equation (5.13) to the case of transport of chemical agents (e.g., growth inhibitory factors) in a solid tumour at the avascular growth stage. This problem has also been investigated, for example, by [3] [7] [8] [16] [47]. In these papers, Fick-type current is defined as 

$$J = -D \nabla q$$

($q$ is the concentration of a given chemical substance) at the same scale at which other macroscopic balance equations are introduced, and the advection-diffusion-reaction equation is written as

$$\frac{\partial q}{\partial t} + \nabla \cdot (q \mathbf{v}_F) = \nabla \cdot [D \nabla q] + q \Pi .$$

By comparing Equation (5.13) with Equation (8.1), we note that the Fick-type current, $J$, found by following the upscaling procedure outlined in this paper, is different from $J$. Although in the literature there are models (proposed, for example, by Garikipati et al. [38] and Loret and Simões [23]) in which Darcy’s and Fick’s Laws for multiphasic systems are derived within a macroscopic constitutive framework, we believe that this difference may serve as a hint for applying the upscaling method to other problems of biological interest, and comparing the results with those obtained from an a priori macroscopic theory in order to understand which model is more adherent to experiments.

We wrote the transport equation (5.13) in material form and, by enforcing the multiplicative decomposition of the deformation gradient tensor (cfr. Equation (6.16)), and considering the case of anisotropic growth, we presented a possible picture describing how the upscaled transport properties (e.g., effective diffusivity tensor, $A$, and material drift velocity, $W$) are modulated by the alteration of material symmetries due to the time variation of the growth tensor, $G$.

We showed how anisotropic growth induces a local rearrangement of the macroscopic concentration of a given chemical substance (in our case, this chemical substance is represented by a GIF). This aspect was investigated by assuming that growth is characterized by a time-scale much slower than the typical time-scale of diffusive phenomena. By virtue of this hypothesis, the transport of a GIF in a growing tumour was regarded as a process occurring in an environment (i.e., the growing tissue) in which the mechanical state and the material symmetries vary adiabatically in time. This approximation allowed for an asymptotic analysis of the transport equation (6.14), and finding a formal solution to Equations (7.24) and (7.25) through the determination of their Green’s function. Moreover, since the Green’s function was written as the sum of an isotropic and an anisotropic contribution, the concentration of the GIF was proved to be “modulated” by the anisotropy of the growth tensor, $G$. We believe that such a “modulation” may have some repercussions on the microscopic concentration of the GIF. Indeed, by noting that the macroscopic density of the GIF can be written as

$$\rho_{\text{GIF}} = \frac{1}{\phi_F} C_{\text{GIF}} = \frac{1}{\phi_F} J C_{\text{GIF}},$$

and assuming that the microscopic density of the GIF, $\mu_{\text{GIF}}(t, r)$, can be expressed as

$$\mu_{\text{GIF}}(t, r) = \rho_{\text{GIF}}(t, r) + b_{\text{GIF}}(t, r) \cdot \nabla \rho_{\text{GIF}}(t, x),$$

(8.3)

(where the vector $b_{\text{GIF}}$ has to be a zero-mean field over the subset $\Omega_F \subset \Omega$), the modulation felt by $\rho_{\text{GIF}}$ is reflected on $\mu_{\text{GIF}}$. In a forthcoming paper, we propose to study the Green’s function defined in Equation (7.30) by employing the Renormalization Group.

We argue that the possibility for modulating the microscopic concentration of the GIF in a growing tumour might play a role because mitosis is regulated by a threshold phenomenon. Indeed, if we hypothesise that growth could be switched from an isotropic to an anisotropic “regime”, then, according to Equation (7.37), the local concentration of the GIF could be enhanced or reduced. Therefore, depending on whether the modulation of the GIF due to anisotropic growth is able to bring its local concentration above or below a certain characteristic threshold value, mitosis could be
controlled by an additional self-regulating mechanism. Our long-term goal is to investigate the possibility for such an effect to occur.

9. Acknowledgments

The Authors are grateful to Prof. Sabine Attinger, Prof. Jean-Louis Auriault, Prof. Majid Hassanizadeh and Prof. Shoji Imatani for useful discussions and crucial references. This work was supported by CNISM - Consorzio Nazionale Interuniversitario di Struttura della Materia (National Inter-university Consortium of Structure of Matter)

References

[1] Fung Y C 1990 *Biomechanics – motion, flow, stress, and growth* (New York: Springer-Verlag Inc.)
[2] Taber L A 1995 *Mech. Rev.* 48 487-545
[3] Ambrosi D and Mollica F 2002 *Int. J. Eng. Science* 40 1297-1316
[4] Gray G W and Hassanizadeh S M 1998 *Adv Water Resources* 21 226-281
[5] Hassanizadeh S M 1986 *Adv Water Resources* 9 196-206
[6] Ambrosi D and Preziosi L 2002 *Math. Mod. and Methods in Appl. Sci.* 12(5) 737-754
[7] Bellomo N, De Angelis E, and Preziosi L 2003 *J. Theoret. Medicine* 5(2) 111-136
[8] Byrne H M, Preziosi L 2003 *Math. Medicine and Biol.* 20 341-366
[9] Quiligotti S 2002 *Theoret. Appl. Mech.* 28-29 277-288
[10] Bowen R M 1976 *Theory of Mixtures in Continuum Physics*, Part I, Vol. III, pages 1-127 – Mixtures and EM Field Theories, Eringen A. C. ed. (New York: Academic Press)
[11] Rajagopal K R and Tao L 1995 *Mechanics of Mixtures* (Singapore: World Scientific)
[12] Epstein M and Maugin G A 2000 *Int J. Plasticity* 16 951-978
[13] Thiffeault J L 2003 *Phys. Lett. A* 309 451-422
[14] Bensoussan A, Lions J L, and Papanicolaou G C 1978 *Asymptotic analysis for periodic structures* (New York: North Holland)
[15] Cioranescu D and Donato P 1999 *An Introduction to Homogenization* (Oxford: Oxford University Press)
[16] Chaplain M A J 1996 *Mathl. Comput. Modelling* 23(6) 47-87
[17] Hassanizadeh S M and Gray W G 1979 *Adv. Water Resources* 2 131-144
[18] Hassanizadeh S M and Gray W G 1979 *Adv. Water Resources* 2 191-203
[19] Hassanizadeh S M and Gray W G 1980 *Adv. Water Resources* 3 25-40
[20] Hassanizadeh S M and Gray W G 1990 *Adv. Water Resources* 13(4) 169-186
[21] Dormieux L, Kondo D and Ulm F-J 2006 *Microporomechanics* (England: J Wiley&Sons)
[22] Quiligotti S, Maugin G A, and Dell’Isola F 2003 *Acta Mech.* 160 45-60
[23] Loret B and Simões F M F 2005 *European Journal of Mechanics A/Solids* 24 757-781
[24] Lubarda V A and Hoger A 2002 *Int. J. Solids Structures* 39 4627-4664
[25] Auriault J L and Adler P M 1995 *Adv. Water Resources* 18(4) 217-226
[26] Lunati I, Attinger S, and Kinzelbach W 2002 *Water Resour. Res.* 30(10) 118
[27] De Boer R 2005 *Trends in Continuum Mechanics of Porous Materials – Theory and Applications of Transport in Porous Media* (The Netherlands: Springer)
[28] Nicholson C 2001 *Rep. Prog. Phys.* 64 815-884
[29] Lehner F K 1979 *Chem. Eng. Sci.* 34 821-825
[30] Biferale L, Crisanti A, Vergassola M, and Vulpiani A 1995 *Phys. Fluids* 7(11) 2725-2734
[31] Moffatt H K 1983 *Rep. Prog. Phys.* 46 621
[32] Farquhar T, Dawson P R, and Torzilli P A 1990 *J Biomech Engng.* 112 414-425.
[33] Wu J Z, and Herzog W 2002 *J Biomech* 35 931-942.
[34] Federico S, Grillo A, La Rosa G, Giaquinta G, and Herzog W 2005 *J. Biomech.* 38 2008-2018
[35] Farina A and Preziosi L 2002 *Int. J. Nonlinear Mech.* 37 485-491
[36] Rajagopal K R 1995 *Rep. Inst. Comput. Appl. Mech.* 6
Table 1. Thermodynamic quantities to use for the fluid components microscopic balance laws

| Quantity | $\psi_j$ | $\delta_{\psi_j}$ | $f_{\psi_j}$ | $g_{\psi_j}$ |
|----------|----------|--------------------|--------------|--------------|
| Mass     | 1        | 0                  | 0            | $\pi_j$      |
| Momentum | $u_j$    | $\Sigma_j$         | $g_j$        | $\pi_j u_j + \lambda_j$ |
| Energy   | $E_j + \frac{1}{2} u_j^2$ | $\Sigma_j u_j + q_j$ | $g_j \cdot u_j + h_j$ | $\pi_j (E_j + \frac{1}{2} u_j^2) + \lambda_j \cdot u_j + e_j$ |
| Entropy  | $\eta_j$ | $\phi_j$          | $b_j$        | $\pi_j \eta_j + \zeta_j + \Gamma_j$ |

Table 2. Thermodynamic quantities to use for the solid-phase microscopic balance laws

| Quantity | $\psi_S$ | $\delta_{\psi_S}$ | $f_{\psi_S}$ | $g_{\psi_S}$ |
|----------|----------|--------------------|--------------|--------------|
| Mass     | 1        | 0                  | 0            | 0            |
| Momentum | $u_S$    | $\Sigma_S$         | $g_S$        | 0            |
| Energy   | $E_S + \frac{1}{2} u_S^2$ | $\Sigma_S u_S + q_S$ | $g_S \cdot u_S + h_S$ | 0            |
| Entropy  | $\eta_S$ | $\phi_S$          | $b_S$        | $\Gamma_S$   |