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Growing Avascular Tumours as Elasto-Plastic Bodies by the Theory of Evolving Natural Configurations

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Abstract

The aim of this article is to propose a simple way of describing a tumour as a linear elastic material from a reference configuration that is continuously evolving in time due to growth and remodelling. The main assumption allowing this simplification is that the tumour mass is a very ductile material, so that it can only sustain moderate stresses while the deformation induced by growth, that can actually be quite big, mainly induces a plastic reorganisation of malignant cells. In mathematical terms this means that the deformation gradient can be split into a volumetric growth term, a term describing the reorganisation of cells, and a term that can be approximated by means of the linear strain tensor. A dimensional analysis of the importance of the different terms also allows to introduce a second simplification consisting of decoupling the equations describing the growth of the tumour mass from those describing the flow of the interstitial fluid.

Keywords: Growth, Elastoplasticity, Remodelling, Tumour, Natural Configurations.

1. Introduction

In order to describe growth and mechanical behaviour of tumour masses, several multiphase models have been developed under the observation that tumours are made of several constituents, including at least a cellular population (that can be classified as belonging either to the tumour or to the host tissue), the interstitial fluid, and the fibrous environment constituted by the extracellular matrix (ECM) with all its components, such as collagen, elastin and proteoglycans. Such models are capable not only of describing the variation of mass density within the tumour and the host tissue, but also of evaluating the evolution of stresses and interstitial pressure, linking the mechanics of tumours to their growth and selected interactions with the outer environment. For more details the reader is referred to the following reviews [1, 2, 3, 4, 5, 6].

Most of the models describe the tumour mass as a fluid, which is of course a strong simplification. On the other hand, in some cases, it is fundamental to be able to describe it as a solid-like material. The generalisation is not trivial at all. In fact, in dealing with the mechanics of tumour growth, one has to take into account that cells duplicate and die, the ECM and the external environment are continuously remodelled, and tumour cells are subjected to an internal re-organisation and to changes in the adhesion properties, which might also be related to the detachment of metastases. All this implies that it is impossible to define a unique natural configuration for the growing mass, leading to difficulties in the development of an elasticity theory in standard terms. After some early immature attempts [7, 8, 9, 10], this problem was tackled in [11, 12, 13, 14] by applying the concept of *evolving natural configurations*, which consists of splitting the evolution in growth, plastic remodelling, and elastic deformation. However, the application of the full theory might result rather cumbersome.

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The aim of this work is to outline a simplified mathematical setting, derived from the theory of evolving natural configurations, that can be used in several biologically relevant problems. The analysis is based on the fact that tumour masses, and the soft tissues they live in, are very ductile materials, so that they can only sustain moderate stresses, while the deformations induced by growth (that can actually be quite big) mainly induce a plastic reorganisation of cells. In mathematical terms, this means that the deformation gradient can be split into a volumetric growth term, a term describing the plastic behaviour, and a term that can be approximated by means of the linear strain tensor. This leads to a strong simplification of the theory of evolving natural configurations, so that it is possible to describe the tumour as a linear elastic material that uses a natural configuration that is continuously changing in time due to growth and remodelling.

Another simplification is made possible by the evaluation of the relative importance of the different terms appearing in the equations. In fact, since the pressure drops are sufficiently smaller than the Young modulus of the tumour, and the characteristic velocity of the interstitial fluid is much larger than the one related to cell duplication, the growth problem decouples from the interstitial flow problem in many practical cases, leading to a strong simplification of the mathematical models usually employed to describe growing systems.

2. A Multiphase Model

For the purposes of this article, a medium comprising three distinct phases is considered and treated as a mixture. The three phases represent the cell population, the extracellular matrix (ECM), and the interstitial (or extra-cellular) fluid. These are labelled by the subscripts “c”, “m”, and “ ℓ ”, respectively. The presence of blood and lymphatic vessels may be included in the ECM because they can be considered as cross-linked with it.

The multiphase approach proposed in [15, 16] to describe tumour and tissue growth consists of a set of mass and momentum balance equations. Within a purely mechanical framework, and under the assumptions that all phases are intrinsically incompressible and external body forces (such as the gravitational force) are negligible, the balance laws write

$$\partial_t \phi_\alpha + \operatorname{div}(\phi_\alpha \mathbf{v}_\alpha) = \Gamma_\alpha, \quad (1)$$

$$\partial_t(\phi_\alpha \mathbf{v}_\alpha) + \operatorname{div}(\phi_\alpha \mathbf{v}_\alpha \otimes \mathbf{v}_\alpha) = \frac{1}{\rho_\alpha} \operatorname{div}(\tilde{\mathbf{T}}_\alpha) + \frac{1}{\rho_\alpha} (\tilde{\mathbf{m}}_\alpha + \rho_\alpha \Gamma_\alpha \mathbf{v}_\alpha). \quad (2)$$

In (1) and (2), and with reference to the α th phase, ϕ_α is the volumetric fraction, \mathbf{v}_α is the velocity, ρ_α is the true volumetric mass density, $\tilde{\mathbf{T}}_\alpha$ is the partial stress tensor, and, finally, Γ_α and $\tilde{\mathbf{m}}_\alpha$ represent, respectively, the rates at which the α th phase exchanges mass and momentum with the other phases. Recently, the action of body forces on tumour growth has been investigated in [17].

In the case of a saturated medium, the constraint $\sum_{\alpha=c,\ell,m} \phi_\alpha = 1$ has to hold. Consequently, summing Eq. (1) over all phases yields

$$\operatorname{div} \left(\sum_{\alpha=c,\ell,m} (\phi_\alpha \mathbf{v}_\alpha) \right) = \sum_{\alpha=c,\ell,m} \Gamma_\alpha. \quad (3)$$

As a first step, the early avascular stage of tumour growth is considered. In this case, mass exchange is assumed to occur only among the constituents taken into account, the mixture is said to be *closed* with respect to mass, and one can write

$$\rho_c \Gamma_c + \rho_\ell \Gamma_\ell + \rho_m \Gamma_m = 0. \quad (4)$$

Note that, if the true mass densities are assumed to be approximately equal to each other, e.g., to the density of water, Eq. (4) becomes $\sum_{\alpha=c,\ell,m} \Gamma_\alpha = 0$.

The term $\tilde{\mathbf{m}}_\alpha$ in Eq. (2) contains all forces acting on the α th phase due to its interactions with the other phases. On the basis of thermodynamic arguments, it can be shown that it is given by the sum $\tilde{\mathbf{m}}_\alpha = \tilde{\mathbf{m}}_\alpha^{(d)} + p \nabla \phi_\alpha$, where p is the pressure of the interstitial fluid, and the summands $\tilde{\mathbf{m}}_\alpha^{(d)}$ and $p \nabla \phi_\alpha$ represent the dissipative and the non-dissipative

57 contribution to $\widetilde{\mathbf{m}}_\alpha$, respectively [18]. If the mixture is required to be closed also with respect to momentum, the
 58 interaction terms $\widetilde{\mathbf{m}}_\alpha$ (with $\alpha = c, \ell, m$) are constrained to satisfy the condition

$$\sum_{\alpha=c,\ell,m} (\widetilde{\mathbf{m}}_\alpha + \rho_\alpha \Gamma_\alpha (\mathbf{v}_\alpha - \mathbf{v})) = \sum_{\alpha=c,\ell,m} (\widetilde{\mathbf{m}}_\alpha^{(d)} + \rho_\alpha \Gamma_\alpha (\mathbf{v}_\alpha - \mathbf{v})) = \mathbf{0}, \quad (5)$$

59 where $\mathbf{v} = \rho^{-1} \sum_{\alpha=c,\ell,m} (\phi_\alpha \rho_\alpha \mathbf{v}_\alpha)$ is referred to as the mixture velocity, and $\rho = \sum_{\alpha=c,\ell,m} \phi_\alpha \rho_\alpha$ is the mass density of
 60 the mixture as a whole [19]. In Eq. (5), the first equality follows from the saturation condition, which implies that the
 61 sum over all phases of the non-dissipative terms $p \nabla \phi_\alpha$ vanishes identically. The dissipative terms $\widetilde{\mathbf{m}}_\alpha^{(d)}$ ($\alpha = c, \ell, m$)
 62 can be expressed as

$$\widetilde{\mathbf{m}}_\alpha^{(d)} = -\frac{\phi_\alpha \rho_\alpha}{\rho} \sum_{\gamma=c,\ell,m} \rho_\gamma \Gamma_\gamma (\mathbf{v}_\gamma - \mathbf{v}) + \overline{\mathbf{m}}_\alpha, \quad (6)$$

63 with $\sum_{\alpha=c,\ell,m} \overline{\mathbf{m}}_\alpha = \mathbf{0}$, and $\overline{\mathbf{m}}_\alpha = \sum_{\beta \neq \alpha} \overline{\mathbf{m}}_{\alpha\beta}$ [19]. Each term $\overline{\mathbf{m}}_{\alpha\beta}$ represents the force acting on the α th phase
 64 due to the β th phase, with $\alpha \neq \beta$. By invoking the action-reaction principle for each interaction pair, it holds that
 65 $\overline{\mathbf{m}}_{\alpha\beta} = -\overline{\mathbf{m}}_{\beta\alpha}$.

66 In particular, the interaction of the fluid with the other constituents can be given by the following expression:

$$\overline{\mathbf{m}}_{\ell\beta} = -\phi_\ell \phi_\beta \mu [\mathbf{K}(\phi_\ell)]^{-1} \mathbf{v}_{\ell\beta}, \quad \beta = c, m, \quad (7)$$

67 where $\mathbf{v}_{\ell\beta} := \mathbf{v}_\ell - \mathbf{v}_\beta$ is the velocity of the fluid relative to that of the β th constituent ($\beta \neq \ell$), μ is the viscosity of the
 68 extra-cellular fluid and $\mathbf{K}(\phi_\ell)$ is related to the permeability tensor. The classical Kozeny-Carman relation [19, 20, 21]
 69 for $\mathbf{K}(\phi_\ell)$ can be recovered by assuming $\mathbf{K}(\phi_\ell) = [\phi_\ell^2 / (1 - \phi_\ell)] \mathbf{K}_0$, with \mathbf{K}_0 independent of ϕ_ℓ . However, in many
 70 practical situations, ϕ_ℓ does not significantly vary, thereby allowing to take \mathbf{K} independent of ϕ_ℓ .

71 The interaction between the cellular phase and the extracellular matrix is generally more complex than that of the
 72 fluid with the other constituents. The higher complexity is due, for instance, to the presence of the adhesion forces
 73 that the cells exchange with the ECM and to the high heterogeneity of this extracellular structure. However, when the
 74 dissipative nature of cell-matrix interactions can be assumed to be exclusively due to the dynamic friction between
 75 the two phases, then, within an approximation of the first order in the relative velocity $\mathbf{v}_{cm} := \mathbf{v}_c - \mathbf{v}_m$, one can write
 76 $\overline{\mathbf{m}}_{cm} = -\mathbf{M}_{cm} \mathbf{v}_{cm}$, where the second-order tensor \mathbf{M}_{cm} is taken to be symmetric, positive semi-definite, and such that
 77 $\mathbf{M}_{cm} = \mathbf{M}_{mc}$ [21]. In general, the tensor \mathbf{M}_{cm} is a function of physical quantities that need not vanish when the relative
 78 velocity \mathbf{v}_{cm} is null.

79 The remainder of this article is based on the hypothesis that inertial forces are negligible in the momentum balance
 80 law of each phase. Therefore, Eq. (2) becomes

$$\operatorname{div}(\widetilde{\mathbf{T}}_\alpha) + \widetilde{\mathbf{m}}_\alpha = \mathbf{0}, \quad \alpha = c, \ell, m. \quad (8)$$

81 Moreover, also the contribution $\sum_{\alpha=c,\ell,m} \rho_\alpha \Gamma_\alpha (\mathbf{v}_\alpha - \mathbf{v})$ shall be neglected both in (5) and in the expression of $\widetilde{\mathbf{m}}_\alpha^{(d)}$ given
 82 in (6). Consequently, $\widetilde{\mathbf{m}}_\alpha^{(d)}$ is set approximately equal to $\overline{\mathbf{m}}_\alpha$, i.e., $\widetilde{\mathbf{m}}_\alpha^{(d)} \approx \overline{\mathbf{m}}_\alpha$, and the closure condition (5) reduces to
 83 $\sum_{\alpha=c,\ell,m} \overline{\mathbf{m}}_\alpha = \mathbf{0}$.

84 2.1. Momentum Balance Laws for the Saturated Case

85 In a saturated mixture, the partial Cauchy stress associated with the α th phase of the mixture can be written as
 86 $\widetilde{\mathbf{T}}_\alpha = -\phi_\alpha p \mathbf{I} + \mathbf{T}_\alpha$, where \mathbf{T}_α is referred to as *effective* (or extra-) stress, and the purely hydrostatic contribution $-\phi_\alpha p \mathbf{I}$
 87 indicates the amount of pressure sustained by the α th phase (note that, in the present theory, p is a Lagrange multiplier
 88 rather than a constitutively determined quantity). Using the definitions of $\widetilde{\mathbf{T}}_\alpha$ and $\widetilde{\mathbf{m}}_\alpha$ given above, Eq. (2) can be
 89 specialised as:

$$-\phi_c \nabla p + \operatorname{div}(\mathbf{T}_c) + \overline{\mathbf{m}}_{cm} - \phi_c \phi_\ell \mu [\mathbf{K}(\phi_\ell)]^{-1} \mathbf{v}_{c\ell} = \mathbf{0}, \quad (9a)$$

$$-\phi_m \nabla p + \operatorname{div}(\mathbf{T}_m) - \overline{\mathbf{m}}_{cm} - \phi_m \phi_\ell \mu [\mathbf{K}(\phi_\ell)]^{-1} \mathbf{v}_{m\ell} = \mathbf{0}, \quad (9b)$$

$$-\phi_\ell \nabla p - \phi_\ell \phi_c \mu [\mathbf{K}(\phi_\ell)]^{-1} \mathbf{v}_{\ell c} - \phi_\ell \phi_m \mu [\mathbf{K}(\phi_\ell)]^{-1} \mathbf{v}_{\ell m} = \mathbf{0}, \quad (9c)$$

90 with $\mathbf{v}_{\alpha\beta} := \mathbf{v}_\alpha - \mathbf{v}_\beta = -\mathbf{v}_{\beta\alpha}$, for all $\alpha, \beta = c, \ell, m$ such that $\alpha \neq \beta$.

Coherently with the hypotheses usually made to deduce Darcy's law, Eq. (9c) is obtained by requiring that the extra-stress \mathbf{T}_ℓ is negligible with respect to the pressure gradient and the interaction forces. It is possible to include vessels among the extracellular constituents, which implies a constrained mixture assumption, meaning that the fibre network of elastin, collagen and proteoglycans is strongly connected to the vessel network, so that they move together with the same velocity. This also implies that the stress tensor \mathbf{T}_m includes a further contribution due to the response of the vessels to deformations.

Computing \mathbf{v}_ℓ explicitly from Eq. (9c), and substituting the result into (9a) and (9b), one obtains

$$-\frac{\phi_c}{1-\phi_\ell}\nabla p + \operatorname{div}(\mathbf{T}_c) + \bar{\mathbf{m}}_{cm} + \frac{\phi_c\phi_\ell\phi_m}{1-\phi_\ell}\mu[\mathbf{K}(\phi_\ell)]^{-1}\mathbf{v}_{mc} = \mathbf{0}, \quad (10a)$$

$$-\frac{\phi_m}{1-\phi_\ell}\nabla p + \operatorname{div}(\mathbf{T}_m) - \bar{\mathbf{m}}_{cm} + \frac{\phi_c\phi_\ell\phi_m}{1-\phi_\ell}\mu[\mathbf{K}(\phi_\ell)]^{-1}\mathbf{v}_{cm} = \mathbf{0}, \quad (10b)$$

$$\mathbf{v}_\ell = \frac{1}{\phi_c + \phi_m} \left(\phi_c\mathbf{v}_c + \phi_m\mathbf{v}_m - \frac{\mathbf{K}(\phi_\ell)}{\mu}\nabla p \right), \quad (10c)$$

where $\phi_\ell = 1 - (\phi_c + \phi_m)$. Equation (1), written once for $\alpha = c$ and once for $\alpha = m$, is used to determine the volumetric fractions ϕ_c and ϕ_m , i.e.,

$$\partial_t\phi_c + \operatorname{div}(\phi_c\mathbf{v}_c) = \Gamma_c, \quad (11a)$$

$$\partial_t\phi_m + \operatorname{div}(\phi_m\mathbf{v}_m) = \Gamma_m, \quad (11b)$$

whereas Eq. (3) is used to determine the pressure p , and can be rewritten as

$$\operatorname{div} \left(\frac{\phi_\ell}{1-\phi_\ell} \frac{\mathbf{K}(\phi_\ell)}{\mu} \nabla p \right) = \operatorname{div} \left(\frac{\phi_c\mathbf{v}_c + \phi_m\mathbf{v}_m}{\phi_c + \phi_m} \right) - \sum_{\alpha=c,\ell,m} \Gamma_\alpha. \quad (12)$$

The last term on the right-hand-side of (12) can be dropped if the mass densities of all the phases are equal to each other (e.g., to the mass density of water) and the mixture is closed (cf. Eq. (4)).

2.2. Dimensional Analysis of the Momentum Balance Laws

To identify the dominant contributions in the momentum equations (10a)–(10c), it is convenient to convert them in the non-dimensional form. For this purpose, a generic physical quantity q shall be compared with a reference value \hat{q} , which is taken as a positive constant, and its dimensionless counterpart shall be denoted by q^* , so that $q = \hat{q}q^*$. In particular, the lengths are scaled with the typical intercapillary distance d , the mass exchange terms Γ_α ($\alpha = c, \ell, m$) with the cell duplication rate $\hat{\Gamma}_c \sim 1 \text{ day}^{-1}$, the permeability \mathbf{K} with the constant value \hat{K} , which is compatible with experimental data taken from the literature (see Table 1), and pressure with $\hat{p} = \Delta p$, which is identified with the pressure drop between the arterial and the venous/lymphatic system within the tissue. The stress tensors \mathbf{T}_c and \mathbf{T}_m are scaled with the tissue's Young elastic modulus E (i.e., for instance, one can define the non-dimensional stress $\mathbf{T}_c^* = \mathbf{T}_c/E$). Moreover, the true mass densities of all the phases are taken equal to the reference value $\rho_w = 10^3 \text{ kg/m}^3$, which approximately corresponds to the mass density of water, the fluid velocity is scaled with $\hat{v}_\ell \sim 10^{-7} \div 10^{-6} \text{ m/s}$, i.e., the velocity of the interstitial fluid in a porous medium measured in [22], and the velocities of the cell population and extracellular matrix are scaled through the cell duplication rate, so that $\hat{v}_m = \hat{v}_c = \hat{\Gamma}_c D$, where D is the mean cell diameter (all scaling factors used in this paper are reported in Table 1). Note that, setting $\hat{v}_\ell = ((\hat{K}/\mu)\Delta p)/d$, and assigning \hat{v}_ℓ , Δp and d as independent scaling factors, it is possible to estimate the ratio \hat{K}/μ (cf. Table 1). Finally, the scaling factor \hat{m}_{cm} , which is associated with the momentum exchange term $\bar{\mathbf{m}}_{cm}$, is assumed to be equal to the ratio E/d . Thus, if $\bar{\mathbf{m}}_{cm}$ is expressed as $\bar{\mathbf{m}}_{cm} = -\mathbf{M}_{cm}\mathbf{v}_{cm}$, the scaling factor associated with \mathbf{M}_{cm} must be equal to $\hat{M}_{cm} = E/(d\hat{\Gamma}_c D)$.

Considering that $\bar{\mathbf{m}}_{cm}$ and the mass exchange rates, say, Γ_c and Γ_m , can be assigned constitutively (recall that Γ_ℓ can be determined univocally by means of Eq. (4) once Γ_c and Γ_m are known), Eqs. (10a)–(12) result in a set of twelve independent equations in the twenty-four unknowns given (in three dimensions) by the motion of the cell population, the motion of the ECM, the fluid velocity \mathbf{v}_ℓ , the volumetric fractions ϕ_c and ϕ_m , the pressure p , and the stress tensors \mathbf{T}_c and \mathbf{T}_m . Thus, in order to close the mathematical problem under study, additional information is required to

126 determine the symmetric second-order tensors \mathbf{T}_c and \mathbf{T}_m . Before addressing this issue, however, it is shown in the
 127 following how the dimensional analysis of the investigated set of equations leads to a considerable simplification of
 128 the problem at hand. From here on, it is hypothesised for simplicity that the permeability tensor is spherical, i.e.,
 129 $\mathbf{K} = K\mathbf{I}$, with \mathbf{I} being the identity tensor, which means that the tissue's hydraulic response is isotropic.

130 Although there are situations in which pressure and (constitutive) stress are naturally made non-dimensional by
 131 the same scaling factor, in the case studied in this manuscript, as in other well-established circumstances [23], the most
 132 natural non-dimensionalisation procedure calls for the introduction of different scaling factors (one for the pressure
 133 and one for the stress). Therefore, the dimensionless form of (10a)–(10c) can be written as

$$\operatorname{div}^*(\mathbf{T}_c^*) + \bar{\mathbf{m}}_{cm}^* + \frac{\Delta p}{E} \left[-\frac{\phi_c}{1-\phi_\ell} \nabla^* p^* + V \frac{\phi_c \phi_\ell \phi_m}{1-\phi_\ell} \frac{\mu^*}{K^*(\phi_\ell)} \mathbf{v}_{mc}^* \right] = \mathbf{0}, \quad (13a)$$

$$\operatorname{div}^*(\mathbf{T}_m^*) - \bar{\mathbf{m}}_{cm}^* + \frac{\Delta p}{E} \left[-\frac{\phi_m}{1-\phi_\ell} \nabla^* p^* + V \frac{\phi_c \phi_\ell \phi_m}{1-\phi_\ell} \frac{\mu^*}{K^*(\phi_\ell)} \mathbf{v}_{cm}^* \right] = \mathbf{0}, \quad (13b)$$

$$\mathbf{v}_\ell^* = V \frac{\phi_c \mathbf{v}_c^* + \phi_m \mathbf{v}_m^*}{1-\phi_\ell} - \frac{1}{(1-\phi_\ell)} \frac{K^*(\phi_\ell)}{\mu^*} \nabla^* p^*, \quad (13c)$$

134 with $V = \hat{v}_c / \hat{v}_\ell = (\mu \hat{\Gamma}_c dD) / (\hat{K} \Delta p)$. By substituting the parameters in Table 1, one obtains $V = 10^{-4} \div 10^{-3}$, meaning
 135 that the first term on the right-hand-side of (13c) can be regarded as negligible compared to the second one. Further-
 136 more, in most cases, the ratio $\Delta p/E$ has order of magnitude between 10^{-2} and 10^{-1} . Indeed, $\Delta p \sim 1$ kPa for normal
 137 tissues, while, for example, $E \sim 10$ kPa for softer fatty regions of the breast and $E \sim 40$ kPa for prostatic tissues [24].
 138 In the case of tumour tissues, Δp increases up to one order of magnitude because of the leakiness of the capillaries and
 139 the lack of efficacy of the lymphatic system. However, also the stiffness of the tumour tissue increases of one order
 140 of magnitude, which means that Δp usually remains at least one order of magnitude smaller than E . This confirms
 141 that, also for tumours, $\Delta p/E$ ranges approximately between 10^{-2} and 10^{-1} . Thus, in the case of both tumour and
 142 healthy tissues, one can try to look for approximate solutions to the set of equations (13a)–(13c) by dropping all terms
 143 coupling the dynamics of the fluid with the dynamics of the cell population and the ECM. Hence, in dimensional
 144 form, the simplified set of equations to study becomes

$$\operatorname{div}(\mathbf{T}_c) + \bar{\mathbf{m}}_{cm} = \mathbf{0}, \quad (14a)$$

$$\operatorname{div}(\mathbf{T}_m) - \bar{\mathbf{m}}_{cm} = \mathbf{0}, \quad (14b)$$

$$\mathbf{v}_\ell = -\frac{1}{(1-\phi_\ell)} \frac{K(\phi_\ell)}{\mu} \nabla p. \quad (14c)$$

145 Equations (14a) and (14b) depend neither on the interstitial pressure nor on the fluid velocity. Therefore, they can be
 146 solved without taking into account (12) and (14c), whose study is only required for the description of the evolution
 147 of the interstitial pressure and the fluid velocity, respectively. Consequently, the set of equations (10a)–(12) splits into
 148 two parts. The first part comprises Eqs. (14a), (14b), (11a) and (11b), with (14a) and (14b) replacing (10a) and (10b),
 149 respectively. The second part, instead, comprises Eqs. (12) and (14c), which can be solved *a posteriori*.

150 Depending on the actual value of $\Delta p/E$, replacing Eqs. (10a)–(10b) with Eqs. (14a)–(14b) may be quite a strong
 151 approximation in some cases. More rigorously, one should expand Eqs. (13a)–(13b) in asymptotic series of $\Delta p/E$
 152 and show that Eqs. (14a) and (14b) supply the conditions that must be satisfied by the terms of the lowest order in
 153 $\Delta p/E$. Thus, the solution to Eqs. (14a)–(14c) may need to be corrected by adding higher order terms, when the ratio
 154 $\Delta p/E$ does not fully justify the asymptotic limit. For this reason, in order to evaluate the reliability of the solution
 155 to Eqs. (14a)–(14c), an *a posteriori* estimate of the results becomes necessary. This will be done in Section 4 by
 156 comparing the results obtained by solving (10a)–(12) with those obtained by solving (14a)–(14c) and (11a)–(12).

157 3. Stress Tensor

158 The scope of this section is to determine a self-consistent evolution law for the Cauchy stress tensor \mathbf{T}_c associated
 159 with the cellular population. For this purpose, it is recalled that a tissue undergoing growth and reorganisation of

Table 1: Characteristic biological scaling factors

d [m]	Δp [N/m ²]	E [N/m ²]	$\hat{\Gamma}_c$ [s ⁻¹]	D [m]	ρ_w [kg/m ³]	\hat{v}_ℓ [m/s]	\hat{v}_c [m/s]	\hat{K}/μ [m ⁴ /(Ns)]
$3 \cdot 10^{-4}$ [25]	$10^3 \div 10^4$ [26, 27]	$10^4 \div 10^5$ [24]	10^{-5} [28]	10^{-5} [28]	10^3	$10^{-7} \div 10^{-6}$ [22]	10^{-10}	$10^{-15} \div 10^{-13}$ ($10^{-15} \div 10^{-12}$) [29]

its internal structure generally experiences inelastic distortions. It is possible to keep track of them by decomposing multiplicatively the deformation gradient of the cellular population, \mathbf{F}_c , as

$$\mathbf{F}_c = \mathbf{F}_e \mathbf{F}_p \mathbf{F}_g. \quad (15)$$

In Eq. (15), \mathbf{F}_e is the purely elastic contribution to the overall deformation gradient, whereas \mathbf{F}_g and \mathbf{F}_p represent the inelastic distortions related to growth and to the “plastic” reorganisation of the tissue’s internal structure. Note that each tensor introduced in (15) is non-singular.

Equation (15) is known as Bilby-Kröner-Lee decomposition and was firstly introduced in the context of the theory of dislocations in finite-strain elastoplasticity. Skalak [30] proposed the idea that growth is accompanied by incompatible deformations and residual stresses. Rodriguez *et al.* [31] suggested to decompose the deformation gradient into an elastic (accommodating) and a growth (inelastic) part. According to the picture put forward by Rajagopal [32], the tensors \mathbf{F}_g and \mathbf{F}_p determine the evolving natural (i.e., stress-free) configurations of a body undergoing inelastic processes.

A consequence of Eq. (15) is that the determinant of the deformation gradient, $J_c = \det(\mathbf{F}_c)$, can be written as $J_c = J_e J_p J_g$, with $J_e = \det(\mathbf{F}_e)$, $J_p = \det(\mathbf{F}_p)$ and $J_g = \det(\mathbf{F}_g)$. In the following, it is assumed that plastic distortions are isochoric, i.e., $J_p = 1$, and that \mathbf{F}_g has the form $\mathbf{F}_g = g\mathbf{I}$, with \mathbf{I} being the identity tensor. Thus, it holds that $\mathbf{F}_p \mathbf{F}_g = g\mathbf{F}_p$, and $J_g = g^3$ [11, 12].

Due to (15), the velocity gradient associated with the motion of the cells is given by the sum of three contributions:

$$\mathbf{L}_c = \dot{\mathbf{F}}_c \mathbf{F}_c^{-1} = \mathbf{L}_e + \mathbf{L}_p + (\dot{g}/g)\mathbf{I}. \quad (16)$$

In Eq. (16), and in the following, a superimposed dot denotes the time derivative following the motion of the cell population. Moreover, $\mathbf{L}_e = \dot{\mathbf{F}}_e \mathbf{F}_e^{-1}$ and $\mathbf{L}_p = \dot{\mathbf{F}}_p \mathbf{F}_p^{-1}$, with $\mathbf{A}_p = \dot{\mathbf{F}}_p \mathbf{F}_p^{-1}$, represent, respectively, the elastic and plastic part of the velocity gradient, whereas the purely volumetric term $(\dot{g}/g)\mathbf{I}$ is the contribution due to growth. Since \mathbf{F}_p is has unitary determinant, both \mathbf{L}_p and \mathbf{A}_p are deviatoric.

Considering the cell population as a quasi-incompressible elastic material [33] exhibiting isotropic behaviour from its natural state, and assuming that the strain energy density function \mathcal{W}_n , expressed per unit volume of the natural state, is of Neo-Hookean type, one can write

$$\mathcal{W}_n(\mathbf{B}_e) = \frac{1}{2}\kappa_0 \left(\sqrt{\det(\mathbf{B}_e)} - 1 \right)^2 + \frac{1}{2}\mu_0 \left(\text{tr}(\overline{\mathbf{B}}_e) - 3 \right). \quad (17)$$

In (17), $\mathbf{B}_e = \mathbf{F}_e \mathbf{F}_e^T$ is said to be the elastic left Cauchy-Green deformation tensor, and $\overline{\mathbf{B}}_e = J_e^{-2/3} \mathbf{B}_e$ is the modified left Cauchy-Green deformation tensor [34], while κ_0 and μ_0 are, respectively, the bulk and shear modulus measured with respect to the natural state of the cell population. The Cauchy stress tensor \mathbf{T}_c can be expressed constitutively as follows:

$$\mathbf{T}_c = \hat{\mathbf{T}}_c(\mathbf{B}_e) = \kappa_0 \left(\sqrt{\det(\mathbf{B}_e)} - 1 \right) \mathbf{I} + \mu_0 [\det(\mathbf{B}_e)]^{-5/6} \text{dev}(\mathbf{B}_e), \quad (18)$$

where the operator $\text{dev}(\cdot)$ extracts the deviatoric part of the second-order symmetric tensor to which it is applied, i.e. $\text{dev}(\mathbf{A}) = \mathbf{A} - \frac{1}{3}\text{tr}(\mathbf{A})\mathbf{I}$, for all $\mathbf{A} \in \text{Lin}$ (here, Lin is the space of all linear applications from the three-dimensional Euclidean vector space into itself).

Since Eq. (15) implies that $\mathbf{B}_e = g^{-2} \mathbf{F}_c (\mathbf{F}_p^{-1} \mathbf{F}_p^{-T}) \mathbf{F}_c^T$, the constitutive expressions of the Cauchy stress tensor \mathbf{T}_c , the elasticity tensor \mathbb{C} , and the strain energy density function \mathcal{W}_n must be accompanied by equations determining \mathbf{F}_c , \mathbf{F}_p and g . However, the tensor \mathbf{F}_c , which is entirely defined by the motion of the cell population, is not an additional unknown for the model. Tensors \mathbf{F}_p and \mathbf{F}_g , instead, must be determined by solving proper evolution equations.

194 The equation determining g can be obtained self-consistently by working out Eq. (11a), see for instance [35, 36].
 195 Firstly, Eq. (11a) is multiplied by J_c and written in the form $\overline{J_c \phi_c} = J_c \Gamma_c$. Secondly, recalling the equality $J_c = J_e J_g$
 196 (which applies because $J_p = 1$), one obtains

$$(J_e \phi_c) \dot{J}_g + J_g \overline{\dot{(J_e \phi_c)}} = J_c \Gamma_c. \quad (19)$$

197 Furthermore, since it holds that $\dot{J}_g = J_g \text{tr}(\mathbf{L}_g)$, with $\mathbf{L}_g = \dot{\mathbf{F}}_g \mathbf{F}_g^{-1}$, Eq. (19) becomes

$$J_c \phi_c \text{tr}(\mathbf{L}_g) + J_g \overline{\dot{(J_e \phi_c)}} = J_c \Gamma_c. \quad (20)$$

198 Thirdly, it is imposed that the rate of mass change of the cell population, Γ_c , is entirely compensated for by the volume
 199 change due to growth. This requirement leads to the condition $J_c \phi_c \text{tr}(\mathbf{L}_g) = J_c \Gamma_c$, which can be rewritten as

$$\frac{\dot{g}}{g} = \frac{1}{3} \frac{\Gamma_c}{\phi_c}, \quad (21)$$

200 as well as it constrains the product $J_e \phi_c$ to be constant in time. Thus, by introducing the constant auxiliary quantity
 201 $\phi_{\text{cn}} := J_e \phi_c$, which measures the volumetric fraction of the cell population per unit volume of the natural state and is
 202 assumed to be known from the outset, ϕ_c is determined by

$$\phi_c = J_e^{-1} \phi_{\text{cn}} = g^3 (\det(\mathbf{F}_c))^{-1} \phi_{\text{cn}}. \quad (22)$$

203 Equation (21), equipped with an initial condition, determines g univocally, provided that Γ_c is given constitutively. An
 204 alternative form of the evolution equation for g can be obtained by substituting (22) into (21).

205 Following the standard theory of isotropic elasto-plastic materials, it can be shown that $\text{sym}(\mathbf{\Lambda}_p)$ can be related to
 206 stress by means of an expression of the type

$$\text{sym}(\mathbf{\Lambda}_p) = \lambda \mathbf{F}_e^T \text{dev}(\mathbf{T}_c) \mathbf{F}_e^{-T}, \quad (23)$$

207 where λ is a non-negative scalar function, see, e.g., [37]. It should be remarked that the constitutive form of \mathbf{T}_c
 208 guarantees that the right-hand-side of Eq. (23) is a symmetric second-order tensor. Furthermore, it can be proven that,
 209 if the plastic spin, $\text{skew}(\mathbf{\Lambda}_p)$, is assumed to vanish identically, Eq. (23) can be equivalently rewritten as

$$\mathbf{L}_p = \text{sym}(\mathbf{L}_p) = \lambda \text{dev}(\mathbf{T}_c). \quad (24)$$

210 By exploiting the kinematic relation $\mathbf{\Lambda}_p = \dot{\mathbf{F}}_p \mathbf{F}_p^{-1}$, and using the result (23) and the assumption $\text{skew}(\mathbf{\Lambda}_p) = \mathbf{0}$, the
 211 following evolution equation for \mathbf{F}_p can be written:

$$\dot{\mathbf{F}}_p = \lambda \left[\mathbf{F}_p^{-T} \left(\mathbf{F}_c^T \text{dev}(\mathbf{T}_c) \mathbf{F}_c^{-T} \right) \mathbf{F}_p^T \right] \mathbf{F}_p. \quad (25)$$

212 In Eqs. (23)–(25), the function λ is defined as in [39, 40]

$$\lambda(\phi_c, \mathbf{T}'_c) = \frac{1}{2\eta(\phi_c)} \left[1 - \frac{\tau(\phi_c)}{f(\mathbf{T}'_c)} \right]_+, \quad (26)$$

213 where $\mathbf{T}'_c \equiv \text{dev}(\mathbf{T}_c)$ denotes the deviatoric part of the Cauchy stress tensor \mathbf{T}_c , $\tau(\phi_c)$ is the maximum stress that can be
 214 sustained by the cell aggregate (this stress is referred to as *yield stress*), $f(\mathbf{T}'_c)$ defines a proper measure of equivalent
 215 stress, and $\eta(\phi_c)$ (with units $[\eta(\phi_c)] = (\text{Ns})/\text{m}^2$) is a function assigned phenomenologically.

216 By means of some algebraic calculations [34, 38], a given constitutive law $\mathbf{T}_c = \hat{\mathbf{T}}_c(\mathbf{B}_e)$ can be rewritten in differ-
 217 ential form as follows

$$\dot{\mathbf{T}}_c - \mathbf{L}_c \mathbf{T}_c - \mathbf{T}_c \mathbf{L}_c^T + \text{tr}(\mathbf{L}_c) \mathbf{T}_c = \mathbb{C} : (\mathbf{D}_c - \mathbf{D}_d) - \mathbf{L}_d \mathbf{T}_c - \mathbf{T}_c \mathbf{L}_d^T + \text{tr}(\mathbf{L}_d) \mathbf{T}_c, \quad (27)$$

218 with $\mathbf{D}_c = \text{sym}(\mathbf{L}_c)$, $\mathbf{L}_d = \mathbf{L}_p + \dot{g} g^{-1} \mathbf{I}$, and $\mathbf{D}_d = \text{sym}(\mathbf{L}_d)$. The left-hand-side of Eq. (27) is referred to as the Truesdell
 219 rate of the Cauchy stress [34], and it is defined by $J_c^{-1} \mathcal{L}_{v_c} (J_c \mathbf{T}_c)$, where \mathcal{L}_{v_c} is the Lie-derivative operator following

220 \mathbf{v}_c (given a second-order tensor \mathbf{A} , $\mathcal{L}_{\mathbf{v}_c} \mathbf{A}$ can be computed as $\mathcal{L}_{\mathbf{v}_c} \mathbf{A} = \mathbf{F}_c \overline{(\mathbf{F}_c^{-1} \mathbf{A} \mathbf{F}_c^{-T})} \mathbf{F}_c^T$). The fourth-order tensor \mathbb{C}
 221 is the spatial elasticity tensor, i.e., the push-forward of the elasticity tensor $\mathbb{C}_n = 4(\partial^2 \mathcal{W}_n / \partial \mathbf{C}_e^2)$ associated with the
 222 natural configuration, and is defined by $J_e \mathbb{C} = \mathbf{F}_e \otimes \mathbf{F}_e : \mathbb{C}_n : \mathbf{F}_e^T \otimes \mathbf{F}_e^T$. For any pair of second-order tensors \mathbf{A} and \mathbf{B} ,
 223 the product $\mathbf{A} \otimes \mathbf{B}$ has components $(\mathbf{A} \otimes \mathbf{B})_{abcd} = A_{ac} B_{bd}$. Note that, to compute \mathbb{C}_n , the strain energy density \mathcal{W}_n has
 224 been reformulated as a function of the elastic right Cauchy-Green deformation tensor $\mathbf{C}_e = \mathbf{F}_e^T \mathbf{F}_e$. For the specific
 225 form of \mathcal{W}_n given in (17), \mathbb{C} becomes

$$\mathbb{C} = -\frac{2}{3} \mu_0 J_e^{-5/3} [\mathbf{B}_e \otimes \mathbf{I} + \mathbf{I} \otimes \mathbf{B}_e] + \left(\kappa_0 + \frac{8}{9} \mu_0 J_e^{-5/3} \text{tr}(\mathbf{B}_e) \right) \mathbf{I} \otimes \mathbf{I} \quad (28)$$

$$+ \left(2\kappa_0 (J_e - 1) - \frac{2}{3} \mu_0 J_e^{-5/3} \text{tr}(\mathbf{B}_e) \right) (\mathbf{I} \otimes \mathbf{I} - \mathbf{I} \underline{\otimes} \mathbf{I}),$$

226 where the symbol \otimes denotes the standard tensor product, and the fourth-order tensor $\mathbf{I} \underline{\otimes} \mathbf{I}$, which has components
 227 $(\mathbf{I} \underline{\otimes} \mathbf{I})_{abcd} = \frac{1}{2}(I_{ac} I_{bd} + I_{ad} I_{bc})$, is such that $(\mathbf{I} \underline{\otimes} \mathbf{I}) : \mathbf{A} = \text{sym}(\mathbf{A})$, for all second-order tensors $\mathbf{A} \in \text{Lin}$, with $\text{sym}(\cdot)$
 228 being the operator that extracts the symmetric part of the second-order tensor to which it is applied.

229 By using the constitutive expression of \mathbb{C} given in Eq. (28), taking the deviatoric part of both sides of Eq. (27),
 230 and performing some algebraic manipulations that involve the relation reported in Eq. (21), one obtains

$$\dot{\mathbf{T}}'_c + \left(\frac{5}{3} \text{div}(\mathbf{v}_c) - \frac{\Gamma_c}{\phi_c} \right) \mathbf{T}'_c + 2\mu_0 \left(\frac{\phi_c}{\phi_{cn}} \right)^{5/3} \text{devsym}(\mathbf{L}_p \mathbf{B}_e) = 2\mu_0 \left(\frac{\phi_c}{\phi_{cn}} \right)^{5/3} \text{devsym}((\nabla \mathbf{v}_c) \mathbf{B}_e). \quad (29)$$

231 Equivalently, substituting \mathbf{L}_p with the right-hand-side of Eq. (24) leads to

$$\dot{\mathbf{T}}'_c + \left(\frac{5}{3} \text{div}(\mathbf{v}_c) - \frac{\Gamma_c}{\phi_c} \right) \mathbf{T}'_c + 2\mu_0 \lambda(\phi_c \mathbf{T}'_c) \left(\frac{\phi_c}{\phi_{cn}} \right)^{5/3} \text{devsym}(\mathbf{T}'_c \mathbf{B}_e) = 2\mu_0 \left(\frac{\phi_c}{\phi_{cn}} \right)^{5/3} \text{devsym}((\nabla \mathbf{v}_c) \mathbf{B}_e). \quad (30)$$

232 In (29) and (30), the operator $\text{devsym}(\cdot)$ extracts the deviatoric part of the symmetric part of the second-order tensor
 233 to which it is applied.

234 Equation (30) can be simplified considerably by assuming that the elastic part of the overall deformation gradient
 235 is small enough throughout the evolution of the system. The experiments reported in [41] give an indication of the
 236 order of magnitude of the yield stress, that depends on ϕ_c , and is below 1 Pa (for $\phi_c = 0.6$, the maximum volume ratio
 237 tested).

238 In the limit of small elastic deformations, i.e., $\mathbf{B}_e \approx \mathbf{I}$, Eq. (30) acquires the simplified form

$$\dot{\mathbf{T}}'_c + \left(\frac{5}{3} \text{div}(\mathbf{v}_c) - \frac{\Gamma_c}{\phi_c} \right) \mathbf{T}'_c + 2\mu_0 \lambda(\phi_c \mathbf{T}'_c) \left(\frac{\phi_c}{\phi_{cn}} \right)^{5/3} \mathbf{T}'_c = 2\mu_0 \left(\frac{\phi_c}{\phi_{cn}} \right)^{5/3} \text{devsym}(\nabla \mathbf{v}_c), \quad (31)$$

239 with $\dot{\mathbf{T}}'_c = \partial_t \mathbf{T}'_c + (\nabla \mathbf{T}'_c) \mathbf{v}_c$. Equation (31), equipped with appropriate initial and boundary conditions, determines
 240 completely the evolution of \mathbf{T}'_c within the approximation of small elastic deformations. Working with (31) permits
 241 to regard \mathbf{T}'_c as an independent (tensorial) unknown, whose determination involves the knowledge of the velocity
 242 \mathbf{v}_c (rather than the motion of the cellular phase) and the volumetric fractions ϕ_c and ϕ_m , which can be found by
 243 solving (11a) and (11b). In particular, there are two main advantages of expressing the constitutive law for the Cauchy
 244 stress in differential form. The first one is that the whole system of equations can be formulated and solved in Eulerian
 245 formalism, i.e., without having to define a reference configuration. The second advantage is that, by formulating the
 246 constitutive law for the stress in differential form, the evolution equations (21) and (25) are already included in (31).
 247 Thus, (21) and (25) need not be explicitly considered in the global system of equations, and can be used *a posteriori*
 248 to determine g and \mathbf{F}_p , if required. Moreover, the partial differential equation (31) offers a formal analogy between the
 249 elasto-plastic model presented in this paper and some viscoelastic constitutive models available in the literature, such
 250 as the Maxwell's model. In principle, a result analogue to Eq. (31) can be obtained for \mathbf{T}'_m .

251 The function λ in Eq. (31) plays the role of a stress relaxation term, which is activated as soon as the stress is
 252 above the yield stress $\tau(\phi_c)$. In principle, the limit in which $[\lambda(\phi_c, \mathbf{T}'_c)]^{-1}$ is much larger than the characteristic time
 253 of the process of interest would lead to the models used in [7, 8, 9, 10]. However, in this case, the procedure is
 254 incompatible with the small deformation assumption because the stress relaxes very slowly and, thus, large stresses
 255 and deformations can build up.

4. The Case of Rigid and Inert ECM and Small Elastic Deformations of the Cellular Phase

Several simplifications can be obtained by assuming that $\bar{\mathbf{m}}_{\text{cm}}$ can be expressed as $\bar{\mathbf{m}}_{\text{cm}} = -\mathbf{M}_{\text{cm}}(\mathbf{v}_c - \mathbf{v}_m)$, with $\mathbf{M}_{\text{cm}} = M_{\text{cm}}\mathbf{I}$ being a spherical tensor, and studying the case in which the ECM is assumed to be rigid and at rest (i.e., $\mathbf{v}_m = \mathbf{0}$), and inert. Requiring the ECM to be inert means that the ECM does not exchange mass with the other constituents, so that the condition $\Gamma_m = 0$ applies. The first consequence of this condition is that Eq. (4) reduces to $\Gamma_\ell = -(\rho_c/\rho_\ell)\Gamma_c$, this implying that, in a closed system, the mass exchange rate of the fluid phase Γ_ℓ is entirely determined by Γ_c and the (constant) ratio ρ_c/ρ_ℓ . The second consequence is that the volumetric fraction of the ECM, ϕ_m , is constant in time. Indeed, setting $\Gamma_m = 0$, and recalling the condition $\mathbf{v}_m = \mathbf{0}$, the mass balance law associated with the ECM becomes $\partial_t \phi_m = 0$ (cf. (11b)), which yields $\phi_m(\mathbf{x}, t) = \phi_{m0}(\mathbf{x})$, with $\phi_{m0}(\mathbf{x})$ being known from the outset. The third consequence is that the volumetric fraction of the fluid phase can be expressed as $\phi_\ell = 1 - (\phi_c + \phi_{m0})$. Furthermore, the momentum balance law (10a), the mass balance law (11a), and Eqs. (12) and (10c) can be put in the following form:

$$\mathbf{v}_c = -\frac{\phi_c}{Q(\phi_c)}\nabla p + \frac{\phi_c + \phi_{m0}}{Q(\phi_c)}\text{div}(\mathbf{T}_c), \quad (32a)$$

$$\partial_t \phi_c + \text{div}(\phi_c \mathbf{v}_c) = \Gamma_c, \quad (32b)$$

$$\text{div}\left(\frac{1 - (\phi_c + \phi_{m0})}{\phi_c + \phi_{m0}} \frac{K}{\mu} \nabla p\right) = \text{div}\left(\frac{\phi_c}{\phi_c + \phi_{m0}} \mathbf{v}_c\right) - \left(1 - \frac{\rho_c}{\rho_\ell}\right)\Gamma_c, \quad (32c)$$

$$\mathbf{v}_\ell = -\frac{1}{\phi_c + \phi_{m0}} \left(\frac{\phi_c^2}{Q(\phi_c)} + \frac{K}{\mu}\right)\nabla p + \frac{\phi_c}{Q(\phi_c)}\text{div}(\mathbf{T}_c), \quad (32d)$$

where the auxiliary function $Q(\phi_c)$ is defined by

$$Q(\phi_c) := (\phi_c + \phi_{m0})M_{\text{cm}} + \phi_c \phi_{m0} \left(1 - \phi_c - \phi_{m0}\right) \frac{\mu}{K}, \quad (33)$$

and, for consistency with Eq. (7), M_{cm} is taken as $M_{\text{cm}} = \phi_c \phi_{m0} M_{\text{cm}}^{(0)}$, with $M_{\text{cm}}^{(0)}$ being a given constant. Note that, if the mass densities of the cellular phase, ρ_c , and of the fluid, ρ_ℓ , are approximately equal to each other, the last term on the right-hand-side of Eq. (32c) can be neglected.

Since the ECM is rigid in the present formulation, the stress tensor \mathbf{T}_m becomes constitutively indeterminate, and only its divergence, $\text{div}(\mathbf{T}_m)$, is determined univocally by the force balance

$$\text{div}(\mathbf{T}_m) = \nabla p - \text{div}(\mathbf{T}_c), \quad (34)$$

which is obtained by adding together Eqs. (10a) and (10b). This means that (34) is decoupled from (32a)–(32d), and $\text{div}(\mathbf{T}_m)$ can be computed *a posteriori* once ∇p and $\text{div}(\mathbf{T}_c)$ are known. Finally, since \mathbf{v}_ℓ features only on the left-hand-side of (32d), it is decoupled from Eqs. (32a)–(32c), and can thus be determined *a posteriori* too.

To close the mathematical problem, \mathbf{T}_c has to be expressed constitutively, as done, e.g., in (18). This requires, however, to consider also the evolution equations for g and \mathbf{F}_p , given by (21) and (25), respectively, in addition to the already introduced model equations. Consequently, the effective unknowns of the problem are fourteen (in three dimensions) and are given by the three components of the motion of the cellular phase, the volumetric fraction ϕ_c , the pressure p , the scalar field g , and the unimodular tensor field \mathbf{F}_p (recall that, due to the constraint $\det(\mathbf{F}_p) = 1$, only eight of the nine components of \mathbf{F}_p can be independent).

4.1. The reduced and the unreduced model

In conclusion, the conditions of rigid, immobile, and inert ECM lead to a highly non-linear, closed mathematical model based on Eqs. (32a)–(32c), (18), (21) and (25). Such a model can be further drastically simplified, if the hypothesis of small elastic deformations is invoked. Indeed, by expressing the Cauchy stress \mathbf{T}_c as

$$\mathbf{T}_c = \kappa_0 \text{tr}(\mathbf{E}_c)\mathbf{I} + \mathbf{T}'_c, \quad (35)$$

where \mathbf{E}_c is the elastic strain tensor, the deviatoric part \mathbf{T}'_c plays the role of an independent tensorial variable involving (in three dimensions, and due to the condition $\text{tr}(\mathbf{T}'_c) = 0$) only five independent scalar unknowns, and the spherical

289 contribution $\kappa_0 \text{tr}(\mathbf{E}_c) \mathbf{I}$ is determined by $\kappa_0 \text{tr}(\mathbf{E}_c) \mathbf{I} = \kappa_0 (\phi_{cn}/\phi_c - 1) \mathbf{I}$. The latter equality is obtained by recalling that,
 290 from (22), the ratio ϕ_{cn}/ϕ_c is equal to J_e , and that J_e can be approximated as $J_e \sim 1 + \text{tr}(\mathbf{E}_c)$ in the limit $\mathbf{E}_c \rightarrow \mathbf{0}$.
 291 Moreover, if Γ_c is assumed to be independent on g and \mathbf{F}_p , neither the growth term g , nor the remodelling tensor
 292 \mathbf{F}_p , appear explicitly in (31), so that Eqs. (21) and (25) can be solved *a posteriori*. By virtue of this reasoning, and
 293 within the range of validity of the hypotheses introduced so far, the mathematical model requires the solution of the
 294 ten coupled equations (32a)–(32c) and (31), which are needed to determine the ten independent unknowns \mathbf{v}_c , ϕ_c , p
 295 and \mathbf{T}'_c . An important consequence of this approach is that \mathbf{v}_c is used as an independent vector variable, in place of
 296 the three components of the motion of the cellular phase.

297 In view of the Finite Element (FE) analysis of Eqs. (32a)–(32c) and (31), it should be remarked that, since the
 298 independent components of \mathbf{T}'_c are regarded as degrees of freedom in the present dissertation, suitable FE functional
 299 spaces have to be introduced to interpolate \mathbf{T}'_c over a given computational domain. Furthermore, in contrast to standard
 300 FE methods, in which the stress is usually evaluated at the integration points of the finite elements, \mathbf{T}'_c is computed at
 301 the nodes of the elements in the present formulation.

302 It is worth to mention that, by taking κ_0 and ϕ_{cn} as model constants and Γ_c as a function of ϕ_c , and rewriting \mathbf{v}_c as

$$\mathbf{v}_c = -\mathcal{D}(\phi_c) \nabla \phi_c + \mathbf{w}_c = - \underbrace{\left(\frac{\kappa_0 \phi_{cn}}{\phi_c^2} \frac{\phi_c + \phi_{m0}}{Q(\phi_c)} \right)}_{:=\mathcal{D}(\phi_c)} \nabla \phi_c + \underbrace{\left(-\frac{\phi_c}{Q(\phi_c)} \nabla p + \frac{\phi_c + \phi_{m0}}{Q(\phi_c)} \text{div}(\mathbf{T}'_c) \right)}_{:=\mathbf{w}_c}, \quad (36)$$

303 the mass balance law (32b) can be recast in the form of a non-linear advection-diffusion-reaction equation in the
 304 variable ϕ_c :

$$\partial_t \phi_c = \text{div} \left(\frac{\kappa_0 \phi_{cn}}{\phi_c} \frac{\phi_c + \phi_{m0}}{Q(\phi_c)} \nabla \phi_c \right) + \text{div} \left[\phi_c \left(\frac{\phi_c}{Q(\phi_c)} \nabla p - \frac{\phi_c + \phi_{m0}}{Q(\phi_c)} \text{div}(\mathbf{T}'_c) \right) \right] + \Gamma_c(\phi_c). \quad (37)$$

305 Indeed, since κ_0 and $Q(\phi_c)$ are positive, and also so are also ϕ_c , ϕ_{cn} and ϕ_{m0} , the coefficient $\mathcal{D}(\phi_c)$ is positive definite
 306 and can be identified with a non-linear diffusion coefficient. The auxiliary velocity \mathbf{w}_c is instead responsible for
 307 advection, and $\Gamma_c(\phi_c)$ is a non-linear reaction term.

308 Finally, by performing the dimensional analysis discussed in Section 2.2 to Eqs. (32a)–(32c) and (31), and noticing
 309 that only Eq. (32a) involves the ratio $\Delta p/E$, one can conclude that, when the ratio $\Delta p/E$ is sufficiently small, the
 310 expression of \mathbf{v}_c simplifies as follows

$$\mathbf{v}_c = \frac{1}{M_{cm}} \left(\nabla \left(\kappa_0 \frac{\phi_{cn}}{\phi_c} \right) + \text{div}(\mathbf{T}'_c) \right), \quad (38)$$

311 and the mathematical model further reduces to Eqs. (38), (32b), and (31), whereas the equations pertaining to the
 312 fluid phase, i.e. (32c) and (32d), become decoupled from the former ones and can thus be solved independently *a*
 313 *posteriori*.

314 In the following, the set of equations (32a)–(32c) and (31) shall be referred to as the *unreduced model*, whereas
 315 Eqs. (32b), (31) and (38) (with the latter one replacing Eq. (32a)) as *reduced model*.

316 4.2. A Benchmark Problem: The Uniaxial Expansion Test

317 To test the mathematical model introduced in the previous sections and, above all, to compare the results obtained
 318 by the reduced model with those of the unreduced one, a benchmark problem is studied hereafter. The problem
 319 considers the evolution of a biological portion of tissue confined in a fixed region of space $\Omega = [-h/2, h/2]^2 \times [0, L]$,
 320 with $h > 0$ and $L > 0$. The boundary of Ω , $\partial\Omega$, is assumed to be rigid. Moreover, only $\partial\Omega_{\text{per}} = [-h/2, h/2]^2 \times \{L\}$
 321 allows exudation of the interstitial fluid, while $\partial\Omega \setminus \partial\Omega_{\text{per}}$ is impermeable. Cancer cells, which undergo abnormal
 322 growth, occupy at time $t \in \mathbb{R}_0^+$ the time-dependent region $\omega_t \subset \Omega$ defined by $\omega_t = \{\mathbf{x} \in \Omega \mid H(\zeta(\mathbf{x}, t)) > 0\}$,
 323 where $H(\cdot)$ is a mollified Heaviside function, and ζ is a level set function introduced to instantaneously separate the
 324 subregion of tissue in which growth occurs from the rest of the tissue.

325 As stated in Section 3, growth is described by purely volumetric inelastic distortions, while the distortions due
 326 to remodelling are taken to be isochoric, so that Eqs. (21) and (24) hold. The mass exchange rate Γ_c is chosen as

327 $\Gamma_c(\phi_c) = \gamma_c \phi_c [\phi_{\max} - \phi_c]_+ H(\zeta)$, where γ_c is a phenomenological coefficient, $\phi_{\max} \leq 1$ is the maximal volumetric
 328 fraction attainable by the cell population, and $[f]_+$ returns f , if f is positive, and zero otherwise.

329 Consistently with what prescribed by Eq. (26), remodelling is triggered only in those regions of the tissue in which
 330 $f(\mathbf{T}'_c)$ exceeds the yield stress, i.e., $f(\mathbf{T}'_c) > \tau(\phi_c)$. In the case of theories based on von Mises' equivalent stress, f is
 331 chosen as $f(\mathbf{T}'_c) = \sqrt{(3/2)}\|\mathbf{T}'_c\| = \sqrt{(3/2)\text{tr}(\mathbf{T}'_c\mathbf{T}'_c)}$ [42], whereas f is defined by

$$2f(\mathbf{T}'_c) = \max \{|\sigma_1 - \sigma_2|, |\sigma_1 - \sigma_3|, |\sigma_2 - \sigma_3|\}, \quad (39)$$

332 with $\{\sigma_i\}_{i=1}^3$ being the principal stresses, in the case of theories based on Tresca's equivalent stress. In the present
 333 treatment, however, the function f is simply given by $f(\mathbf{T}'_c) = |T'_{c_{xx}}|$, where $T'_{c_{xx}}$ is the axial component of the
 334 deviatoric part of \mathbf{T}'_c . Although $|T'_{c_{xx}}|$ does not necessarily represent an equivalent stress, setting $f(\mathbf{T}'_c) = |T'_{c_{xx}}|$ has the
 335 advantage that the yield criterium, i.e., the condition $|T'_{c_{xx}}| > \tau(\phi_c)$, to be met for triggering plastic (i.e., remodelling)
 336 distortions, does not require the knowledge of the transversal components of the stress.

337 As previously discussed, by considering the case in which the extracellular matrix is inert ($\Gamma_m = 0$), homogeneous
 338 ($\phi_{m0}(\mathbf{x}) = \bar{\phi}_{m0}$, with $\bar{\phi}_{m0}$ being a model constant), rigid and immobile ($\mathbf{v}_m(\mathbf{x}, t) = \mathbf{0}$), and assuming that the elastic
 339 deformations of the cellular phase are small, the evolution of the system is represented by Eqs. (32a)–(32c), (31), and
 340 a proper equation representing the evolution of the level set function ζ , i.e.,

$$\partial_t \zeta + \nabla \zeta \cdot \mathbf{v}_c = 0, \quad (40a)$$

$$\zeta(\mathbf{x}, 0) = \zeta_0(\mathbf{x}). \quad (40b)$$

341 The problem can be strongly simplified by assuming $\zeta_0(\mathbf{x}) = \zeta_0(x)$ and $\mathbf{v}_c(\mathbf{x}, t) = v_{cx}(x, t)\mathbf{e}_x$, with $x \in [0, L]$, and
 342 \mathbf{e}_x being the unit vector along the axial direction of Ω (normal to its cross section), and exploiting the fact that \mathbf{T}'_c
 343 is diagonal. Therefore, the effective unknowns characterising the unreduced model are six and are given by v_{cx} , ϕ_c ,
 344 p , $T'_{c_{xx}}$, $T'_{c_{yy}}$, and the level set function ζ . Moreover, the particularly simple choice of the function $f(\mathbf{T}'_c) = |T'_{c_{xx}}|$
 345 decouples Eq. (31), written for $T'_{c_{yy}}$, from the rest of the system of equations. This allows to eliminate $T'_{c_{yy}}$ from the
 346 list of the effective unknowns of the unreduced model.

347 By invoking the same hypotheses as above also for the case of the reduced model, the effective unknowns become
 348 v_{cx} , ϕ_c and $T'_{c_{xx}}$, while p , together with all other quantities pertaining to the fluid phase, can be computed *a posteriori*.

349 In order to solve the problem, proper boundary conditions should be provided. In particular, the velocity of the
 350 solid phase should vanish at both $x = 0$ and $x = L$, since the border of the domain is rigid. This leads to the constraints
 351 $\partial_x T'_{c_{xx}}|_{x=0,L} = 0$ and $\partial_x \phi_c|_{x=0,L} = 0$. On the other hand, for what concerns the calculation of the pressure, the boundary
 352 conditions $\partial_x p|_{x=0} = 0$ (impermeable wall) and $p|_{x=L} = 0$ (permeable wall) are imposed.

353 Fig. 1 shows a comparison between the results obtained for the cell volume fraction, ϕ_c , the component $T'_{c_{xx}}$ of
 354 the deviatoric part of the cellular stress tensor, the constitutive part of the normal stress along the x -direction, $T_{c_{xx}}$,
 355 and the pressure p , obtained by employing both the reduced model (solid lines) and the unreduced model (dots). The
 356 results almost overlap in the first instant of time. However, some slight differences are perceivable only for very long
 357 times, mostly in the pressure field (see Fig. 1-d), and mainly due to its smallness.

358 From Fig. 1-a, it is clear that the tumour mass located in the right-region of the tissue grows and expands, so that
 359 the healthy tissue, that does not experience growth, is compressed (see Fig. 1-c). For the particular case shown in
 360 Fig. 1, remodelling is not triggered for the chosen value of $\tau(\phi_c)$, since $|T'_{c_{xx}}|$ is always smaller than the yield stress.
 361 Moreover, it is possible to see from Fig. 1-d that the pressure drop in the tissue is very small compared with the elastic
 362 modulus of the tissue ($E = 0.02$ MPa): indeed, the assumptions needed for decoupling the model are satisfied.

363 The reduced model proposed in this paper also allows to study the effects of remodelling on the tissue. In particular
 364 the results obtained for ϕ_c and $T'_{c_{xx}}$ using the reduced model are reported in Fig. 2, where the solid blue line refers
 365 to the case in which remodelling occurs ($\tau(\phi_c) = \tau_0 = 0.0025$ MPa), and the red dashed lines to the case in which
 366 remodelling is not triggered, with $\tau(\phi_c) = \tau_0$ unrealistically set to 25 MPa. The unreduced model leads to similar
 367 results. As it is possible to see in Fig. 2, remodelling starts when $|T'_{c_{xx}}| > \tau_0$ and it has the effect of limiting the
 368 magnitude of $|T'_{c_{xx}}|$ to a value slightly bigger than τ_0 (because of the particular chosen remodelling criterion), see
 369 Fig. 2-b. Moreover, as it is possible to notice in Fig. 2-a, the effect of remodelling is also to redistribute the volumetric
 370 fraction of the cellular phase in the whole region, reducing the amplitude of the discontinuity in ϕ_c between the
 371 proliferative and the non-proliferative region.

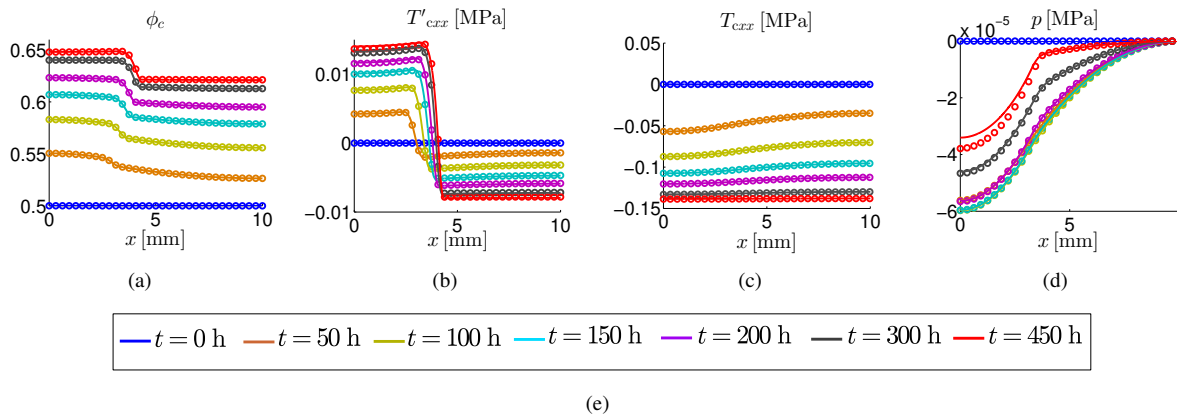


Figure 1: Comparison of the results obtained in terms of (a) ϕ_c , (b) T'_{cex} , (c) T_{cex} and (d) p for the uniaxial expansion test, solving the unreduced problem (dots) and the reduced problem (solid lines) when remodelling does not occur. Simulation parameter setting: $\kappa_0 = 0.667$ MPa, $\mu_0 = 0.019$ MPa, $\phi_{cn} = 0.5$, $\phi_{max} = 0.65$, $\gamma_c = 1/24 \text{ h}^{-1}$, $\chi = \mu_0/\eta = 0.1 \text{ h}^{-1}$, $\tau(\phi_c) = \tau_0 = 25$ MPa, $\mu = 1$ cP, $K/\mu = 10^{-12} \text{ m}^4/(\text{Ns})$ and $M_{cm}^{(0)} = 10^4 \text{ (MPa s)/mm}^2$. At time $t = 0$, the initial configuration of the tumour is given by $\omega_0 = \{x \in \Omega \mid H(x_T - x) > 0\}$, with $x_T = 2.5$ mm.

5. Conclusions

In this work, a *reduced model* has been proposed, which has been derived from the theory of evolving natural configurations. Such reduced model is applicable whenever the assumptions discussed in Sections 2.2, 3 and 4.1 hold. The two principal facts, on which the reduced model relies, are: (i) that many living tissues can sustain only moderate elastic deformations, so that the elastic part of the deformation gradient can be approximated by means of the linear strain tensor; (ii) that, as shown by some experimental results, the typical pressure drops Δp are smaller than the Young modulus of the tumour, and the characteristic velocity related to cell duplication is much smaller than the one of the interstitial fluid. These biological observations allow to decouple the growth problem from the interstitial flow one, and lead to a strong simplification of the mathematical description. The analytical speculation is confirmed by the numerical simulations.

In conclusion, this work demonstrates that, in many relevant biological problems, the equations describing the theory of evolving natural configurations strongly simplifies, becoming easily manageable without much loss of accuracy.

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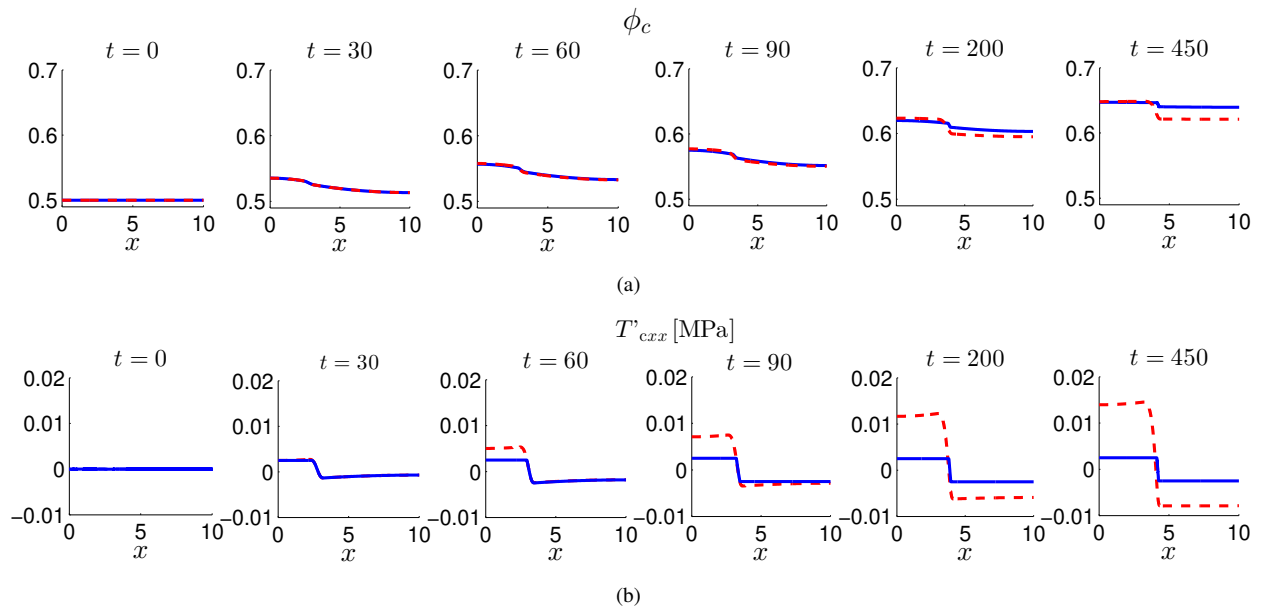


Figure 2: Comparison at different time instants of time, between (a) ϕ_c and (b) T'_{cxx} in the absence of remodelling (red dashed lines) and in the presence of remodelling (blue solid lines). The results are obtained solving the reduced problem. Solving the unreduced problem leads to similar results. The yield stress is equal to $\tau(\phi_c) = \tau_0 = 25$ MPa in the case in which no remodelling occurs, whereas it is $\tau(\phi_c) = \tau_0 = 0.0025$ MPa in the simulations with remodelling. All the other parameters are the same as in Fig. 1.

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