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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

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

$$\partial_t(\phi_\alpha \mathbf{v}_\alpha) + \mathrm{div}(\phi_\alpha \mathbf{v}_\alpha \otimes \mathbf{v}_\alpha) = \frac{1}{\rho_\alpha}\mathrm{div}\left(\widetilde{\mathbf{T}}_\alpha\right) + \frac{1}{\rho_\alpha}\left(\widetilde{\mathbf{m}}_\alpha + \rho_\alpha \Gamma_\alpha \mathbf{v}_\alpha\right). \tag{2}$$

In (1) and (2), and with reference to the αth phase, ϕ_α is the volumetric fraction, $\mathbf{v}_\alpha$ is the velocity, ρ_α is the true volumetric mass density, $\widetilde{\mathbf{T}}_\alpha$ is the partial stress tensor, and, finally, Γ_α and $\widetilde{\mathbf{m}}_\alpha$ represent, respectively, the rates at which the αth 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 $\sum_{\alpha=\mathrm{c},\ell,\mathrm{m}} \phi_\alpha = 1$ has to hold. Consequently, summing Eq. (1) over all phases yields

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

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

$$\rho_\mathrm{c}\Gamma_\mathrm{c} + \rho_\ell\Gamma_\ell + \rho_\mathrm{m}\Gamma_\mathrm{m} = 0\,. \tag{4}$$

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 $\sum_{\alpha=\mathrm{c},\ell,\mathrm{m}} \Gamma_\alpha = 0$.

The term $\widetilde{\mathbf{m}}_\alpha$ in Eq. (2) contains all forces acting on the αth 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 $\widetilde{\mathbf{m}}_\alpha = \widetilde{\mathbf{m}}_\alpha^{(\mathrm{d})} + p\nabla\phi_\alpha$, where p is the pressure of the interstitial fluid, and the summands $\widetilde{\mathbf{m}}_\alpha^{(\mathrm{d})}$ and $p\nabla\phi_\alpha$ represent the dissipative and the non-dissipative contribution to $\widetilde{\mathbf{m}}_\alpha$, respectively [18]. If the mixture is required to be closed also with respect to momentum, the interaction terms $\widetilde{\mathbf{m}}_\alpha$ (with $\alpha = \mathrm{c}, \ell, \mathrm{m}$) are constrained to satisfy the condition

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

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

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

with $\sum_{\alpha=\mathrm{c},\ell,\mathrm{m}} \overline{\mathbf{m}}_\alpha = \mathbf{0}$, 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 αth phase due to the βth phase, with $\alpha \neq \beta$. By invoking the action-reaction principle for each interaction pair, it holds that $\overline{\mathbf{m}}_{\alpha\beta} = -\overline{\mathbf{m}}_{\beta\alpha}$.

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

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

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

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

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

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

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

2.1. Momentum Balance Laws for the Saturated Case

In a saturated mixture, the partial Cauchy stress associated with the αth phase of the mixture can be written as $\widetilde{\mathbf{T}}_\alpha = -\phi_\alpha p \mathbf{I} + \mathbf{T}_\alpha$, where $\mathbf{T}_\alpha$ is referred to as *effective* (or extra-) stress, and the purely hydrostatic contribution $-\phi_\alpha p \mathbf{I}$ indicates the amount of pressure sustained by the αth phase (note that, in the present theory, p is a Lagrange multiplier 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 specialised as:

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

$$-\phi_\mathrm{m} \nabla p + \mathrm{div}\,(\mathbf{T}_\mathrm{m}) - \overline{\mathbf{m}}_{\mathrm{cm}} - \phi_\mathrm{m} \phi_\ell \mu \left[\mathbf{K}(\phi_\ell)\right]^{-1} \mathbf{v}_{\mathrm{m}\ell} = \mathbf{0}, \tag{9b}$$

$$-\phi_\ell \nabla p - \phi_\ell \phi_\mathrm{c} \mu \left[\mathbf{K}(\phi_\ell)\right]^{-1} \mathbf{v}_{\ell\mathrm{c}} - \phi_\ell \phi_\mathrm{m} \mu \left[\mathbf{K}(\phi_\ell)\right]^{-1} \mathbf{v}_{\ell\mathrm{m}} = \mathbf{0}, \tag{9c}$$

with $\mathbf{v}_{\alpha\beta} := \mathbf{v}_\alpha - \mathbf{v}_\beta = -\mathbf{v}_{\beta\alpha}$, for all $\alpha, \beta = \mathrm{c}, \ell, \mathrm{m}$ 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 $\mathbf{T}_\ell$ 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 $\mathbf{T}_\mathrm{m}$ includes a further contribution due to the response of the vessels to deformations.

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

$$-\frac{\phi_\mathrm{c}}{1-\phi_\ell}\nabla p + \mathrm{div}\,(\mathbf{T}_\mathrm{c}) + \overline{\mathbf{m}}_\mathrm{cm} + \frac{\phi_\mathrm{c}\phi_\ell\phi_\mathrm{m}}{1-\phi_\ell}\mu[\mathbf{K}(\phi_\ell)]^{-1}\mathbf{v}_\mathrm{mc} = \mathbf{0}, \tag{10a}$$

$$-\frac{\phi_\mathrm{m}}{1-\phi_\ell}\nabla p + \mathrm{div}\,(\mathbf{T}_\mathrm{m}) - \overline{\mathbf{m}}_\mathrm{cm} + \frac{\phi_\mathrm{c}\phi_\ell\phi_\mathrm{m}}{1-\phi_\ell}\mu[\mathbf{K}(\phi_\ell)]^{-1}\mathbf{v}_\mathrm{cm} = \mathbf{0}, \tag{10b}$$

$$\mathbf{v}_\ell = \frac{1}{\phi_\mathrm{c}+\phi_\mathrm{m}}\left(\phi_\mathrm{c}\mathbf{v}_\mathrm{c} + \phi_\mathrm{m}\mathbf{v}_\mathrm{m} - \frac{\mathbf{K}(\phi_\ell)}{\mu}\nabla p\right), \tag{10c}$$

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

$$\partial_t\phi_\mathrm{c} + \mathrm{div}(\phi_\mathrm{c}\mathbf{v}_\mathrm{c}) = \Gamma_\mathrm{c}\,, \tag{11a}$$

$$\partial_t\phi_\mathrm{m} + \mathrm{div}(\phi_\mathrm{m}\mathbf{v}_\mathrm{m}) = \Gamma_\mathrm{m}\,, \tag{11b}$$

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

$$\mathrm{div}\left(\frac{\phi_\ell}{1-\phi_\ell}\,\frac{\mathbf{K}(\phi_\ell)}{\mu}\nabla p\right) = \mathrm{div}\left(\frac{\phi_\mathrm{c}\mathbf{v}_\mathrm{c}+\phi_\mathrm{m}\mathbf{v}_\mathrm{m}}{\phi_\mathrm{c}+\phi_\mathrm{m}}\right) - \sum_{\alpha=\mathrm{c},\ell,\mathrm{m}}\Gamma_\alpha\,. \tag{12}$$

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 ($\alpha = \mathrm{c}, \ell, \mathrm{m}$) with the cell duplication rate $\hat{\Gamma}_\mathrm{c} \sim 1\,\mathrm{day}^{-1}$, 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 $\mathbf{T}_\mathrm{c}$ and $\mathbf{T}_\mathrm{m}$ are scaled with the tissue's Young elastic modulus E (i.e., for instance, one can define the non-dimensional stress $\mathbf{T}_\mathrm{c}^* = \mathbf{T}_\mathrm{c}/E$). Moreover, the true mass densities of all the phases are taken equal to the reference value $\rho_\mathrm{w} = 10^3\,\mathrm{kg/m}^3$, which approximately corresponds to the mass density of water, the fluid velocity is scaled with $\hat{v}_\ell \sim 10^{-7} \div 10^{-6}\,\mathrm{m/s}$, 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 $\hat{v}_\mathrm{m} = \hat{v}_\mathrm{c} = \hat{\Gamma}_\mathrm{c}D$, 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 $\hat{v}_\ell$, Δp and d as independent scaling factors, it is possible to estimate the ratio $\hat{K}/\mu$ (cf. Table 1). Finally, the scaling factor $\hat{\overline{m}}_\mathrm{cm}$, which is associated with the momentum exchange term $\overline{\mathbf{m}}_\mathrm{cm}$, is assumed to be equal to the ratio E/d. Thus, if $\overline{\mathbf{m}}_\mathrm{cm}$ is expressed as $\overline{\mathbf{m}}_\mathrm{cm} = -\mathbf{M}_\mathrm{cm}\mathbf{v}_\mathrm{cm}$, the scaling factor associated with $\mathbf{M}_\mathrm{cm}$ must be equal to $\hat{M}_\mathrm{cm} = E/(d\hat{\Gamma}_\mathrm{c}D)$.

Considering that $\overline{\mathbf{m}}_\mathrm{cm}$ 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 $\mathbf{v}_\ell$, the volumetric fractions ϕ_c and ϕ_m, the pressure p, and the stress tensors $\mathbf{T}_\mathrm{c}$ and $\mathbf{T}_\mathrm{m}$. Thus, in order to close the mathematical problem under study, additional information is required to determine the symmetric second-order tensors $\mathbf{T}_{\rm c}$ and $\mathbf{T}_{\rm m}$. Before addressing this issue, however, it is shown in the following how the dimensional analysis of the investigated set of equations leads to a considerable simplification of the problem at hand. From here on, it is hypothesised for simplicity that the permeability tensor is spherical, i.e., $\mathbf{K} = K\mathbf{I}$, with $\mathbf{I}$ being the identity tensor, which means that the tissue's hydraulic response is isotropic.

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

$$\mathrm{div}^*(\mathbf{T}_{\rm c}^*) + \overline{\mathbf{m}}_{\rm cm}^* + \frac{\Delta p}{E}\left[-\frac{\phi_{\rm c}}{1-\phi_\ell}\nabla^* p^* + V\frac{\phi_{\rm c}\phi_\ell\phi_{\rm m}}{1-\phi_\ell}\frac{\mu^*}{K^*(\phi_\ell)}\mathbf{v}_{\rm mc}^*\right] = \mathbf{0}\,, \tag{13a}$$

$$\mathrm{div}^*(\mathbf{T}_{\rm m}^*) - \overline{\mathbf{m}}_{\rm cm}^* + \frac{\Delta p}{E}\left[-\frac{\phi_{\rm m}}{1-\phi_\ell}\nabla^* p^* + V\frac{\phi_{\rm c}\phi_\ell\phi_{\rm m}}{1-\phi_\ell}\frac{\mu^*}{K^*(\phi_\ell)}\mathbf{v}_{\rm cm}^*\right] = \mathbf{0}\,, \tag{13b}$$

$$\mathbf{v}_\ell^* = V\frac{\phi_{\rm c}\mathbf{v}_{\rm c}^* + \phi_{\rm m}\mathbf{v}_{\rm m}^*}{1-\phi_\ell} - \frac{1}{(1-\phi_\ell)}\frac{K^*(\phi_\ell)}{\mu^*}\nabla^* p^*\,, \tag{13c}$$

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

$$\mathrm{div}(\mathbf{T}_{\rm c}) + \overline{\mathbf{m}}_{\rm cm} = \mathbf{0}\,, \tag{14a}$$

$$\mathrm{div}(\mathbf{T}_{\rm m}) - \overline{\mathbf{m}}_{\rm cm} = \mathbf{0}\,, \tag{14b}$$

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

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

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

3. Stress Tensor

The scope of this section is to determine a self-consistent evolution law for the Cauchy stress tensor $\mathbf{T}_{\rm c}$ associated 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]	$\hat{\Gamma}_{\rm c}$ [s^{-1}]	D [m]	$\rho_{\rm w}$ [kg/m^3]	$\hat{v}_\ell$ [m/s]	$\hat{v}_{\rm c}$ [m/s]	$\hat{K}/\mu$ [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, $\mathbf{F}_{\rm c}$, as

$$\mathbf{F}_{\rm c} = \mathbf{F}_{\rm e}\mathbf{F}_{\rm p}\mathbf{F}_{\rm g}. \tag{15}$$

In Eq. (15), $\mathbf{F}_{\rm e}$ is the purely elastic contribution to the overall deformation gradient, whereas $\mathbf{F}_{\rm g}$ and $\mathbf{F}_{\rm p}$ 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 $\mathbf{F}_{\rm g}$ and $\mathbf{F}_{\rm p}$ 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, $J_{\rm c} = \det(\mathbf{F}_{\rm c})$, can be written as $J_{\rm c} = J_{\rm e}J_{\rm p}J_{\rm g}$, with $J_{\rm e} = \det(\mathbf{F}_{\rm e})$, $J_{\rm p} = \det(\mathbf{F}_{\rm p})$ and $J_{\rm g} = \det(\mathbf{F}_{\rm g})$. In the following, it is assumed that plastic distortions are isochoric, i.e., $J_{\rm p} = 1$, and that $\mathbf{F}_{\rm g}$ has the form $\mathbf{F}_{\rm g} = g\mathbf{I}$, with $\mathbf{I}$ being the identity tensor. Thus, it holds that $\mathbf{F}_{\rm p}\mathbf{F}_{\rm g} = g\mathbf{F}_{\rm p}$, and $J_{\rm g} = g^3$ [11, 12].

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

$$\mathbf{L}_{\rm c} = \dot{\mathbf{F}}_{\rm c}\mathbf{F}_{\rm c}^{-1} = \mathbf{L}_{\rm e} + \mathbf{L}_{\rm p} + (\dot{g}/g)\mathbf{I}. \tag{16}$$

In Eq. (16), and in the following, a superimposed dot denotes the time derivative following the motion of the cell population. Moreover, $\mathbf{L}_{\rm e} = \dot{\mathbf{F}}_{\rm e}\mathbf{F}_{\rm e}^{-1}$ and $\mathbf{L}_{\rm p} = \mathbf{F}_{\rm e}\mathbf{\Lambda}_{\rm p}\mathbf{F}_{\rm e}^{-1}$, with $\mathbf{\Lambda}_{\rm p} = \dot{\mathbf{F}}_{\rm p}\mathbf{F}_{\rm p}^{-1}$, 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 $\mathbf{F}_{\rm p}$ is has unitary determinant, both $\mathbf{L}_{\rm p}$ and $\mathbf{\Lambda}_{\rm p}$ 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 $\mathcal{W}_{\rm n}$, expressed per unit volume of the natural state, is of Neo-Hookean type, one can write

$$\mathcal{W}_{\rm n}(\mathbf{B}_{\rm e}) = \tfrac{1}{2}\kappa_0\left(\sqrt{\det(\mathbf{B}_{\rm e})} - 1\right)^2 + \tfrac{1}{2}\mu_0\left(\operatorname{tr}\left(\overline{\mathbf{B}}_{\rm e}\right) - 3\right). \tag{17}$$

In (17), $\mathbf{B}_{\rm e} = \mathbf{F}_{\rm e}\mathbf{F}_{\rm e}^T$ is said to be the elastic left Cauchy-Green deformation tensor, and $\overline{\mathbf{B}}_{\rm e} = J_{\rm e}^{-2/3}\mathbf{B}_{\rm e}$ 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 $\mathbf{T}_{\rm c}$ can be expressed constitutively as follows:

$$\mathbf{T}_{\rm c} = \hat{\mathbf{T}}_{\rm c}(\mathbf{B}_{\rm e}) = \kappa_0\left(\sqrt{\det(\mathbf{B}_{\rm e})} - 1\right)\mathbf{I} + \mu_0[\det(\mathbf{B}_{\rm e})]^{-5/6}\operatorname{dev}(\mathbf{B}_{\rm e}), \tag{18}$$

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

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

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

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

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

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

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

$$\frac{\dot{g}}{g} = \frac{1}{3}\frac{\Gamma_c}{\phi_c}, \tag{21}$$

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

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

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

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

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

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

$$\mathbf{L}_p = \mathrm{sym}(\mathbf{L}_p) = \lambda\,\mathrm{dev}(\mathbf{T}_c). \tag{24}$$

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

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

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

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

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

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 differential form as follows

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

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

$\mathbf{v}_c$ (given a second-order tensor $\mathbf{A}$, $\mathcal{L}_{\mathbf{v}_c}\mathbf{A}$ can be computed as $\mathcal{L}_{\mathbf{v}_c}\mathbf{A} = \mathbf{F}_c\dot{\overline{(\mathbf{F}_c^{-1}\mathbf{A}\mathbf{F}_c^{-T})}}\mathbf{F}_c^T$). The fourth-order tensor $\mathbb{C}$ 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 natural configuration, and is defined by $J_e\mathbb{C} = \mathbf{F}_e \underline{\otimes} \mathbf{F}_e : \mathbb{C}_n : \mathbf{F}_e^T \underline{\otimes} \mathbf{F}_e^T$. For any pair of second-order tensors $\mathbf{A}$ and $\mathbf{B}$, the product $\mathbf{A} \underline{\otimes} \mathbf{B}$ has components $(\mathbf{A} \underline{\otimes} \mathbf{B})_{abcd} = A_{ac}B_{bd}$. Note that, to compute $\mathbb{C}_n$, the strain energy density $\mathcal{W}_n$ has 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 form of $\mathcal{W}_n$ given in (17), $\mathbb{C}$ becomes

$$\begin{aligned}\mathbb{C} = &-\tfrac{2}{3}\mu_0 J_e^{-5/3}[\mathbf{B}_e \otimes \mathbf{I} + \mathbf{I} \otimes \mathbf{B}_e] + \left(\kappa_0 + \tfrac{8}{9}\mu_0 J_e^{-5/3}\mathrm{tr}(\mathbf{B}_e)\right)\mathbf{I} \otimes \mathbf{I} \\ &+ \left(2\kappa_0(J_e - 1) - \tfrac{2}{3}\mu_0 J_e^{-5/3}\mathrm{tr}(\mathbf{B}_e)\right)(\mathbf{I} \otimes \mathbf{I} - \mathbf{I} \overline{\underline{\otimes}} \mathbf{I}),\end{aligned} \tag{28}$$

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

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

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

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

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

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

Equation (30) can be simplified considerably by assuming that the elastic part of the overall deformation gradient is small enough throughout the evolution of the system. The experiments reported in [41] give an indication of the 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 tested).

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

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

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

The function λ in Eq. (31) plays the role of a stress relaxation term, which is activated as soon as the stress is 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 of the process of interest would lead to the models used in [7, 8, 9, 10]. However, in this case, the procedure is incompatible with the small deformation assumption because the stress relaxes very slowly and, thus, large stresses 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 $\overline{\mathbf{m}}_{\text{cm}}$ can be expressed as $\overline{\mathbf{m}}_{\text{cm}} = -\mathbf{M}_{\text{cm}}(\mathbf{v}_{\text{c}} - \mathbf{v}_{\text{m}})$, 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., $\mathbf{v}_{\text{m}} = \mathbf{0}$), and inert. Requiring the ECM to be inert means that the ECM does not exchange mass with the other constituents, so that the condition $\Gamma_{\text{m}} = 0$ applies. The first consequence of this condition is that Eq. (4) reduces to $\Gamma_{\ell} = -(\rho_{\text{c}}/\rho_{\ell})\Gamma_{\text{c}}$, 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 $\rho_{\text{c}}/\rho_{\ell}$. The second consequence is that the volumetric fraction of the ECM, ϕ_{m}, is constant in time. Indeed, setting $\Gamma_{\text{m}} = 0$, and recalling the condition $\mathbf{v}_{\text{m}} = \mathbf{0}$, the mass balance law associated with the ECM becomes $\partial_t\phi_{\text{m}} = 0$ (cf. (11b)), which yields $\phi_{\text{m}}(\mathbf{x}, t) = \phi_{\text{m}0}(\mathbf{x})$, with $\phi_{\text{m}0}(\mathbf{x})$ being known from the outset. The third consequence is that the volumetric fraction of the fluid phase can be expressed as $\phi_{\ell} = 1-(\phi_{\text{c}}+\phi_{\text{m}0})$. Furthermore, the momentum balance law (10a), the mass balance law (11a), and Eqs. (12) and (10c) can be put in the following form:

$$\mathbf{v}_{\text{c}} = -\frac{\phi_{\text{c}}}{Q(\phi_{\text{c}})}\nabla p + \frac{\phi_{\text{c}} + \phi_{\text{m}0}}{Q(\phi_{\text{c}})}\text{div}(\mathbf{T}_{\text{c}})\,, \tag{32a}$$

$$\partial_t\phi_{\text{c}} + \text{div}(\phi_{\text{c}}\mathbf{v}_{\text{c}}) = \Gamma_{\text{c}}\,, \tag{32b}$$

$$\text{div}\left(\frac{1-(\phi_{\text{c}}+\phi_{\text{m}0})}{\phi_{\text{c}}+\phi_{\text{m}0}}\,\frac{K}{\mu}\nabla p\right) = \text{div}\left(\frac{\phi_{\text{c}}}{\phi_{\text{c}}+\phi_{\text{m}0}}\mathbf{v}_{\text{c}}\right) - \left(1-\frac{\rho_{\text{c}}}{\rho_{\ell}}\right)\Gamma_{\text{c}}, \tag{32c}$$

$$\mathbf{v}_{\ell} = -\frac{1}{\phi_{\text{c}}+\phi_{\text{m}0}}\left(\frac{\phi_{\text{c}}^2}{Q(\phi_{\text{c}})} + \frac{K}{\mu}\right)\nabla p + \frac{\phi_{\text{c}}}{Q(\phi_{\text{c}})}\text{div}(\mathbf{T}_{\text{c}})\,, \tag{32d}$$

where the auxiliary function $Q(\phi_{\text{c}})$ is defined by

$$Q(\phi_{\text{c}}) := (\phi_{\text{c}}+\phi_{\text{m}0})M_{\text{cm}} + \phi_{\text{c}}\phi_{\text{m}0}(1-\phi_{\text{c}}-\phi_{\text{m}0})\frac{\mu}{K}\,, \tag{33}$$

and, for consistency with Eq. (7), M_{cm} is taken as $M_{\text{cm}} = \phi_{\text{c}}\phi_{\text{m}0}M_{\text{cm}}^{(0)}$, 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 $\mathbf{T}_{\text{m}}$ becomes constitutively indeterminate, and only its divergence, $\text{div}(\mathbf{T}_{\text{m}})$, is determined univocally by the force balance

$$\text{div}(\mathbf{T}_{\text{m}}) = \nabla p - \text{div}(\mathbf{T}_{\text{c}})\,, \tag{34}$$

which is obtained by adding together Eqs. (10a) and (10b). This means that (34) is decoupled from (32a)–(32d), and $\text{div}(\mathbf{T}_{\text{m}})$ can be computed *a posteriori* once ∇p and $\text{div}(\mathbf{T}_{\text{c}})$ are known. Finally, since $\mathbf{v}_{\ell}$ 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, $\mathbf{T}_{\text{c}}$ has to be expressed constitutively, as done, e.g., in (18). This requires, however, to consider also the evolution equations for g and $\mathbf{F}_{\text{p}}$, 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 $\mathbf{F}_{\text{p}}$ (recall that, due to the constraint $\det(\mathbf{F}_{\text{p}}) = 1$, only eight of the nine components of $\mathbf{F}_{\text{p}}$ 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 $\mathbf{T}_{\text{c}}$ as

$$\mathbf{T}_{\text{c}} = \kappa_0\text{tr}(\mathbf{E}_{\text{e}})\mathbf{I} + \mathbf{T}_{\text{c}}'\,, \tag{35}$$

where $\mathbf{E}_{\text{e}}$ is the elastic strain tensor, the deviatoric part $\mathbf{T}_{\text{c}}'$ plays the role of an independent tensorial variable involving (in three dimensions, and due to the condition $\text{tr}(\mathbf{T}_{\text{c}}') = 0$) only five independent scalar unknowns, and the spherical contribution $\kappa_0 \mathrm{tr}(\mathbf{E}_e)\mathbf{I}$ is determined by $\kappa_0 \mathrm{tr}(\mathbf{E}_e)\mathbf{I} = \kappa_0(\phi_{cn}/\phi_c - 1)\mathbf{I}$. The latter equality is obtained by recalling that, from (22), the ratio ϕ_{cn}/ϕ_c is equal to J_e, and that J_e can be approximated as $J_e \sim 1 + \mathrm{tr}(\mathbf{E}_e)$ in the limit $\mathbf{E}_e \to \mathbf{0}$. Moreover, if Γ_c is assumed to be independent on g and $\mathbf{F}_p$, neither the growth term g, nor the remodelling tensor $\mathbf{F}_p$, appear explicitly in (31), so that Eqs. (21) and (25) can be solved *a posteriori*. By virtue of this reasoning, and within the range of validity of the hypotheses introduced so far, the mathematical model requires the solution of the ten coupled equations (32a)–(32c) and (31), which are needed to determine the ten independent unknowns $\mathbf{v}_c$, ϕ_c, p 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 the three components of the motion of the cellular phase.

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

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

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

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

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

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 and can be identified with a non-linear diffusion coefficient. The auxiliary velocity $\mathbf{w}_c$ is instead responsible for advection, and $\Gamma_c(\phi_c)$ is a non-linear reaction term.

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

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

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

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

4.2. A Benchmark Problem: The Uniaxial Expansion Test

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

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

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

Consistently with what prescribed by Eq. (26), remodelling is triggered only in those regions of the tissue in which $f(\mathbf{T}'_c)$ 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 chosen as $f(\mathbf{T}'_c) = \sqrt{(3/2)}\|\mathbf{T}'_c\| = \sqrt{(3/2)\mathrm{tr}(\mathbf{T}'_c\mathbf{T}'_c)}$ [42], whereas f is defined by

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

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

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

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

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

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 $\mathbf{e}_x$ being the unit vector along the axial direction of Ω (normal to its cross section), and exploiting the fact that $\mathbf{T}'_c$ is diagonal. Therefore, the effective unknowns characterising the unreduced model are six and are given by v_{cx}, ϕ_c, p, T'_{cxx}, T'_{cyy}, and the level set function ζ. Moreover, the particularly simple choice of the function $f(\mathbf{T}'_c) = |T'_{cxx}|$ decouples Eq. (31), written for T'_{cyy}, from the rest of the system of equations. This allows to eliminate T'_{cyy} from the list of the effective unknowns of the unreduced model.

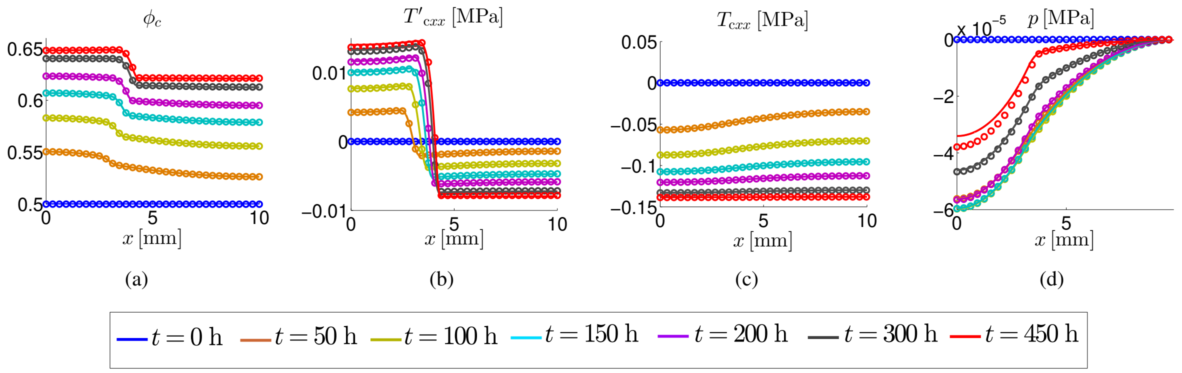
By invoking the same hypotheses as above also for the case of the reduced model, the effective unknowns become v_{cx}, ϕ_c and T'_{cxx}, while p, together with all other quantities pertaining to the fluid phase, can be computed *a posteriori*.

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

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

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

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



(a) (b) (c) (d)

(e)

Figure 1: Comparison of the results obtained in terms of (a) ϕ_c, (b) T'_{cxx}, (c) T_{cxx} 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: $\kappa_0 = 0.667\,\mathrm{MPa}$, $\mu_0 = 0.019\,\mathrm{MPa}$, $\phi_{\rm cn} = 0.5$, $\phi_{\max} = 0.65$, $\gamma_{\rm c} = 1/24\,\mathrm{h}^{-1}$, $\chi = \mu_0/\eta = 0.1\,\mathrm{h}^{-1}$, $\tau(\phi_{\rm c}) = \tau_0 = 25\,\mathrm{MPa}$, $\mu = 1\,\mathrm{cP}$, $K/\mu = 10^{-12}\,\mathrm{m}^4/(\mathrm{Ns})$ and $M^{(0)}_{\rm cm} = 10^4\,(\mathrm{MPa\,s})/\mathrm{mm}^2$. At time $t = 0$, the initial configuration of the tumour is given by $\omega_0 = \{\mathbf{x} \in \Omega \mid H(x_{\rm T} - x) > 0\}$, with $x_{\rm T} = 2.5$ 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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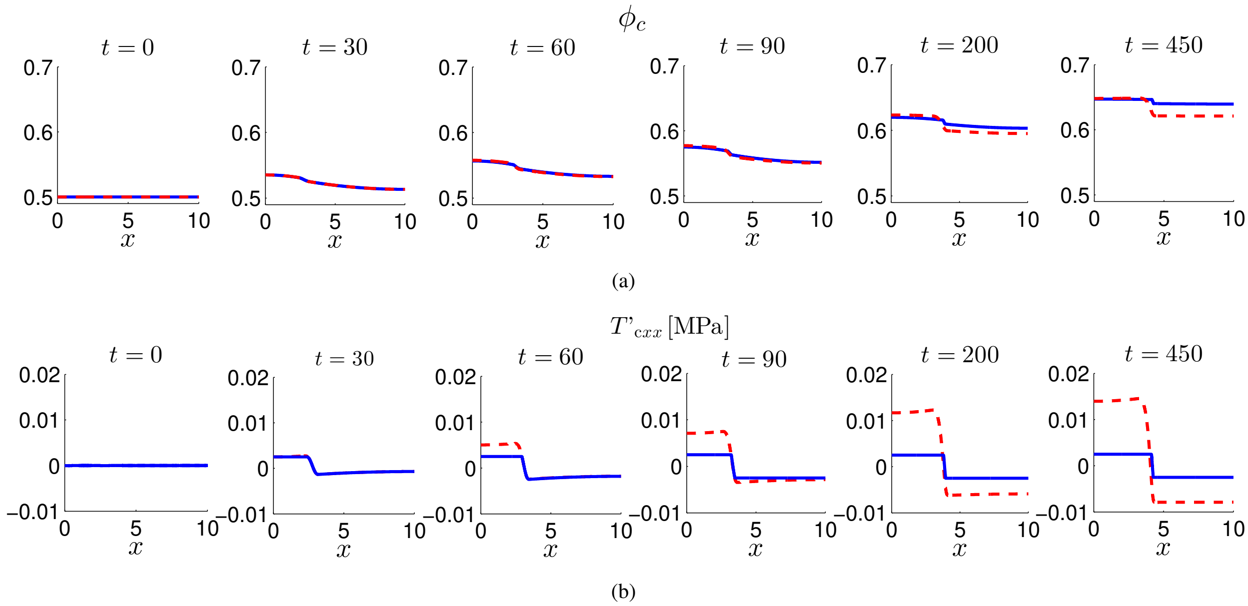

Figure 2: Comparison at different time instants of time, between (a) ϕ_c and (b) T'_{cxx} in the absence of remodelling (red dashed lines) and in the presence of remodelling (blue solid lines). The results are obtained solving the reduced problem. Solving the unreduced problem leads to similar results. 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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