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(Article begins on next page)

1 ORIGINAL RESEARCH ARTICLE

2 **A study of growth and remodelling in isotropic tissues,**
3 **based on the Anand-Aslan-Chester theory**
4 **of strain-gradient Plasticity.[†]**

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Motivated by the increasing interest of the biomechanical community towards the employment of strain-gradient theories for solving biological problems, we study the growth and remodelling of a biological tissue on the basis of a strain-gradient formulation of remodelling. Our scope is to evaluate the impact of such an approach on the principal physical quantities that determine the growth of the tissue. For our purposes, we assume that remodelling is characterised by a coarse and a fine length scale and, taking inspiration from a work by L. Anand, O. Aslan, and S.A. Chester, we introduce a kinematic variable that resolves the fine scale inhomogeneities induced by remodelling. With respect to this variable, a strain-gradient framework of remodelling is developed. We adopt this formulation in order to investigate how a tumour tissue grows *and* how it remodels *in response* to growth. In particular, we focus on a type of remodelling that manifests itself in two different, but complementary, ways: on the one hand, it finds its expression in a stress-induced reorganisation of the adhesion bonds among the tumour cells, and, on the other hand, it leads to a change of shape of the cells and of the tissue, which is generally not recovered when external loads are removed. To address this situation, we resort to a generalised Bilby-Kröner-Lee decomposition of the deformation gradient tensor. We test our model on a benchmark problem taken from the literature, which we rephrase in two ways: micro-scale remodelling is disregarded in the first case, and accounted for in the second one. Finally, we compare and discuss the obtained numerical results.

KEYWORDS:

Growth, Remodelling, Strain-gradient Plasticity, Aifantis’ theory

7 **1 | INTRODUCTION**8 **1.1 | A brief review on growth and remodelling**

9 The growth of a biological tissue consists of the variation and redistribution of its mass, and is the consequence of processes
10 that influence each other reciprocally in spite of their being characterised by different time and length scales^[1–3].

11 Besides genetic, bio-chemical, and bio-physical phenomena, which pertain to the molecular and intra-cellular scales, the
12 growth of a tissue also depends on interactions that occur at the inter-cellular level, as well as on those that involve the tissue as

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13 a whole. The latter two types of interactions are often studied with the purpose of describing how a tissue evolves, for instance,
14 by adapting its internal structure and material properties in response to the changes of its environment.

15 In fact, the structural adaptation of a tissue may manifest itself in several different ways, and it may involve one or more classes
16 of phenomena, which are often referred to with the common name of *remodelling*. For the types of problems addressed in this
17 work, in which a tissue is viewed as an aggregate of cells, a reorganisation of its internal structure is assumed to occur through
18 the dissolution and reformation of the adhesion bonds among the cells^[4–6], or through a rearrangement of the position, shape,
19 and orientation of the cells in the aggregate^[7,8]. In both cases, remodelling acquires the character of a *configurational* process
20 at the inter-cellular scale, and may result in an inelastic change of shape of the tissue as a whole. More generally, however,
21 when the extracellular matrix (ECM) is accounted for, or in the case of fibre-reinforced tissues, the structural changes take place
22 through the distortion of the ECM's collagenous network^[9], or through the reorientation of the collagen fibres.

23 The problem of fibre reorientation has been addressed in several works, sometimes in connection with growth, and for different
24 types of tissues, these ranging from blood vessels (see e.g.^[10–13]) to articular cartilage (see e.g.^[14–19]). In other situations, as is
25 the case for bone, the concept of structural adaptation is introduced to interpret the formation of cracks^[20], the onset of damage,
26 and the occurrence of inelastic distortions that are remnant of the phenomenon of plasticity in metals (see e.g.^[21,22]).

27 To describe the processes mentioned so far, a tissue may be viewed as a continuum, or a mixture of continua, and its dynamics
28 may be revealed, at least *partially*, by formulating mathematical models based on the laws of continuum mechanics. Such models
29 should capture the “two-level” nature of the phenomena that they are meant to resolve, thereby trying to connect the visible
30 transformations of a tissue with the chemical, electrical, and mechanical interactions occurring inside it. For instance, in the
31 case of growth, a connection of this kind is established by *mechanotransduction*^[23,24], i.e., the modulation that mechanical stress
32 exerts on the tissue's growth rate due to its interplay with the tissue's mass sources. Mechanotransduction has also been recently
33 discussed by Ehret et al.^[25] in the context of “*inverse poroelasticity*” for “*soft biomembranes*” and, in particular, in the case of
34 the interplay between mechanical stress and chemical potential that results in the possibility of driving the variations of osmotic
35 pressure through mechanical loading.

36 A number of papers has been produced in which growth and remodelling have been described by adopting the language and
37 formalism of continuum theories (see e.g.^[26] and the references therein). In some works devoted to the theoretical foundations
38 of volumetric growth (see e.g.^[27–29]), emphasis is put on the necessity of defining variables that, together with the descriptors
39 of the tissue's *standard* mechanical state, are capable of catching its structural transformations. In^[27], this is done by having
40 recourse to the theory of uniformity^[30,31], and introducing the concepts of “*archetype*” and “*transplant operator*”^[27,30,31]. On
41 the other hand, in several other contexts, the Bilby-Kröner-Lee multiplicative decomposition of the deformation gradient tensor
42 is adopted, along with its generalisations, in order to frame remodelling in terms of “plastic-like distortions” (see e.g.^[32]). We
43 use this terminology in order to underline that, in the presence of remodelling, the structural transformations of the tissues
44 considered in this work recall the plastic distortions of non-living, elasto-plastic materials. Sometimes, we use the adjectives
45 “plastic” and “remodelling” interchangeably: we take this liberty when a physical quantity, historically conceived for the theory
46 of plasticity, has to be re-interpreted in compliance with the physical context of the present work. A relevant example is the
47 *accumulated plastic strain*, a variable for which we use both its original name and the name *accumulated remodelling strain*.
48 In other cases, however, we use quotation marks for “plastic” and “plasticity”, if we need to recall that we are borrowing terms
49 from the theory of plasticity. For instance, we use this convention when we speak of *micro-scale plasticity*.

50 When a tissue is modelled as a mixture of continua—typically a fluid phase and one or more solid phases—^[6,33–37], its growth
51 is usually identified with an inter-phase exchange of mass. Such process is assumed to yield either an accretion of the solid mass
52 at the expenses of the fluid or a loss of solid mass, induced by the disintegration of the tissue cells, which become necrotic and
53 are then dissolved into the fluid. In such a framework, the solid phase is taken as a representation of the tissue cells (and, where
54 appropriate, of the ECM), and a mathematical model of growth should be able to relate the mass variation of the solid phase
55 with the availability of nutrients and with the structural transformations that possibly accompany growth. As already mentioned
56 above, the latter ones are assumed to have inelastic nature and may refer to the redistribution of the solid mass, to the change
57 of the cells' arrangement inside the tissue, so as to mimic the result of the dissolution and reformation of the cellular adhesion
58 bonds, or to a combination of both phenomena.

59 To further clarify the type of remodelling addressed in this work, and to contextualise the wording “plastic-like distortions”,
60 we provide an explicit example of the inelastic rearrangement of the cells of a tissue. For this purpose, we discuss the results of
61 an experiment commented in^[8]. In Figure 1 (which corresponds to Figure 7 of^[8]), Forgacs et al.^[8] show three different stages
62 of a cellular aggregate subjected to a loading history referred to as “*centrifugation*”^[8]. The first column of Figure 1 reports the
63 configuration of the aggregate “*before centrifugation*”^[8], when the cells are “*isodiametric*” and the aggregate is spherical. The

64 second column, instead, shows the aggregate after a 5 minute centrifugation: at this stage, the aggregate is no longer spherical,
 65 the cells have changed their shape and are said to be in a “*rapidly relaxing, more elastic phase*”^[8]. Finally, the third column
 66 depicts the configuration of the aggregate after 36 hour centrifugation. In this configuration, the aggregate is believed to have
 67 reached a new state of equilibrium, and its cells seem to have attained a state free of stress. Most importantly, the cells seem to
 68 have changed their positions and to have redistributed their shape and orientation in a permanent manner, so that the aggregate
 69 does not spontaneously tend to recover its original configuration, regardless of the absence of external loads. Forgacs et al.^[8]
 70 use the theory of viscoelasticity to model the experiment described so far. To us, however, the inelastic behaviour of the cellular
 71 aggregate may also suggest interpretations other than, and perhaps complementary to, viscoelasticity. Indeed, looking at the
 72 third column of Figure 1, one observes that the internal structure of the aggregate has changed, and this change seems to be
 73 due to the fact that the cells, relaxed or not, have modified their shape and arrangement inside the tissue. Therefore, at least
 74 in our opinion, viscoelasticity alone may be insufficient to accurately account for the irreversible deformations (distortions) of
 75 the tissue. Rather, the interpretation of the just discussed phenomenology may necessitate concepts borrowed from the theories
 76 of plasticity or viscoplasticity, since these are able to describe the tissue’s internal kinematics in a way that is similar to the
 77 motion of the defects in solids. This view seems to be corroborated also by other experiments conducted on tumour spheroids
 78 (see e.g.^[38] and references therein). In such experiments, a spheroid is allowed to grow and, after growth has occurred, it is cut
 79 radially for a length of about the 80% of its diameter: what is observed is a relaxation of the stresses, resulting in the opening
 80 of the spheroid, with the edges of the cut drifting away from one another (see Figure 1 d). This behaviour, in fact, suggests the
 81 existence of an incompatible, stress-free state of the tumour, which is consistent with the description of the tumour as an elasto-
 82 plastic material. To us, this observation justifies the approach followed in our work, although it does not exclude visco-plastic
 83 effects. While bearing this in mind, for simplicity we restrict here our investigations to the case of plasticity alone, and we adopt
 84 this approach to model the internal rearrangement, i.e., the remodelling, of the tissues studied in our work.

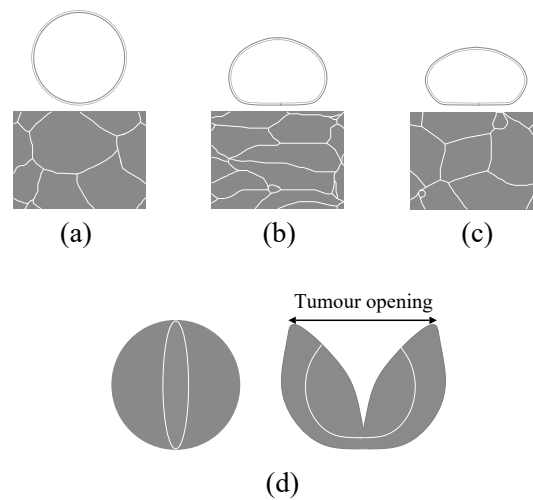


FIGURE 1 First row (redrawn and adapted from Forgacs et al.^[8]): Schematic representation of the cells rearrangement in an spherical aggregate (a) before centrifugation, (b) after a 5 minute centrifugation, and (c) after 36 hour centrifugation. Second row (redrawn and adapted from Stylianopoulos et al.^[38]): Stress relaxation of a tumour spheroid after a radial cut is performed.

85 Understanding how growth and remodelling are related to each other is a necessary step towards the comprehension of the
 86 evolution of biological tissues. In this respect, we remark that the coupling of growth and remodelling has been investigated
 87 in several papers (see e.g.^[4,24,37] and the references therein), without considering strain-gradient constitutive laws, while second-order
 88 theories have been proposed e.g. by Ciarletta et al.^[39–41] to investigate the transport of mass in the presence of morphogenesis
 89 (see also^[27] for a discussion on this issue).

90 To move forward in the comprehension of how growth and remodelling interact, an important question to answer is how to
 91 relate mechanical stress with both phenomena (see e.g.^[26,42]). For example, the tearing of the inter-cellular bonds in a tumour,
 92 which can be interpreted as an expression of remodelling^[4,5], leads to the relaxation of stress, and stress, apart from mechan-
 93 otransduction, may play a role on the growth of the tumour. Indeed, a recent result of some of us seems to show that remodelling

enhances the growth of a tumour in the avascular stage by increasing the speed at which the tumour's boundary advances in space^[24]. Although this result necessitates validations, it may help to estimate qualitatively a possible interplay between remodelling and growth. To this end, Mascheroni et al.^[24], drew the conclusion that the observed behaviour was the consequence of the smoothing effect of the plastic-like distortions on mechanical stress, and that such effect was transferred to the term describing growth through the mechanotransduction.

The type of remodelling induced by mechanical stress can be viewed as a plastic-like behaviour and, if one assumes plastic response to be triggered by a yield stress (as is the case, for instance, in rate-independent^[22,43] or in Perzyna-like plasticity^[22]), one may conclude that remodelling commences in the regions of the tissue in which the stress exceeds a certain threshold. Since in a growing tissue such regions are those in which the growth is predominant and the deformation is inhibited, it is very important to resolve accurately the plastic-like distortions. This exigency becomes stringent when the "plastic" strains accumulate in very narrow zones. In such cases, a useful tool of investigation could be to switch from a local to a "non-local" model of plasticity. A possible way of accomplishing this task is supplied by the theory proposed by Anand et al. in^[44]. However, before exposing such theory and adapting it to our purposes, we should clarify that the framework within which Anand et al.^[44-46] and Gurtin et al.^[45] developed their work is deeply different from ours. Indeed, the "gradient regularisation" presented in their paper is introduced for numerical reasons, that is, with the purpose of correctly resolving the accumulated plastic strain in the shear bands that arise in strain-softening materials. Anand et al.^[44] justify such regularisation by means of the concept of "micro-scale plasticity" and, by doing this, they actually admit the existence of a physics that cannot be captured by standard theories of plasticity. The Authors, in fact, end up with a yield condition expressed by a partial differential equation in the variable that resolves the fine scale remodelling ("micro-plasticity", in the jargon of Anand et al.^[44]). Such equation resolves the length scale over which the plastic strain is accumulated, and allows to recover a yield condition in the style of Aifantis^[47,48]. Starting from the approach suggested by Anand et al.^[44], and in spite of the differences between their framework and ours, we investigate how the introduction of a fine scale remodelling affects our growth problem.

1.2 | Aim of our work

The main goal of our work is to determine the consequences of a strain-gradient formulation of remodelling on the growth of a biological tissue. Many different paths could be followed to address this question. Indeed, one may adopt the framework developed in^[27], in which a constitutive theory is developed that features the first- and second-order gradient of the deformation as well as the first- and second-order "transplant operators"^[39-41]. Alternatively, one may turn to a gradient theory of remodelling in continua with micro-structure by elaborating the Cosserat-type approach put forward in^[31]. Another possibility is to have recourse to the higher-order gradient theories presented, for example, by^[49] for the case of partially saturated porous media, and by^[50] for problems of bone reconstruction (see also^[51] for a review).

In this work, we focussed on the approach based on the "micro-scale plasticity" of Anand et al.^[44] because of its "simplicity". This approach, indeed, is "simple" because it describes the phenomenon of micro-plasticity by means of a *scalar* variable, which makes its use and implementation rather straightforward in the study of growth and remodelling as coupled phenomena.

As explained by^[44], the micro-scale plasticity describes the inhomogeneities that arise, in the plastic regions of a material, at a length scale much smaller than the one at which the standard accumulated plastic strains are resolved. According to the theory of Anand et al.^[44,46], and similarly to what is done in Gurtin^[52] and by Gurtin and Anand^[45], the micro-scale plasticity is investigated by enriching the standard kinematics that describes an elasto-plastic body. In this respect, a dedicated kinematic descriptor is introduced, whose task is to capture the fine scale plastic inhomogeneities, and, along with it, a force balance equation is added to the list of balance laws of a classical elasto-plastic problem. Such additional force balance is deduced by the means of the Principle of Virtual Powers and, under suitable hypotheses, the forces featuring in it can be obtained constitutively by exploiting the dissipation inequality of the considered system.

For our purposes, we consider a benchmark problem taken from the literature^[53,54], and we adapt it to our framework. We elaborate two different formulations of this problem. In the first one, referred to as "standard model" (or approach), we give no room to micro-scale "plasticity", and we adopt the accumulated "plastic" strain, denoted by ϵ_p , as the only measure of the plastic-like distortions representing the tissue's remodelling. In the second formulation, referred to as "non-standard model", we switch on the micro-scale "plasticity" and, as done by^[44], we assume that the information about this type of fine scale remodelling is disclosed by a scalar variable, denoted by e_p . Then, the difference between e_p and ϵ_p indicates to what extent remodelling tends to be a two-scale phenomenon.

142 We emphasise that our leading motivation is to weigh the influence of the strain-gradient approach outlined above on the main
143 descriptors of growth in the considered benchmark problem.

144 **1.3 | Limitations and novelties**

145 Once that our work plan is explained, we recall that, as is known from the literature, the non-standard approach is necessary for
146 materials exhibiting strain-softening elasto-plastic behaviour, and when the plastic distortions tend to be markedly localised. The
147 occurrence of the strain-softening behaviour is related to the definition of the yield stress of the considered material, expressed as
148 a monotonically decreasing function of the accumulated plastic strain, whereas the localisation of plastic strains may be strongly
149 problem dependent. Before going further, we should thus clarify that, to the best of our knowledge, no strain-softening behaviour
150 has been observed in the biological tissues under investigation: it might occur or not, and, if it occurs, it is not necessarily
151 ascribable to the accumulated plastic strain. Moreover, in the problem analysed in the sequel, the localisation of the accumulated
152 “plastic” strain is not so pronounced to call at all costs for the non-standard approach. It should also be mentioned that the type
153 of remodelling addressed in our work cannot be employed, as it stands, for any kind of biological tissue. In fact, our model
154 might be adequate for tumours^[4], as it describes stress-driven irreversible deformations, which are related to a rearrangement
155 of the cells’ shape and of the cellular adhesion network. However, it is very likely inappropriate for tissues capable of bearing
156 loads, such as tendons and blood vessels. For such tissues, indeed, the occurrence of remodelling is put in relation to “*tensional*
157 *homeostasis*”^[55]. Furthermore, we can speak of “irreversibility” only for processes occurring over relatively short time windows.
158 Indeed, even though plastic-like distortions take place, the tissue may recover its initial shape because cells grow or because
159 the cells move actively towards their original configuration. In addition to these considerations, we clarify that, in this work, we
160 study only the case in which growth is inhibited by the lack of nutrients or boosted by their consumption. This hypothesis is
161 typical for tumours, in which cells thrive as long as nourishment is at their disposal. However, more generally, and especially in
162 tissues other than tumours, nutrients are not the only agents responsible for cell proliferation. The latter, indeed, can be repressed
163 or enhanced, depending, for instance, on the presence of physical barriers, lack of space, or the occurrence of contact inhibition
164 mechanisms.

165 In spite of the limitations outlined above, our approach offers some essential novelties that can improve the interpretation
166 of benchmark problems in which the accumulated remodelling strain is sufficiently localised. This could be the case when the
167 growth of a tissue is strongly promoted by a great availability of nutrients, while its deformation is prohibited by the presence
168 of constraints, like undeformable walls or contact with much stiffer materials. In such situations, indeed, the mechanical stress
169 increases and, when it overcomes a given threshold, a plastic-like remodelling is activated. In the cases in which a confinement of
170 the accumulated “plastic” strain takes place, e.g. close to an interface separating two materials or at the constrained boundaries
171 of a tissue, the non-standard approach proposed in our work can help to achieve a better resolution of its growth and remodelling.

172 More in detail, the novelties of the present study with respect to previous publications of some of us^[24,54] are the following: (i)
173 we analyse the coupling between growth and remodelling both theoretically and computationally, and we resolve the remodelling
174 at two different length scales; (ii) with the aid of the theory developed by Anand et al.^[44], we formulate remodelling within a
175 strain-gradient framework, thereby generalising our past approaches, which were of “grade zero” in the remodelling variables¹.

176 Furthermore, the major novelties of our contribution with respect to the work of Anand et al.^[44] are the following: (a) in our
177 work, the material is a biphasic medium, featuring a solid and a fluid phase, with the solid phase comprising two populations of
178 cells, and the fluid carrying chemical substances; (b) the interplay between growth and remodelling leads to several interactions
179 that are accounted for in several parts of the mathematical model, and that address, for instance, the evolution of the fluid
180 pressure, of the nutrients, and of the cell populations. Moreover, with reference to point (b), we emphasise the generalisation of
181 the equation for the micro-scale plasticity^[44], in which the length associated with the spatial evolution of e_p , rather than being
182 a constant (cf. ^[44]), depends on growth and on the coarse scale plastic-like distortions.

¹We remark that, in Grillo et al.^[18] and Crevacore et al.^[19], we do present a first grade theory for the considered remodelling variable, but such variable does not represent plastic-like distortions. Rather, it is the order parameter describing the mean fibre orientation in a fibre-reinforced biological tissue.

2 | THEORETICAL BACKGROUND

The problem under investigation involves the motion of the solid phase, the motion of the fluid phase, the distortions related to growth, and plastic-like distortions, which are associated with the reorganisation of the tissue's internal structure. The definitions supplied in this section can be encountered in many works addressing Mixture Theory, and have been recently used for establishing the theoretical framework of previous works of some of us^[18,19,54,56]. Such framework, in turn, has been adapted from the kinematic description of biphasic mixtures as developed by Quiligotti^[57] and Quiligotti et al.^[58].

2.1 | Mass balance laws

Following Mascheroni et al.^[24] and Di Stefano et al.^[54], the solid phase of the tissue is assumed to comprise only two types of cells, i.e., the proliferating cells and the necrotic ones. Their presence in the tissue is measured by the mass densities $\varphi_s \rho_s c_p$ and $\varphi_s \rho_s c_n$, respectively, where φ_s is the volumetric fraction of the solid phase, ρ_s is its true mass density, while c_p and c_n are the cells' mass fractions, compelled to satisfy the constraint $c_p + c_n = 1$, everywhere in \mathcal{E}_t and \mathcal{I} . Here, $\mathcal{I} \subset \mathbb{R}$ is an interval of time, and \mathcal{E}_t is the subset of the three-dimensional Euclidean space, \mathcal{E} , occupied by the biphasic system at time t . Note that the indices "p" and "n" stand for "proliferating" and "necrotic", respectively. Once the composition of the solid phase is specified, it is possible to characterise the mass balance of the solid phase by writing one balance law for each cell population, i.e.,

$$\partial_t(\varphi_s \rho_s c_p) + \operatorname{div}(\varphi_s \rho_s c_p \mathbf{v}_s) = r_{fp} + r_{pn} + r_{py}, \quad (1a)$$

$$\partial_t(\varphi_s \rho_s c_n) + \operatorname{div}(\varphi_s \rho_s c_n \mathbf{v}_s) = r_{nf} - r_{pn} + r_{ny}. \quad (1b)$$

As reported by Mascheroni et al.^[24] and Di Stefano et al.^[54], r_{fp} describes the transfer of mass from the fluid phase to the solid phase, r_{nf} measures the dissolution per unit time of the necrotic cells in the fluid, r_{pn} is the rate at which the proliferating cells become necrotic, and the last two terms r_{py} and r_{ny} have been introduced Di Stefano et al.^[54] to evaluate how the growth-induced structural transformations of the tissue influence the local density changes of the solid constituents. Both terms, however, are assumed to be identically zero in the present work. Equations (1a) and (1b) have been obtained under the assumption that both the proliferating and the necrotic cells move with the velocity of the solid phase, \mathbf{v}_s . Moreover, because of the constraint on the mass fractions, they can be rephrased as

$$\partial_t(\varphi_s \rho_s c_p) + \operatorname{div}(\varphi_s \rho_s c_p \mathbf{v}_s) = r_{pn} + r_{fp}, \quad (2a)$$

$$\partial_t(\varphi_s \rho_s) + \operatorname{div}(\varphi_s \rho_s \mathbf{v}_s) = r_{fp} + r_{nf} \equiv r_s. \quad (2b)$$

Note that the last equality of Equation (2b) defines the overall source/sink of mass of the solid phase, i.e., the term r_s , which describes the variation of the tissue's mass due to growth.

Finally, we relate the occurrence of growth with the presence of nutrients in the tissue. These are conveyed by the fluid phase to the proliferating cells and are believed to activate or inhibit growth depending on whether or not they exceed a certain threshold. To characterise the evolution of the nutrients, we introduce the *nutrients' mass fraction*, c_N , and the mass density $\varphi_f \rho_f c_N$, where φ_f and ρ_f indicate the volumetric fraction and the mass density of the fluid phase, respectively. In addition, we require that the tissue obeys the saturation condition, i.e., $\varphi_f = 1 - \varphi_s$, and we consider the mass balance laws of the nutrients and of the fluid phase as a whole, i.e.^[24,54],

$$\partial_t(\varphi_f \rho_f c_N) + \operatorname{div}(\varphi_f \rho_f c_N \mathbf{v}_f + \mathbf{y}_N) = r_{Np}, \quad (3a)$$

$$\partial_t(\varphi_f \rho_f) + \operatorname{div}(\varphi_f \rho_f \mathbf{v}_f) = -r_s. \quad (3b)$$

In (3a) and (3b), \mathbf{v}_f is the velocity of the fluid phase, \mathbf{y}_N is the mass flux vector associated with the motion of the nutrients relative to \mathbf{v}_f , r_{Np} is the rate at which the nutrients are consumed by the proliferating cells, and the right-hand-side of (3b) is taken equal to the negative of r_s in order to ensure the local conservation of mass for the biphasic mixture under study.

Next, we hypothesise that the mass densities of the solid and of the fluid phase can be regarded as constants in the range of interest for the problem at hand. Hence, we set $\rho_s(x, t) = \rho_{s0}$ and $\rho_f(x, t) = \rho_{f0}$ for all $x \in \mathcal{E}_t$ and $t \in \mathcal{I}$, and we summarise (2a), (2b), (3a), and (3b) in the following system of equations

$$\varphi_s \rho_{s0} D_s c_p = r_{pn} + r_{fp} - r_s c_p, \quad (4a)$$

$$\rho_{s0} D_s \varphi_s + \rho_{s0} \varphi_s \operatorname{div} \mathbf{v}_s = r_s, \quad (4b)$$

$$\varphi_f \rho_{f0} D_s c_N + \varphi_f \rho_{f0} \boldsymbol{\omega} \nabla c_N + \operatorname{div} \mathbf{y}_N = r_{Np} + r_s c_N, \quad (4c)$$

$$\operatorname{div} \mathbf{v}_s + \operatorname{div} (\varphi_f \mathbf{w}) = \left(\frac{1}{\rho_{s0}} - \frac{1}{\rho_{f0}} \right) r_s, \quad (4d)$$

where, for any given physical quantity f , the symbol $D_s f \equiv \partial_t f + (\nabla f) \mathbf{v}_s$ denotes the substantial derivative of f with respect to the solid phase velocity, and $\mathbf{w} \equiv \mathbf{v}_f - \mathbf{v}_s$ is the velocity of the fluid relative to the solid. Note that the product $\varphi_f \mathbf{w}$ is often referred to as *filtration velocity*^[59], although it actually represents a specific mass flux vector^[60].

For future use, we remark that the mass balance law (4d) can also be recast in the equivalent representation

$$\varphi_s \operatorname{div} \mathbf{v}_s + \varphi_f \operatorname{div} \mathbf{v}_f + (\nabla \varphi_f) \mathbf{w} = \left(\frac{1}{\rho_{s0}} - \frac{1}{\rho_{f0}} \right) r_s. \quad (5)$$

2.2 | Kinematics

The motion of the solid phase is described by the smooth mapping $\chi : \mathcal{B} \times \mathcal{I} \rightarrow \mathcal{S}$, where \mathcal{B} is the tissue's reference configuration. For each pair $(X, t) \in \mathcal{B} \times \mathcal{I}$, the spatial point occupied by the solid phase is given by $x = \chi(X, t) \in \mathcal{S}$. By differentiating χ with respect to its arguments, we obtain the deformation gradient tensor, i.e., the tangent map of χ , defined by $\mathbf{F}(X, t) = T\chi(X, t) : T_X \mathcal{B} \rightarrow T_{\chi(X, t)} \mathcal{S}$ ^[61], and the solid phase velocity $\mathbf{V}_s(X, t) = \dot{\chi}(X, t)$. Here, $T_X \mathcal{B}$ and $T_{\chi(X, t)} \mathcal{S}$ are the tangent space of \mathcal{B} at X and the tangent space of \mathcal{S} at $\chi(X, t)$, respectively^[61], and the superimposed dot means partial differentiation with respect to time. For completeness, we recall the relationship between \mathbf{V}_s and the Eulerian velocity of the solid phase, i.e., $\mathbf{v}_s(x, t) = \mathbf{v}_s(\chi(X, t), t) = \mathbf{V}_s(X, t)$, so that the composition $\mathbf{v}_s(\cdot, t) \circ \chi(\cdot, t) = \mathbf{V}_s(\cdot, t)$ holds true for all $t \in \mathcal{I}$.

The fluid motion is described by the Eulerian velocity $\mathbf{v}_f(x, t)$, evaluated at every point $x \in \mathcal{S}$ occupied by the fluid and at time $t \in \mathcal{I}$. Note that, since the system under investigation is a mixture, the fluid co-exists with the solid at every point $x \in \mathcal{S}$ at which the tissue is observed. Thus, the point x can also be viewed as the image of X through the solid motion, i.e., $x = \chi(X, t)$, and the fluid motion can be studied by means of the composition $\mathbf{V}_f(\cdot, t) \equiv \mathbf{v}_f(\cdot, t) \circ \chi(\cdot, t)$, such that $\mathbf{V}_f(X, t) = \mathbf{v}_f(\chi(X, t), t)$.

To account for the growth and structural reorganisation of the tissue, we have recourse to the multiplicative decomposition of the deformation gradient tensor, which we propose in the form^[4,37,62]

$$\mathbf{F} = \mathbf{F}_e \mathbf{F}_p \mathbf{F}_\gamma. \quad (6)$$

In (6), \mathbf{F}_γ , \mathbf{F}_p , and \mathbf{F}_e describe the distortions associated with the uptake or loss of mass, the distortions accompanying the plastic-like rearrangement of the tissue's internal structure, and the distortions due to the elastic accommodation of the tissue, respectively. In the sequel, \mathbf{F}_p and \mathbf{F}_γ will also be referred to as *remodelling tensor*² and *growth tensor*, respectively. We notice that, whereas it is rather standard to consider \mathbf{F}_e as the first factor of the right-hand-side of (6), the order of appearance of \mathbf{F}_p and \mathbf{F}_γ is not standard at all. Indeed, it is conceivable to formulate a decomposition of \mathbf{F} in which the inelastic contributions to the overall deformation appear in reverse order. In addition, there exist also cases in which the accommodating part of the deformation is put at the end of the decomposition^[63]. We adopt the order shown above because, in the present work, we have in mind a tissue that grows *and* that remodels its internal structure *in response* to growth. This statement notwithstanding, we regard growth and structural reorganisation as independent, yet mutually interacting processes. Consequently, we consider \mathbf{F}_p and \mathbf{F}_γ as independent kinematic (tensor) variables and, following the same philosophy outlined in some previous publications^[13,19,29,36,54,64], we associate each of them with degrees of freedom having the same "dignity" as those related to the other kinematic descriptors, i.e., \mathbf{V}_s and \mathbf{V}_f . Finally, we emphasise that the decomposition (6) is a generalised Bilby-Kröner-Lee decomposition (see e.g. Mićunović^[22] for similar decompositions in the case of damage or other inelastic processes). Since we have recently discussed the decomposition (6) in Di Stefano^[54] for the case of growth, here we do not fuss over the physics behind it, and we suggest the reviews^[22,65] for details. However, we recall that, for every $X \in \mathcal{B}$ and $t \in \mathcal{I}$, the product $\mathbf{F}_p(X, t) \mathbf{F}_\gamma(X, t)$ maps vectors of the tangent space $T_X \mathcal{B}$ into vectors of the image vector space $\mathcal{N}_t(X)$, attached at X . By ideally performing such transformation for all $X \in \mathcal{B}$, the solid phase is brought into a relaxed state at time t , the latter being characterised by the absence of *any* stresses, including the residual ones. Such state is also referred to as *natural state*^[22,66].

Differentiation of \mathbf{F} with respect to time and left-multiplication by $\mathbf{F}^{-1} = \mathbf{F}_\gamma^{-1} \mathbf{F}_p^{-1} \mathbf{F}_e^{-1}$ yield

$$\dot{\mathbf{F}} \mathbf{F}^{-1} = \dot{\mathbf{F}}_e \mathbf{F}_e^{-1} + \mathbf{F}_e \mathbf{L}_p \mathbf{F}_e^{-1} + \mathbf{F}_e \mathbf{F}_p \mathbf{L}_\gamma \mathbf{F}_p^{-1} \mathbf{F}_e^{-1}, \quad (7)$$

²We use the subscript "p" to emphasise the fact that the distortions associated with remodelling are plastic-like. In this respect, we could have also referred to \mathbf{F}_p as "plasticity tensor". However, we prefer to speak here of "remodelling tensor", because the concept of remodelling is more specific for the addressed biological materials.

255 where we introduced the tensor of *rate of remodelling-induced distortions*, $\mathbf{L}_p \equiv \dot{\mathbf{F}}_p \mathbf{F}_p^{-1}$, and the tensor of *rate of growth-*
 256 *induced distortions*, $\mathbf{L}_\gamma \equiv \dot{\mathbf{F}}_\gamma \mathbf{F}_\gamma^{-1}$. In compliance with (6), the *volume ratio* $J \equiv \det \mathbf{F}$ can be rewritten as $J = J_e J_p J_\gamma$,
 257 where $J_e \equiv \det \mathbf{F}_e$, $J_p \equiv \det \mathbf{F}_p$, and $J_\gamma \equiv \det \mathbf{F}_\gamma$ denote, respectively, the volumetric distortions associated with the elastic,
 258 remodelling, and growth part of the deformation gradient tensor. We use these definitions to perform the Piola transformations
 259 of (4a)–(4d), thereby obtaining

$$\rho_{s0} \Phi_s \dot{\omega}_p = R_{pn} + R_{fp} - R_s \omega_p, \quad (8a)$$

$$\rho_{s0} \dot{\Phi}_s = R_s, \quad (8b)$$

$$\rho_{f0} \Phi_f \dot{\omega}_N + \rho_{f0} \mathbf{Q} \text{Grad } \omega_N + \text{Div } \mathbf{Y}_N = R_{Np} + R_s \omega_N, \quad (8c)$$

$$\mathbf{J} + \text{Div } \mathbf{Q} = \left(\frac{1}{\rho_{s0}} - \frac{1}{\rho_{f0}} \right) R_s, \quad (8d)$$

260 where, for every $X \in \mathcal{B}$ and $t \in \mathcal{I}$, we denote by

$$\Phi_\alpha(X, t) = J(X, t) \varphi_\alpha(\chi(X, t), t), \quad \alpha \in \{f, s\}, \quad (9a)$$

$$R_\beta(X, t) = J(X, t) r_\beta(\chi(X, t), t), \quad \beta \in \{pn, fp, s, Np\}, \quad (9b)$$

$$\omega_v(X, t) = c_v(\chi(X, t), t), \quad v \in \{p, N\}, \quad (9c)$$

261 the material volumetric fractions, the material sources/sinks of mass, and the mass fractions expressed as functions of X and
 262 time, respectively. Moreover, we introduced the material flux vectors associated with the filtration velocity $\varphi_f \mathbf{w}$ and with the
 263 nutrients' mass flux vector \mathbf{y}_N , respectively, i.e.,

$$\mathbf{Q}(X, t) = \Phi_f(X, t) \mathbf{w}(\chi(X, t), t) \mathbf{F}^{-T}(X, t), \quad (10a)$$

$$\mathbf{Y}_N(X, t) = J(X, t) [\mathbf{y}_N(\chi(X, t), t)] \mathbf{F}^{-T}(X, t). \quad (10b)$$

264 In particular, \mathbf{Q} will also be referred to as *material filtration velocity* in the sequel.

265 The kinematic picture of the problem under study is completed with a scalar descriptor, denoted by $e_p : \mathcal{C}_t \times \mathcal{I} \rightarrow \mathbb{R}$.
 266 This quantity and its gradient, ∇e_p , have been introduced by^[44] with the purpose of constructing indicators of the inelastic
 267 transformations occurring in the body at the scale of its micro-structure. More precisely, Anand et al.^[44] speak of e_p in terms
 268 of a “*measure of the inhomogeneity of the microscale plasticity*”. In our framework, it is more appropriate to interpret e_p as a
 269 variable defined to resolve explicitly the inhomogeneities induced by the remodelling of the tissue. To this end, we define the
 270 “Lagrangian field” e_p , such that $e_p(X, t) = e_p(\chi(X, t), t)$, and the material gradient $\text{Grade}_p(X, t) = [\nabla e_p(\chi(X, t), t)] \mathbf{F}(X, t)$.

271 2.3 | Constraints on the kinematic variables

272 By virtue of the presence of growth in our model, the study conducted in this work may be thought of as a slight generalisation
 273 of the framework depicted by Anand et al.^[44], where the Authors develop a scalar theory of strain-gradient plasticity based
 274 on several *ab initio* restrictions on the kinematic variables of their problem. Such restrictions are expressed in terms of the
 275 generalised velocities of the proposed theory, and are thus cast in non-holonomic form. To highlight their role on the overall
 276 dynamics of the system under investigation, we specify the imposed constraints, and we discuss in detail their impact on the
 277 kinematic descriptors that they involve.

278 For the sake of clarity, we start with rephrasing, in our formalism, the constraints on \mathbf{F}_p and $\dot{\mathbf{F}}_p$ introduced by Anand et
 279 al.^[44]. On the top of those, we exploit the mass balance laws in order to extract pieces of information that can be interpreted as
 280 constraints on the growth tensor, \mathbf{F}_γ , and on its rate \mathbf{L}_γ .

281 If \mathbf{L}_p is assigned, \mathbf{F}_p can be computed by integrating the ordinary differential equation $\dot{\mathbf{F}}_p = \mathbf{L}_p \mathbf{F}_p$, which can be rewritten as

$$\dot{\mathbf{F}}_p = (\boldsymbol{\eta}^{-1} \mathbf{D}_p + \boldsymbol{\eta}^{-1} \mathbf{W}_p) \mathbf{F}_p, \quad (11)$$

282 where $\boldsymbol{\eta}$ is the metric tensor associated with the tissue's natural state, while \mathbf{D}_p and \mathbf{W}_p are the symmetric part and the skew-
 283 symmetric part of \mathbf{L}_p , respectively, i.e.,

$$\mathbf{D}_p = \text{sym}(\boldsymbol{\eta} \mathbf{L}_p) = \frac{1}{2} (\boldsymbol{\eta} \mathbf{L}_p + \mathbf{L}_p^T \boldsymbol{\eta}), \quad (12a)$$

$$\mathbf{W}_p = \text{skew}(\boldsymbol{\eta} \mathbf{L}_p) = \frac{1}{2} (\boldsymbol{\eta} \mathbf{L}_p - \mathbf{L}_p^T \boldsymbol{\eta}). \quad (12b)$$

284 Following the theory of^[44], the *first constraint* on F_p is supplied by requiring from the outset that the “*plastic*” spin tensor, W_p
 285 vanishes identically, i.e., $W_p = \mathbf{0}$. Hence, we obtain the identity $L_p = \eta^{-1} D_p$, and, consequently, Equation (11) becomes

$$\dot{F}_p = \eta^{-1} D_p F_p. \quad (13)$$

286 The *second constraint* on F_p stems from the hypothesis of isochoric remodelling distortions, i.e., $J_p = \det F_p = 1$. This relation,
 287 in turn, can be put in differential form, i.e., $\dot{J}_p = J_p \text{tr}[\dot{F}_p F_p^{-1}] = 0$, and implies $\text{tr}[\eta^{-1} D_p] = 0$, as can be deduced by right-
 288 multiplying Equation (13) by F_p^{-1} and taking the trace of the resulting expression. Accordingly, only the deviatoric part of D_p ,
 289 i.e., $\tilde{D}_p = D_p - \frac{1}{3} \text{tr}[\eta^{-1} D_p] \eta$, is involved in (13), which reduces to

$$\dot{F}_p = \eta^{-1} \tilde{D}_p F_p. \quad (14)$$

290 In analogy with^[44], we base our model on the further hypothesis that \tilde{D}_p is *co-directional* with a tensor N_v , associated with
 291 the tissue’s natural state, and obtained by normalising a symmetric tensorial measure of stress, which will be specified later. In
 292 formulae, by indicating with Σ_v such measure of stress, we define N_v as

$$N_v \equiv \frac{\eta \tilde{\Sigma}_v \eta}{\|\tilde{\Sigma}_v\|_\eta}, \quad (15)$$

293 where $\tilde{\Sigma}_v \equiv \Sigma_v - \frac{1}{3} \text{tr}[\eta \Sigma_v] \eta^{-1}$ is the deviatoric part of Σ_v , and $\eta \tilde{\Sigma}_v \eta$ is the covariant representation of $\tilde{\Sigma}_v$, and we enforce the
 294 co-directionality condition as the *third constraint* on F_p , i.e.,

$$\tilde{D}_p = \|\tilde{D}_p\|_{\eta^{-1}} N_v. \quad (16)$$

295 Equation (16) follows from the hypothesis that the distortions associated with remodelling obey an evolution law of the same
 296 type as the normality rule of isotropic, associative, finite-strain plasticity. For this reason, the physical quantity that represents
 297 them, i.e., \tilde{D}_p , has to be co-directional with $\tilde{\Sigma}_v$ (see Sections 95.5 and 98 of Gurtin et al.^[43]). In turn, this condition is auto-
 298 matically satisfied by introducing the direction tensor N_v and requiring \tilde{D}_p to be proportional to N_v . Clearly, this identifies the
 299 corresponding proportionality factor with the norm of \tilde{D}_p .

300 In (15) and (16), the norms $\|\tilde{\Sigma}_v\|_\eta$ and $\|\tilde{D}_p\|_{\eta^{-1}}$ are defined by

$$\|\tilde{\Sigma}_v\|_\eta = \sqrt{\text{tr}[(\eta \tilde{\Sigma}_v \eta)^T \tilde{\Sigma}_v]}, \quad (17a)$$

$$\|\tilde{D}_p\|_{\eta^{-1}} = \sqrt{\text{tr}[\eta^{-1} \tilde{D}_p \eta^{-1} \tilde{D}_p]}, \quad (17b)$$

301 and their product coincides with the double contraction $\tilde{\Sigma}_v : \tilde{D}_p = \|\tilde{\Sigma}_v\|_\eta \|\tilde{D}_p\|_{\eta^{-1}}$. Moreover, to simplify the notation, we invoke
 302 the definition of *accumulated plastic strain*^[22,44], ε_p , i.e.,

$$\varepsilon_p(X, t) \equiv \sqrt{\frac{2}{3}} \int_0^t \|\tilde{D}_p(X, \tau)\|_{\eta^{-1}} d\tau \quad \Rightarrow \quad \dot{\varepsilon}_p(X, t) = \sqrt{\frac{2}{3}} \|\tilde{D}_p(X, t)\|_{\eta^{-1}}, \quad (18)$$

303 so that Equation (16) becomes

$$\tilde{D}_p = \sqrt{\frac{3}{2}} \dot{\varepsilon}_p N_v. \quad (19)$$

304 Finally, by substituting (19) into (14), we obtain

$$\dot{F}_p = \left(\sqrt{\frac{3}{2}} \dot{\varepsilon}_p \eta^{-1} N_v \right) F_p \quad \Rightarrow \quad L_p = \sqrt{\frac{3}{2}} \dot{\varepsilon}_p \eta^{-1} N_v. \quad (20)$$

305 Equation (20) implies that, once N_v is assigned, L_p has only one independent coefficient, given by $\dot{\varepsilon}_p$. The important consequence
 306 of this result is that the body’s structural degrees of freedom, originally represented by the tensorial quantity F_p , condense into
 307 the scalar variable ε_p .

308 *Remark 1. Descriptive adequacy of ε_p .* According to Equation (18), $\varepsilon_p(X, t)$ is well-defined for all the tensor fields \tilde{D}_p such
 309 that the norm $\|\tilde{D}_p(X, \cdot)\|_{\eta^{-1}}$ is an integrable function of time over $[0, t]$, for every $X \in \mathcal{B}$ and $t \in [0, +\infty[$. Coherently with
 310 this definition, $\varepsilon_p(X, t)$ keeps track of all the magnitudes of the rates of inelastic distortions, $\tilde{D}_p(X, \tau)$, which have occurred in
 311 a given material over $[0, t]$. For this reason, ε_p is a suitable descriptor of the mechanical response of materials that are capable
 312 of “perfectly memorising” inelastic distortions, as is the case for metals exhibiting rate-independent plasticity^[67]. Biological

313 tissues, on the contrary, are often modelled as viscoelastic materials^[7,8], and show fading memory effects. Nonetheless, as
 314 discussed in the Introduction, the experiments on cellular aggregates reported in^[8,38] seem to suggest the existence of inelastic
 315 distortions that do not fade away in time, unless some active process restores the original configuration of the aggregates. For
 316 these reasons, ϵ_p can be regarded as appropriate for describing the inelastic distortions accumulated in a tissue from the beginning
 317 of its loading history. Should the active processes be considered, they could be accounted for by introducing another factor,
 318 denoted e.g. by F_a , and representing the active part of the tissue's deformation^[68].

319 We switch now to the constraints placed on F_γ , and we analyse their impact on the way in which the mass balance law (8b) can
 320 be reformulated. Upon using the decomposition $J = J_e J_p J_\gamma$, and recalling the condition $J_p = 1$, we rewrite Φ_s as $\Phi_s = J_\gamma \Phi_{sv}$,
 321 where Φ_{sv} is such that $\Phi_{sv}(X, t) = J_e(X, t) \varphi_s(\chi(X, t), t)$, and indicates, thus, the solid phase volumetric fraction with respect to
 322 the volume measure of the *natural state*. Hence, Equation (8b) becomes

$$\rho_{s0} \dot{J}_\gamma \Phi_{sv} + \rho_{s0} J_\gamma \dot{\Phi}_{sv} = R_s. \quad (21)$$

323 A rather standard hypothesis in the mechanics of growth, see e.g.^[27,28,53,69], is to choose F_γ in such a way that the time derivative
 324 of its determinant, \dot{J}_γ , compensates for the mass source R_s . In other words, by exploiting the identity $\dot{J}_\gamma = J_\gamma \text{tr}[\dot{F}_\gamma F_\gamma^{-1}] =$
 325 $J_\gamma \text{tr}[\mathbf{L}_\gamma]$, we require the fulfilment of the auxiliary condition

$$\rho_{s0} J_\gamma \Phi_{sv} \text{tr}[\mathbf{L}_\gamma] = R_s \quad \Rightarrow \quad \text{tr}[\mathbf{L}_\gamma] = \frac{R_s}{\rho_{s0} \Phi_{sv} J_\gamma}, \quad (22)$$

326 which constitutes the *first constraint* on F_γ . Such constraint has, in fact, non-holonomic nature, since it is defined through a
 327 non-homogeneous algebraic condition on the generalised (tensorial) velocity \mathbf{L}_γ . Plugging (22) into (21) yields $\rho_{s0} J_\gamma \dot{\Phi}_{sv} = 0$,
 328 thereby implying that the volumetric fraction Φ_{sv} is necessarily independent of time.

329 The *second constraint* on F_γ is provided by the phenomenological evidence according to which, for the class of problems
 330 under study, growth occurs isotropically^[4]. The consequences of this fact on the admissible choices of the growth tensor can be
 331 deduced by looking at the polar decompositions of F_γ . Indeed, by considering for instance the right decomposition, $F_\gamma = \mathcal{R}_\gamma \mathbf{U}_\gamma$,
 332 where \mathcal{R}_γ is the rotation tensor and \mathbf{U}_γ is the stretch tensor associated with F_γ , the isotropy of growth translates to the kinematic
 333 restrictions $\mathcal{R}_\gamma = \mathbf{I}$ and $\mathbf{U}_\gamma = \gamma \mathbf{I}$, where \mathbf{I} is the identity tensor. Therefore, it holds that $F_\gamma = \gamma \mathbf{I}$ and (22) can be rephrased as

$$\frac{\dot{\gamma}}{\gamma} = \frac{R_s}{3\rho_{s0} \Phi_{sv} J_\gamma} \quad \Rightarrow \quad \dot{\gamma} = \frac{R_s}{3\rho_{s0} \Phi_{sv} \gamma^2}. \quad (23)$$

334 Finally, we notice that Equation (8d) can be regarded as a constraint on the material filtration velocity, \mathbf{Q} , expressed through
 335 a restriction on its divergence.

336 3 | PRINCIPLE OF VIRTUAL POWERS

337 After laying down the kinematic picture that describes the problem under investigation, we select the generalised velocities upon
 338 which the system's mechanical power is defined. Summarising the discussion reported above, such velocities may be enlisted
 339 in the following collection of fields

$$\mathcal{V} = (\mathbf{v}_s, \nabla \mathbf{v}_s, D_s \epsilon_p, D_s e_p, \nabla(D_s e_p) \mid \mathbf{v}_f, \nabla \mathbf{v}_f), \quad (24)$$

340 which will be employed to define the internal and the external mechanical powers. We remark that, whereas the fluid phase
 341 requires only \mathbf{v}_f and $\nabla \mathbf{v}_f$ for the characterisation of the system's internal power, the solid phase necessitates both *standard* and
 342 *non-standard* descriptors. The standard ones, i.e., \mathbf{v}_s and $\nabla \mathbf{v}_s$, account only for the “*visible*” changes of shape of the system
 343 (here, the word “*visible*” is meant in the sense of DiCarlo and Quiligotti^[29]), while the non-standard terms are the generalised
 344 velocities $D_s \epsilon_p$, $D_s e_p$, and $\nabla(D_s e_p)$, introduced to define the power expended to accomplish the structural changes of the system.
 345 As anticipated in the Introduction, the main motivation for taking the approach of Anand et al.^[44] and specialising it to our
 346 problem is that it allows to develop a strain-gradient formulation of remodelling based on the scalar variable e_p . The latter is
 347 defined as the micro-scale counterpart of the accumulated remodelling strain, ϵ_p , and, as such, it is assumed to “condense” in itself
 348 all the information about the inelastic processes that determine the micro-scale remodelling of the tissue under study. Moreover,
 349 since it is an “effective” representative of these processes, it prevents from the introduction of a micro-scale, second-order
 350 remodelling tensor, which would render the theoretical and numerical analysis of the problem at hand much more complicated.
 351 Accordingly, the generalised velocities associated with e_p , i.e., $D_s e_p$ and $\nabla(D_s e_p)$, are a scalar and a co-vector field, rather than

being a second-order and a third-order tensor field, respectively. It follows from these considerations that an inelastic model built on ε_p and e_p has the right to stand on its own, independently on any numerical issue, even though Anand et al.^[44] have originally introduced e_p for numerical purposes. Clearly, such a model represents the limit case of more elaborated theories that involve tensor fields, rather than scalar ones.

Coherently with (24), we introduce the collection of virtual velocities

$$\mathcal{V}_v = (\mathbf{u}_s, \nabla \mathbf{u}_s, u_\varepsilon, u_p, \nabla u_p | \mathbf{u}_f, \nabla \mathbf{u}_f) \in \mathcal{V}_v, \quad (25)$$

where \mathcal{V}_v is referred to as the set of all virtual velocities. The elements \mathbf{u}_s , $\nabla \mathbf{u}_s$, \mathbf{u}_f , and $\nabla \mathbf{u}_f$ are the virtual counterparts of \mathbf{v}_s , $\nabla \mathbf{v}_s$, \mathbf{v}_f , and $\nabla \mathbf{v}_f$, respectively, and the non-standard fields u_ε , u_p , and ∇u_p denote the virtual velocities corresponding to the rates $D_s \varepsilon_p$, $D_s e_p$, and $\nabla(D_s e_p)$, respectively.

Once the virtual velocities of the model are identified, it is possible to write the internal and the external virtual powers of the system. These two linear and continuous functionals are defined over \mathcal{V}_v , and are specified through the expressions

$$\mathcal{W}_v^{(i)}(\mathcal{V}_v) \equiv \int_{\mathcal{E}_i} \left\{ \boldsymbol{\sigma}_s : \mathbf{g} \nabla \mathbf{u}_s + \mathbf{m}_s \cdot \mathbf{u}_s + \boldsymbol{\sigma}_f : \mathbf{g} \nabla \mathbf{u}_f + \mathbf{m}_f \cdot \mathbf{u}_f + h_\varepsilon^{(i)} u_\varepsilon + h_p^{(i)} u_p + \boldsymbol{\xi}_p \nabla u_p \right\}, \quad (26a)$$

$$\mathcal{W}_v^{(e)}(\mathcal{V}_v) \equiv \int_{\Gamma^N} \left\{ \boldsymbol{\tau}_s \cdot \mathbf{u}_s + \boldsymbol{\tau}_f \cdot \mathbf{u}_f + \zeta_p u_p \right\} + \int_{\mathcal{E}_i} \left\{ h_\varepsilon^{(e)} u_\varepsilon + h_p^{(e)} u_p \right\}, \quad (26b)$$

respectively. Here, $\mathcal{E}_i \subset \mathcal{S}$ is the portion of the Euclidean space in which the solid and the fluid phase co-exist, and $\Gamma_i^N \subset \partial \mathcal{E}_i$ is the portion of the boundary of \mathcal{E}_i on which Neumann conditions are imposed. In (26a), $\boldsymbol{\sigma}_s$ and $\boldsymbol{\sigma}_f$ are the Cauchy stress tensors of the solid and of the fluid, \mathbf{m}_s and \mathbf{m}_f are internal forces that describe the gain or loss of momentum of the solid and of the fluid in response to exchange interactions between the two phases, $h_\varepsilon^{(i)}$ and $h_p^{(i)}$ are internal generalised forces dual to u_ε and u_p , respectively, and $\boldsymbol{\xi}_p$ is the generalised stress-like field dual to ∇u_p . We notice that, since the virtual velocities u_ε and u_p are scalar fields, the forces dual to them must be representable by scalars. Following the same logic, supplied by duality, since ∇u_p is a co-vector by definition, its power-conjugate force, $\boldsymbol{\xi}_p$, must be a vector-like field. On the same footing, in addition to the standard vector-like contact forces $\boldsymbol{\tau}_s$ and $\boldsymbol{\tau}_f$, in (26b) we introduce the contact force ζ_p and the ‘‘bulk’’ external forces $h_\varepsilon^{(e)}$ and $h_p^{(e)}$, all being scalar-like for the reasons explained above.

By requiring the internal virtual power, $\mathcal{W}_v^{(i)}(\mathcal{V}_v)$, to be invariant under the superposition of arbitrary rigid motions, we deduce the symmetry of the total stress tensor, $\boldsymbol{\sigma} = \boldsymbol{\sigma}_s + \boldsymbol{\sigma}_f$, and that the sum of the internal forces \mathbf{m}_s and \mathbf{m}_f must vanish identically, i.e., we obtain the condition $\mathbf{m}_s + \mathbf{m}_f = \mathbf{0}$ ^[58]. Consistently with the *a priori* exclusion of all inertial terms from our model, this last result constitutes an approximation of the more general balance of internal forces that, for a biphasic medium with mass exchange between the phases, is given by $\mathbf{m}_s + r_s \mathbf{v}_s + \mathbf{m}_f - r_s \mathbf{v}_f = \mathbf{0}$. In fact, the approximation consists of dropping the term $r_s \mathbf{v}_s - r_s \mathbf{v}_f = -r_s \mathbf{w}$, and is based on the argument that the interphase mass transfer, r_s , depends on the micro-scale velocity with which the mass passes from the fluid to the solid, and vice versa. Such velocity, multiplied by the relative macro-scale velocity \mathbf{w} , is assumed to produce a rate of momentum exchange that weighs much less than \mathbf{m}_s and \mathbf{m}_f , thereby leading to the desired approximation.

We emphasise that, in writing the expressions of $\mathcal{W}_v^{(i)}(\mathcal{V}_v)$ and $\mathcal{W}_v^{(e)}(\mathcal{V}_v)$, we have omitted *all* inertial and long-range (e.g. gravity) forces, which we regard as negligible from the outset. Moreover, the nature of the forces $h_p^{(i)}$ and $\boldsymbol{\xi}_p$ is necessarily coherent with the hypothesis that the kinematics of the solid phase micro-structure is represented by e_p and ∇e_p . In this sense, the model features some important similarities with Gurtin’s approach to the derivation of the generalised Allen-Cahn equation^[52], in which the scalar field describing the micro-structural kinematics of the considered medium is regarded as an order parameter.

Looking at (26a) and (26b), we also notice that, in principle, also the velocity and the velocity gradient of the nutrients should be considered, along with their virtual counterparts, in (24) and (25). However, in view of a comprehensive formulation of the Principle of Virtual Powers, this would call for the definition of the generalised forces expending power on them, and, above all, for the introduction of surface tractions, acting on Γ_i^N . Individuating a physically sound way for expressing such contact forces is not easy and taking them into account leads unavoidably to both theoretical and computational complications (see, e.g., Grillo et al.^[36] for an attempt of including these forces, based on a work by Sciarra et al.^[70]). For these reasons, we present here a simplified framework in which we account for the nutrients through the balance law (3a), while we omit to study their kinematics and dynamics in detail. In other words, due to their tantamount importance for activating growth, we do include them in our model, but we do not treat them systematically. Hence, we do not consider any force balance associated with the nutrients, nor do we investigate their contribution to the dissipation inequality (see Section 4). Rather, with reference

395 to (3a), we “guess” that the mass flux vector, \mathbf{y}_N , obeys a diffusion dynamics of Fickian type, so that it is prescribed to have
 396 the form $\mathbf{y}_N = -\rho_{f0} \mathbf{d} \nabla c_N$ in the Eulerian description and $\mathbf{Y}_N = -\rho_{f0} \mathbf{D} \text{Grad} \omega_N$ in material formalism, with \mathbf{d} being the
 397 diffusivity tensor and \mathbf{D} its material counterpart. Note that the latter is related to \mathbf{d} through the backward Piola transformation
 398 $\mathbf{D}(X, t) = J(X, t) \mathbf{F}^{-1}(\chi(X, t), t) \mathbf{d}(\chi(X, t), t) \mathbf{F}^{-T}(X, t)$.

399 By invoking the Principle of Virtual Powers, we enforce the condition $\mathcal{W}_v^{(i)}(\mathcal{V}_v) = \mathcal{W}_v^{(e)}(\mathcal{V}_v)$, which is required to be fulfilled
 400 for any admissible set of generalised velocities \mathcal{V}_v , thereby leading to

$$\begin{aligned} & \int_{\mathcal{C}_t} \left\{ [-\text{div} \boldsymbol{\sigma}_s + \mathbf{m}_s] \cdot \mathbf{u}_s + [-\text{div} \boldsymbol{\sigma}_f + \mathbf{m}_f] \cdot \mathbf{u}_f + [h_\varepsilon^{(i)} - h_\varepsilon^{(e)}] u_\varepsilon + [h_p^{(i)} - \text{div} \boldsymbol{\xi}_p - h_p^{(e)}] u_p \right\} \\ & + \int_{\Gamma_t^N} \left\{ [\boldsymbol{\sigma}_s \cdot \mathbf{n} - \boldsymbol{\tau}_s] \cdot \mathbf{u}_s + [\boldsymbol{\sigma}_f \cdot \mathbf{n} - \boldsymbol{\tau}_f] \cdot \mathbf{u}_f + [\boldsymbol{\xi}_p \cdot \mathbf{n} - \zeta_p] u_p \right\} = 0. \end{aligned} \quad (27)$$

401 By adopting the usual localisation procedure that extracts the local form of the equations of motion from the Principle of Virtual
 402 Powers, Equation (27) yields the following balances of generalised forces

$$\mathbf{m}_s - \text{div} \boldsymbol{\sigma}_s = \mathbf{0}, \quad (28a)$$

$$\mathbf{m}_f - \text{div} \boldsymbol{\sigma}_f = \mathbf{0}, \quad (28b)$$

$$h_\varepsilon^{(i)} - h_\varepsilon^{(e)} = 0, \quad (28c)$$

$$h_p^{(i)} - \text{div} \boldsymbol{\xi}_p - h_p^{(e)} = 0, \quad (28d)$$

403 which hold in \mathcal{C}_t , and the balances of contact forces on Γ_t^N

$$\boldsymbol{\sigma}_s \cdot \mathbf{n} - \boldsymbol{\tau}_s = \mathbf{0}, \quad (29a)$$

$$\boldsymbol{\sigma}_f \cdot \mathbf{n} - \boldsymbol{\tau}_f = \mathbf{0}, \quad (29b)$$

$$\boldsymbol{\xi}_p \cdot \mathbf{n} - \zeta_p = 0. \quad (29c)$$

404 It is worthwhile to mention that, in general, upon defining the field of *total* contact forces $\boldsymbol{\tau} = \boldsymbol{\tau}_s + \boldsymbol{\tau}_f$, and the *total* Cauchy
 405 stress tensor $\boldsymbol{\sigma} = \boldsymbol{\sigma}_s + \boldsymbol{\sigma}_f$, it is rather natural to provide on Γ_t^N boundary conditions of the kind $\boldsymbol{\sigma} \cdot \mathbf{n} = \boldsymbol{\tau}$ (see^[70] for details).
 406 Nevertheless, even in that case, the boundary conditions (29a) and (29b) can be recovered under the assumption that $\boldsymbol{\tau}_s$ and $\boldsymbol{\tau}_f$
 407 are obtained by partitioning $\boldsymbol{\tau}$ as $\boldsymbol{\tau}_s = (\rho_{s0} \varphi_s / \rho) \boldsymbol{\tau}$ and $\boldsymbol{\tau}_f = (\rho_{f0} \varphi_f / \rho) \boldsymbol{\tau}$, respectively.

408 4 | DISSIPATION AND DYNAMIC EQUATIONS

409 To extract constitutive information on the internal forces presented so far, we study the dissipation inequality of the system. For
 410 this purpose, we enrich the picture proposed in Grillo et al.^[36], which, in turn, was inspired by Hassanizadeh^[71] and Benethum
 411 et al.^[72]. This is done by framing the formulation of Anand et al.^[44] in the context of biphasic media and, above all, by rephrasing
 412 it in order to account for growth. The first step in this direction is to introduce the dissipation density, \mathcal{D} , measured per unit
 413 volume of the current configuration of the medium, and defining the dissipation associated with an open subset $\Omega_t \subset \mathcal{C}_t$ as

$$\begin{aligned} \int_{\Omega_t} \mathcal{D} = & - \int_{\Omega_t} \left\{ r_s (\psi_s - \psi_f) + \rho_{s0} \varphi_s D_s \psi_s + \rho_{f0} \varphi_f D_s \psi_f + (\rho_{f0} \varphi_f \nabla \psi_f) \cdot \mathbf{w} \right\} \\ & + \int_{\partial \Omega_t} \left\{ (\boldsymbol{\sigma}_s \cdot \mathbf{n}) \cdot \mathbf{v}_s + (\boldsymbol{\sigma}_f \cdot \mathbf{n}) \cdot \mathbf{v}_f + (\boldsymbol{\xi}_p \cdot \mathbf{n}) D_s e_p \right\} + \int_{\Omega_t} \left\{ h_\varepsilon^{(e)} D_s \varepsilon_p + h_p^{(e)} D_s e_p \right\} + \int_{\Omega_t} \mathcal{D}_\gamma \geq 0. \end{aligned} \quad (30)$$

414 As shown in (30), the dissipation can be written as the sum of four different contributions: with reference to the first integral of
 415 the sum defining $\int_{\Omega_t} \mathcal{D}$, we recognise that, by indicating with ψ_s and ψ_f the Helmholtz free energies per unit mass of the solid
 416 and of the fluid, the term $r_s (\psi_s - \psi_f)$ expresses the rate of change of the free energy densities, $\rho_{s0} \varphi_s \psi_s$ and $\rho_{f0} \varphi_f \psi_f$, due to the
 417 mass exchange between the phases. Moreover, $\rho_{s0} \varphi_s D_s \psi_s$ and $\rho_{f0} \varphi_f D_s \psi_f$ are the rates of change of the Helmholtz free energy
 418 densities measured with respect to the solid phase motion, and $(\nabla \psi_f) \cdot \mathbf{w}$ describes how ψ_f is transported due to the motion of
 419 the fluid relative to the solid. The terms in the surface integral denote the contributions to the net power expended on Ω_t due to
 420 the contact forces with the surrounding medium, while the terms in the third integral represent the part of net power ascribable

421 to the non-standard forces $h_\varepsilon^{(e)}$ and $h_p^{(e)}$. Finally, \mathcal{D}_γ is a dissipation density introduced to account for the fact that the medium
 422 experiences growth (see e.g. ^[66] for a discussion on this issue).

423 By applying Gauss Theorem to the surface integral of Equation (30), and using the balance laws (28a)–(28d) and (29a)–(29c),
 424 the dissipation inequality becomes

$$\int_{\Omega_t} \mathcal{D} = - \int_{\Omega_t} \left\{ r_s(\psi_s - \psi_f) + \rho_{s0} \varphi_s \mathcal{D}_s \psi_s + \rho_{f0} \varphi_f \mathcal{D}_s \psi_f + (\rho_{f0} \varphi_f \nabla \psi_f) \mathbf{w} \right\} \\ + \int_{\Omega_t} \left\{ \mathbf{m}_s \cdot \mathbf{v}_s + \boldsymbol{\sigma}_s : \mathbf{g} \nabla \mathbf{v}_s + \mathbf{m}_f \cdot \mathbf{v}_f + \boldsymbol{\sigma}_f : \mathbf{g} \nabla \mathbf{v}_f + h_p^{(i)} \mathcal{D}_s \varepsilon_p + \boldsymbol{\xi}_p \nabla (\mathcal{D}_s \varepsilon_p) + h_\varepsilon^{(i)} \mathcal{D}_s \varepsilon_p \right\} + \int_{\Omega_t} \mathcal{D}_\gamma \geq 0. \quad (31)$$

425 By localising Equation (31) and invoking the condition $\mathbf{m}_s + \mathbf{m}_f = \mathbf{0}$, we obtain

$$\mathcal{D} = r_s(\psi_f - \psi_s) - \rho_{s0} \varphi_s \mathcal{D}_s \psi_s - \rho_{f0} \varphi_f \mathcal{D}_s \psi_f + [\mathbf{m}_f - \mathbf{g}^{-1}(\rho_{f0} \varphi_f \nabla \psi_f)] \cdot \mathbf{w} \\ + \boldsymbol{\sigma}_s : \mathbf{g} \nabla \mathbf{v}_s + \boldsymbol{\sigma}_f : \mathbf{g} \nabla \mathbf{v}_f + h_p^{(i)} \mathcal{D}_s \varepsilon_p + \boldsymbol{\xi}_p \nabla (\mathcal{D}_s \varepsilon_p) + h_\varepsilon^{(i)} \mathcal{D}_s \varepsilon_p + \mathcal{D}_\gamma \geq 0. \quad (32)$$

426 As a simplifying assumption, we approximate the Helmholtz free energy density of the fluid, ψ_f , with a constant, so that
 427 $\rho_{f0} \varphi_f \mathcal{D}_s \psi_f$ and $\nabla \psi_f$ are negligible with respect to all the other terms featuring in the dissipation inequality. Such situation occurs,
 428 for instance, when the state variables characterising ψ_f are, at the most, the temperature and the mass fraction of the nutrients
 429 dissolved in the fluid, and the latter is so low that ψ_f can be safely set equal to the (constant) Helmholtz free energy density of
 430 water at constant temperature. Under these hypotheses, Equation (32) becomes

$$\mathcal{D} = r_s(\psi_f - \psi_s) - \rho_{s0} \varphi_s \mathcal{D}_s \psi_s + \mathbf{m}_f \cdot \mathbf{w} + \boldsymbol{\sigma}_s : \mathbf{g} \nabla \mathbf{v}_s + \boldsymbol{\sigma}_f : \mathbf{g} \nabla \mathbf{v}_f + h_p^{(i)} \mathcal{D}_s \varepsilon_p + \boldsymbol{\xi}_p \nabla (\mathcal{D}_s \varepsilon_p) + h_\varepsilon^{(i)} \mathcal{D}_s \varepsilon_p + \mathcal{D}_\gamma \geq 0. \quad (33)$$

431 It is convenient to rewrite the dissipation inequality per unit volume of \mathcal{B} . To do this, we perform a Piola transformation of
 432 (33), which yields

$$\mathcal{D}_R = R_s(\Psi_f - \Psi_s) - \rho_{s0} J_\gamma \Phi_{sv} \dot{\Psi}_s + \Phi_f^{-1} \mathcal{Q} \mathbf{M}_f + \mathbf{P}_s : \mathbf{g} \dot{\mathbf{F}} + \mathbf{P}_f : \mathbf{g} \text{Grad} \mathbf{V}_f + H_p^{(i)} \dot{\varepsilon}_p + \boldsymbol{\Xi}_p \text{Grad} \dot{\varepsilon}_p + H_\varepsilon^{(i)} \dot{\varepsilon}_p + J \mathcal{D}_\gamma \geq 0, \quad (34)$$

433 where, as anticipated above, $R_s(X, t) r_s(\chi(X, t), t)$ is the material form of the source/sink of mass for the solid phase
 434 as a whole, and we introduced the notation

$$\Psi_\alpha(X, t) = \psi_\alpha(\chi(X, t), t), \quad \alpha \in \{f, s\}, \quad (35a)$$

$$\mathbf{P}_\alpha(X, t) = \mathbf{J}(X, t) \boldsymbol{\sigma}_\alpha(\chi(X, t), t) \mathbf{F}^{-T}(X, t), \quad \alpha \in \{f, s\}, \quad (35b)$$

$$H_\beta^{(i)}(X, t) = \mathbf{J}(X, t) h_\beta^{(i)}(\chi(X, t), t), \quad \beta \in \{p, \varepsilon\}, \quad (35c)$$

$$\boldsymbol{\Xi}_p(X, t) = \mathbf{J}(X, t) \boldsymbol{\xi}_p(\chi(X, t), t) \mathbf{F}^{-T}(X, t), \quad (35d)$$

$$\mathbf{M}_f(X, t) = \mathbf{J}(X, t) [\mathbf{g}(\chi(X, t)) \mathbf{m}_f(\chi(X, t), t)] \mathbf{F}(X, t). \quad (35e)$$

435 Here, \mathbf{P}_f and \mathbf{P}_s indicate the first Piola-Kirchhoff stress tensors of the fluid and the solid phase, $H_p^{(i)}$ and $H_\varepsilon^{(i)}$ express, in material
 436 form, the internal generalised forces dual to $\dot{\varepsilon}_p$ and $\dot{\varepsilon}_p$, respectively, $\boldsymbol{\Xi}_p$ is the material representation of the stress-like generalised
 437 force, $\boldsymbol{\xi}_p$, and is thus dual to $\text{Grad} \dot{\varepsilon}_p$, and \mathbf{M}_f , re-defined as a covector, is the material counterpart of the momentum exchange
 438 rate \mathbf{m}_f .

439 Finally, by generalising the Helmholtz free energy density proposed by ^[44], we prescribe Ψ_s to be given by the sum of three
 440 terms, i.e.,

$$\hat{\Psi}_s(\mathbf{F}, \mathbf{F}_p, \mathbf{F}_\gamma, \varepsilon_p, \varepsilon_p, \text{Grad} \varepsilon_p) = \hat{\Psi}_s^{(st)}(\mathbf{F} \mathbf{F}_\gamma^{-1} \mathbf{F}_p^{-1}) + \frac{1}{2} a_0 [\varepsilon_p - \varepsilon_p]^2 + \frac{1}{2} b_0 \mathbf{F}_\gamma^{-1} \mathbf{B}_p \mathbf{F}_\gamma^{-T} : \text{Grad} \varepsilon_p \otimes \text{Grad} \varepsilon_p, \quad (36)$$

441 with $\mathbf{B}_p = \mathbf{F}_p^{-1} \cdot \mathbf{F}_p^{-T}$, so that the time derivative of Ψ_s reads

$$\dot{\Psi}_s = \left(\frac{\partial \hat{\Psi}_s^{(st)}}{\partial \mathbf{F}_e} \mathbf{F}_p^{-T} \mathbf{F}_\gamma^{-T} \right) : \dot{\mathbf{F}} - \frac{1}{3} \frac{\text{tr}(\boldsymbol{\eta} \boldsymbol{\Sigma}_v)}{\rho_{s0} \Phi_{sv}} \frac{R_s}{\rho_{s0} \Phi_{sv} J_\gamma} - \frac{1}{\rho_{s0} \Phi_{sv}} \left\{ \sqrt{\frac{3}{2}} \|\tilde{\boldsymbol{\Sigma}}_v\|_\eta - A_v [\varepsilon_p - \varepsilon_p] \right\} \dot{\varepsilon}_p \\ - \frac{A_v}{\rho_{s0} \Phi_{sv}} [\varepsilon_p - \varepsilon_p] \dot{\varepsilon}_p + \frac{B_v}{\rho_{s0} \Phi_{sv}} [(\mathbf{F}_\gamma^{-1} \mathbf{B}_p \mathbf{F}_\gamma^{-T}) \text{Grad} \varepsilon_p] \overline{\text{Grad} \varepsilon_p}, \quad (37)$$

442 where $\hat{\Psi}_s^{(st)}$ is differentiated with respect to $\mathbf{F}_e = \mathbf{F} \mathbf{F}_\gamma^{-1} \mathbf{F}_p^{-1}$. In (37), we introduced the notation

$$\boldsymbol{\Sigma}_v = \boldsymbol{\eta}^{-1} \mathbf{F}_e^T \left(\rho_{s0} \Phi_{sv} \frac{\partial \hat{\Psi}_s^{(st)}}{\partial \mathbf{F}_e} \right) + B_v [\boldsymbol{\eta}^{-1} \mathbf{F}_p^{-T} \mathbf{F}_\gamma^{-T} (\text{Grad} \varepsilon_p \otimes \text{Grad} \varepsilon_p) \mathbf{F}_\gamma^{-1} \mathbf{F}_p^{-1} \boldsymbol{\eta}^{-1}], \quad (38a)$$

$$\tilde{\Sigma}_v = \Sigma_v - \frac{1}{3} \text{tr}[\eta \Sigma_v] \eta^{-1}, \quad (38b)$$

$$A_v = \rho_{s0} \Phi_{sv} a_0, \quad (38c)$$

$$B_v = \rho_{s0} \Phi_{sv} b_0, \quad (38d)$$

where A_v and B_v are the counterparts of the strictly positive constants a_0 and b_0 , expressed per unit volume of the tissue's natural state, and Σ_v is a generalised Mandel stress tensor that comprises both the standard definition of the Mandel stress tensor, i.e.,

$$\Sigma_v^{(st)} = \eta^{-1} F_e^T \left(\rho_{s0} \Phi_{sv} \frac{\partial \hat{\Psi}_s^{(st)}}{\partial F_e} \right), \quad (39)$$

and the non-standard stress-like contribution

$$\Sigma_v^{(n-st)} = B_v \left[\eta^{-1} F_p^{-T} F_\gamma^{-T} (\text{Grade}_p \otimes \text{Grade}_p) F_\gamma^{-1} F_p^{-1} \eta^{-1} \right]. \quad (40)$$

We remark that $\Sigma_v^{(n-st)}$ is purely configurational, and it descends from the introduction of the micro-scale plasticity variable e_p . Moreover, $\Sigma_v^{(n-st)}$ is independent of deformation, whereas it does depend on the growth and remodelling distortions, F_γ and F_p .

Remark 2. Tensor Σ_v and co-directionality. In our work, the deviatoric part of the generalised Mandel stress tensor, $\tilde{\Sigma}_v$, is the stress tensor used to define N_v in (15). Therefore, it is the tensor with which the rate of plastic distortions, \dot{D}_p , is co-directional. By virtue of the definition of N_v , the direction of \dot{D}_p in the space of the symmetric second-order tensors is determined, partially, by the deviatoric part of the standard Mandel stress tensor, $\tilde{\Sigma}_v^{(st)}$, and partially by $\tilde{\Sigma}_v^{(n-st)}$, which includes the contributions of the micro-scale ‘‘plasticity’’, through Grade_p , and of the growth and remodelling distortions through F_γ and F_p , respectively. In the work of Anand et al. [44], instead, N_v is determined by $\Sigma_v^{(st)}$ only.

By substituting (37) into (34), D_R becomes

$$\begin{aligned} D_R = & \left\{ -J_\gamma \left(\rho_{s0} \Phi_{sv} \frac{\partial \hat{\Psi}_s^{(st)}}{\partial F_e} F_p^{-T} F_\gamma^{-T} \right) + \mathbf{g} P_s \right\} : \dot{F} + \left\{ \Psi_f - \Psi_s + \frac{1}{3} \frac{\text{tr}(\eta \Sigma_v)}{\rho_{s0} \Phi_{sv}} \right\} R_s \\ & + \left\{ H_\varepsilon^{(i)} + J_\gamma \sqrt{\frac{3}{2}} \|\tilde{\Sigma}_v\|_\eta - J_\gamma A_v [\varepsilon_p - e_p] \right\} \dot{\varepsilon}_p \\ & + \left\{ H_p^{(i)} + J_\gamma A_v [\varepsilon_p - e_p] \right\} \dot{e}_p + \left\{ \Xi_p - J_\gamma B_v [(F_\gamma^{-1} B_p F_\gamma^{-T}) \text{Grade}_p] \right\} \overline{\text{Grade}_p} \\ & + \Phi_f^{-1} Q M_f + P_f : \mathbf{g} \text{Grad} V_f + J D_\gamma \geq 0. \end{aligned} \quad (41)$$

We study the dissipation inequality (41) by regarding the mass balance law (5) as a constraint [72,73], and appending it to D_R . To this end, we perform the Piola transformation of (5), thereby obtaining (see e.g. [36,72])

$$C_R \equiv \Phi_s F^{-T} : \dot{F} + \Phi_f F^{-T} : \text{Grad} V_f + J \Phi_f^{-1} Q \text{Grad}(J^{-1} \Phi_f) - \left(\frac{1}{\rho_{s0}} - \frac{1}{\rho_{f0}} \right) R_s = 0, \quad (42)$$

where C_R stands for ‘‘constraint’’. Then, we multiply (42) by a Lagrange multiplier, p , which plays the role of hydrostatic pressure, and we attach the resulting expression to (41). This leads to a ‘‘new’’ dissipation function, $D_R^{\text{new}} \equiv D_R + p C_R$, that is equal to D_R , but is put in the form

$$\begin{aligned} D_R^{\text{new}} = & \left\{ -J_\gamma \left(\rho_{s0} \Phi_{sv} \frac{\partial \hat{\Psi}_s^{(st)}}{\partial F_e} F_p^{-T} F_\gamma^{-T} \right) + p \Phi_s F^{-T} + \mathbf{g} P_s \right\} : \dot{F} + \left\{ p \Phi_f F^{-T} + \mathbf{g} P_f \right\} : \text{Grad} V_f \\ & + \Phi_f^{-1} Q \left\{ M_f + J p \text{Grad}(J^{-1} \Phi_f) \right\} + \left\{ \left(\Psi_f + \frac{p}{\rho_{f0}} \right) - \left(\Psi_s + \frac{p}{\rho_{s0}} \right) + \frac{1}{3} \frac{\text{tr}(\eta \Sigma_v)}{\rho_{s0} \Phi_{sv}} \right\} R_s + J D_\gamma \\ & + \left\{ H_\varepsilon^{(i)} + J_\gamma \sqrt{\frac{3}{2}} \|\tilde{\Sigma}_v\|_\eta - J_\gamma A_v [\varepsilon_p - e_p] \right\} \dot{\varepsilon}_p \\ & + \left\{ H_p^{(i)} + J_\gamma A_v [\varepsilon_p - e_p] \right\} \dot{e}_p + \left\{ \Xi_p - J_\gamma B_v [(F_\gamma^{-1} B_p F_\gamma^{-T}) \text{Grade}_p] \right\} \overline{\text{Grade}_p} \geq 0. \end{aligned} \quad (43)$$

4.1 | Constitutive Laws

We require that the inequality (43) be valid for arbitrary values of $\dot{\mathbf{F}}$, $\text{Grad}\mathbf{V}_f$, $\dot{\mathbf{e}}_p$, and $\overline{\text{Grade}}_p$. Hence, the Coleman-Noll method implies the following identifications

$$\mathbf{P}_s = -\Phi_s p \mathbf{g}^{-1} \mathbf{F}^{-T} + J_\gamma \left(\rho_{s0} \Phi_{sv} \mathbf{g}^{-1} \frac{\partial \hat{\Psi}_s^{(st)}}{\partial \mathbf{F}_e} \mathbf{F}_p^{-T} \mathbf{F}_\gamma^{-T} \right), \quad (44a)$$

$$\mathbf{P}_f = -\Phi_f p \mathbf{g}^{-1} \mathbf{F}^{-T}, \quad (44b)$$

$$H_p^{(i)} = -J_\gamma A_v [\varepsilon_p - \mathbf{e}_p], \quad (44c)$$

$$\Xi_p = J_\gamma B_v [\mathbf{F}_\gamma^{-1} \mathbf{B}_p \mathbf{F}_\gamma^{-T}] \text{Grade}_p. \quad (44d)$$

In (44a), and in the sequel, the standard part of the solid phase Helmholtz free energy density, $\hat{\Psi}_s^{(st)}$, is assumed to be of the Holmes-Mow type^[59], i.e.,

$$\hat{\Psi}_s^{(st)}(\mathbf{F}_e) = \frac{\alpha_0}{\rho_{s0} \Phi_{sv}} \{ \exp(\hat{f}(\mathbf{C}_e)) - 1 \}, \quad (45)$$

where $\mathbf{C}_e = \mathbf{F}_e^T \cdot \mathbf{F}_e$ is the elastic Cauchy-Green deformation tensor, α_0 is a material coefficient having physical units of energy per unit volume, and the function \hat{f} is given by

$$\begin{aligned} \hat{f}(\mathbf{C}_e) &= \check{f}(\hat{I}_1(\mathbf{C}_e), \hat{I}_2(\mathbf{C}_e), \hat{I}_3(\mathbf{C}_e)) \\ &= \alpha_1 [\hat{I}_1(\mathbf{C}_e) - 3] + \alpha_2 [\hat{I}_2(\mathbf{C}_e) - 3] - \alpha_3 \ln(\hat{I}_3(\mathbf{C}_e)), \end{aligned} \quad (46)$$

with $\hat{I}_1(\mathbf{C}_e)$, $\hat{I}_2(\mathbf{C}_e)$, and $\hat{I}_3(\mathbf{C}_e)$ denoting the first three principal invariants of \mathbf{C}_e . The material parameters α_1 , α_2 , and α_3 are all assumed to be constant in this work. Moreover, it holds that $\alpha_1 + 2\alpha_2 = \alpha_3$ ^[59], and the following relations connect α_0 , α_1 , α_2 , and α_3 with Lamé's elastic parameters of the material (see e.g.^[56]):

$$\alpha_0 = \frac{2\mu + \lambda}{4\alpha_3}, \quad \alpha_1 = \alpha_3 \frac{2\mu - \lambda}{2\mu + \lambda}, \quad \alpha_2 = \alpha_3 \frac{\lambda}{2\mu + \lambda}. \quad (47)$$

In the forthcoming calculations, we set $\alpha_3 = 1$, and we give μ and λ the values reported in Table 1 .

We recognise the dissipative parts of \mathbf{M}_f and $H_\varepsilon^{(i)}$, which we identify with the following quantities

$$\mathbf{M}_f^{(d)} = \mathbf{M}_f + J p \text{Grad}(J^{-1} \Phi_f), \quad (48a)$$

$$H_\varepsilon^{(i,d)} = H_\varepsilon^{(i)} + J_\gamma \sqrt{\frac{3}{2}} \|\tilde{\Sigma}_v\|_\eta - J_\gamma A_v [\varepsilon_p - \mathbf{e}_p], \quad (48b)$$

and the dissipation inequality becomes

$$D_R = \Phi_f^{-1} \mathbf{Q} \mathbf{M}_f^{(d)} + H_\varepsilon^{(i,d)} \dot{\varepsilon}_p + \left\{ \left(\Psi_f + \frac{p}{\rho_{f0}} \right) - \left(\Psi_s + \frac{p}{\rho_{s0}} \right) + \frac{1}{3} \frac{\text{tr}(\boldsymbol{\eta} \Sigma_v)}{\rho_{s0} \Phi_{sv}} \right\} R_s + J D_\gamma \geq 0. \quad (49)$$

We notice that, in (48b), growth influences the expression of $H_\varepsilon^{(i,d)}$ through the determinant J_γ in the term $J_\gamma A_v [\varepsilon_p - \mathbf{e}_p]$.

According to (49), our model predicts that the system under study features three independent dissipative processes. The first one is due to the power loss associated with the resistance to the fluid flow and, under the hypothesis of negligible inertial forces, it leads to Darcy's law, i.e.,

$$\mathbf{M}_f^{(d)} = \Phi_f \mathbf{K}^{-1} \mathbf{Q}. \quad (50)$$

Equation (50) represents the material form of Darcy's law and, accordingly, the tensor \mathbf{K} is the *material* permeability tensor of the medium, defined by

$$\mathbf{K}(X, t) = J(X, t) \mathbf{F}(X, t) \mathbf{k}(\chi(X, t), t) \mathbf{F}^{-T}(X, t), \quad (51)$$

with \mathbf{k} being the spatial permeability tensor. Finally, we remark that, in deriving (50), we have tacitly assumed that \mathbf{K} is invertible, whereas sometimes this may not be necessarily the case. By substituting (50) into the first term on the right-hand-side of (49), we obtain that the dissipation due to fluid flow is always non-negative, i.e., for all \mathbf{Q} , it holds that $\Phi_f^{-1} \mathbf{Q} \mathbf{M}_f^{(d)} = \mathbf{K}^{-1} : (\mathbf{Q} \otimes \mathbf{Q}) \geq 0$, as long as \mathbf{K} is positive-definite. Note that, by putting together the results (48a) and (50), \mathbf{M}_f is determined constitutively as

$$\mathbf{M}_f = \Phi_f \mathbf{K}^{-1} \mathbf{Q} - J p \text{Grad}(J^{-1} \Phi_f). \quad (52)$$

483 The second process contributing to the dissipation, D_R , is given by $H_\epsilon^{(i,d)} \dot{\epsilon}_p$, which represents the power that the solid phase
 484 expends in order to remodel its internal structure by accumulating plastic strain ϵ_p . We assume that $H_\epsilon^{(i,d)} \dot{\epsilon}_p$ is non-negative for
 485 all $\dot{\epsilon}_p$ and, since $\dot{\epsilon}_p$ is always non-negative by virtue of its own definition (see (18)), we conclude that $H_\epsilon^{(i,d)}$ has to be non-negative
 486 too. In our work, we hypothesise that the tissue remodels in a rate-dependent way and, in particular, we assign $H_\epsilon^{(i,d)}$ as

$$H_\epsilon^{(i,d)} = J \tau_p \dot{\epsilon}_p, \quad (53)$$

487 where τ_p is here taken as a strictly positive coefficient with the physical units of a generalised viscosity. By plugging (53) into
 488 (48b), we determine $H_\epsilon^{(i)}$ through the constitutive law

$$H_\epsilon^{(i)} = J \tau_p \dot{\epsilon}_p - J_\gamma \sqrt{\frac{3}{2}} \|\tilde{\Sigma}_v\|_\eta + J_\gamma A_v [\epsilon_p - e_p]. \quad (54)$$

489 The third dissipative phenomenon is given by growth, and is represented by the last two summands on the right-hand-side of
 490 (49), which we denote by D_g and refer to as the ‘‘growth part of D_R ’’. In contrast to what we have done for the other dissipative
 491 processes, and even though the terms between braces in (49) may be understood as the generalised force power-conjugate to
 492 $\dot{\gamma}/\gamma$ through R_s , we do not try to look for information on R_s from the requirement that D_g has to be non-negative. Rather,
 493 following^[4,6,24,33,37,53,54], we enforce a phenomenological law for R_s , which is translated into the kinematic constraint (23) on
 494 $\dot{\gamma}/\gamma$, and we use D_γ to adjust D_g and guarantee that it remains non-negative. We emphasise that, although this path may seem
 495 artificial, it can be justified by noticing that D_γ represents processes, related to growth, that are not resolved explicitly by our
 496 model but that are necessary for growth to occur. In fact, a motivation for introducing a term like D_γ in the dissipation inequality
 497 of a growth problem can be found in^[66].

4.2 | Dynamic Equations

499 By adopting the material form of the momentum balance laws (28a) and (28b), and by invoking the force balance $\mathbf{m}_s + \mathbf{m}_f = \mathbf{0}$,
 500 we obtain

$$- \mathbf{g}^{-1} \mathbf{F}^{-T} \mathbf{M}_f - \text{Div} \mathbf{P}_s = \mathbf{0}, \quad (55a)$$

$$\mathbf{g}^{-1} \mathbf{F}^{-T} \mathbf{M}_f - \text{Div} \mathbf{P}_f = \mathbf{0}, \quad (55b)$$

501 where the constitutive expressions of \mathbf{P}_s , \mathbf{P}_f , and \mathbf{M}_f are given in (44a), (44b), and (52), respectively. Furthermore, by adding
 502 together (55a) with (55b), and using the explicit expression for \mathbf{M}_f in (55b), we find

$$\text{Div}(\mathbf{P}_s + \mathbf{P}_f) = \mathbf{0}, \quad (56a)$$

$$\mathbf{K}^{-1} \mathbf{Q} + \text{Grad} p = \mathbf{0}. \quad (56b)$$

503 We exploit now the generalised force balance (28c), which becomes $H_\epsilon^{(i)} = H_\epsilon^{(e)}$ in material form and, by replacing $H_\epsilon^{(i)}$ with
 504 the right-hand-side of (54), we determine an evolution law for ϵ_p , i.e.,

$$J \tau_p \dot{\epsilon}_p - J_\gamma \sqrt{\frac{3}{2}} \|\tilde{\Sigma}_v\|_\eta + J_\gamma A_v [\epsilon_p - e_p] = H_\epsilon^{(e)}. \quad (57)$$

505 To close this equation, we prescribe $H_\epsilon^{(e)}$ as

$$H_\epsilon^{(e)} = - [J \sigma_{th} + J_\gamma Z_v [\epsilon_p - e_p]], \quad (58)$$

506 where σ_{th} is a threshold stress, and Z_v is a material parameter^[44]. Hence, setting $\lambda_p = 1/\tau_p$, Equation (57) takes on the form

$$\dot{\epsilon}_p = \frac{\lambda_p}{J} \left\{ \left(J_\gamma \sqrt{\frac{3}{2}} \|\tilde{\Sigma}_v\|_\eta - J \sigma_{th} \right) - J_\gamma (A_v + Z_v) [\epsilon_p - e_p] \right\}. \quad (59)$$

507 The last dynamic equation is supplied by (28d). Recalling that, in the present framework, the external force $h_p^{(e)}$ is zero, the
 508 material form of (28d) reads

$$H_p^{(i)} - \text{Div} \Xi_p = 0. \quad (60)$$

509 Hence, by substituting (44c) and (44d) into (60), we obtain

$$-J_\gamma A_v [\epsilon_p - e_p] - \text{Div} (J_\gamma B_v [F_\gamma^{-1} B_p F_\gamma^{-T}] \text{Grade}_p) = 0. \quad (61)$$

510 In particular, since we take F_γ as $F_\gamma = \gamma I$, (61) acquires the equivalent form

$$-\gamma^3 A_v[\varepsilon_p - e_p] - \text{Div}(\gamma B_v B_p \text{Grade}_p) = 0. \quad (62)$$

511 *Remark 3. The equation for e_p .* The result (62) is our generalisation to Equation (4.40) of Anand et al.^[44], which, in our notation,
512 and assuming constant values for A_v and B_v , would read

$$-A_v[\varepsilon_p - e_p] - B_v \Delta e_p = 0 \quad \Rightarrow \quad e_p - l_v^2 \Delta e_p = \varepsilon_p, \quad l_v = \sqrt{B_v/A_v}, \quad (A)$$

513 with Δ being the Laplace operator, and l_v the characteristic length scale associated with the micro-scale plasticity variable, e_p .
514 For a given distribution of ε_p , Equation (A) returns a “regularised” version of ε_p . In particular, since e_p is required to satisfy
515 Neumann-zero boundary conditions, if ε_p is constant in \mathcal{B} , then the unique solution to (A) is the constant solution $e_p = \varepsilon_p$.
516 However, when ε_p is strongly localised, the output of (A), i.e., e_p , tends to be a lot more homogeneous, the more l_v increases.

517 Our generalisation to (A) is twofold: first, the plastic-like distortions determine the evolution of e_p both through ε_p and through
518 the second-order tensor $B_p = F_p^{-1} \cdot F_p^{-T}$. While ε_p is an input for (A), B_p modulates, together with the growth parameter
519 γ , the non-locality of e_p , which is thus measured by the tensorial coefficient $\gamma B_v B_p$. We notice that the occurrence of this
520 coefficient is due to the last term in the definition of $\hat{\Psi}_s$ given in (36). Switching to the Eulerian formalism, and using the identity
521 $\text{Grade}_p(X, t) = (\nabla e_p(\chi(X, t), t))F(X, t)$, this term reads

$$\frac{1}{2} b_0 \mathbf{b}_e : \nabla e_p \otimes \nabla e_p,$$

522 thereby meaning that, in the spatial description, the non-locality of the micro-“plastic” variable, e_p , is modulated by the elastic
523 left Cauchy-Green deformation tensor, $\mathbf{b}_e = F_e \cdot F_e^T$. To eliminate B_p from (62), and obtain a model closer to that of Anand et
524 al.^[44], we should substitute \mathbf{b}_e with the left Cauchy-Green deformation tensor $\mathbf{b} = F \cdot F^T$. Such a choice would lead to replace
525 the last term of (36) with

$$\frac{1}{2} b_0 \mathbf{G}^{-1} : \text{Grade}_p \otimes \text{Grade}_p,$$

526 and would have the consequence of defining the unit tensor N_v just in terms of the standard Mandel stress tensor, $\Sigma_v^{(st)}$ (see
527 Remark 2). We recall that \mathbf{G} denotes here the natural material metric tensor associated with \mathcal{B} .

528 The second aspect of our generalisation is related to the fact that, in our model, the evolution of e_p is influenced by the growth
529 parameter, γ , which couples with the coefficients A_v and B_v , thereby rescaling the characteristic length scale associated with e_p
530 in a generally inhomogeneous way, i.e., as $l_v \rightarrow l = l_v \|B_p\|_G^{1/2} / \gamma$, so that, for a given l_v , the condition $\gamma > 1$ tends to reduce the
531 length scale associated with e_p . Note that $\|B_p\|_G = [\text{tr}(\mathbf{G} B_p \mathbf{G} B_p)]^{1/2}$.

532 *Remark 4. Choice of $H_\varepsilon^{(e)}$.* In the literature on remodelling (see e.g.^[11,13,19]), when an external force, like $H_\varepsilon^{(e)}$, is taken into
533 account, it is often chosen in such a way that a homeostatic state exists for the system under study. If we had followed such
534 philosophy, we should have admitted homeostatic terms for ε_p and e_p , denoted by $\varepsilon_p^{(h)}$ and $e_p^{(h)}$, and we should have expressed
535 $H_\varepsilon^{(e)}$ as

$$H_\varepsilon^{(e)} = -J_\gamma \sqrt{\frac{3}{2}} \|\tilde{\Sigma}_v^{(h)}\|_\eta + J_\gamma A_v [\varepsilon_p^{(h)} - e_p^{(h)}], \quad (63)$$

536 where $\tilde{\Sigma}_v^{(h)}$ is the Mandel-like stress tensor in homeostatic conditions (that is, when its arguments attain the homeostatic state).
537 This consideration notwithstanding, in our work we opted for the expression (58) because, in order to formulate a proof of
538 concept for our problem, we needed to remain as close as possible to the framework supplied by^[44].

539 *Remark 5. Evolution law for ε_p .* Equation (58) represents an essential difference with respect to the evolution law for ε_p given
540 by^[44]. Indeed, Anand et al.^[44] set $H_\varepsilon^{(i)} = H_\varepsilon^{(e)} = 0$, and assign $H_\varepsilon^{(i,d)}$ constitutively as a law that plays the role of an *effective*
541 *yield stress*, i.e., $H_\varepsilon^{(i,d)} = J \sigma_{th} + J_\gamma Z_v [\varepsilon_p - e_p]$, where $\sigma_{th} > 0$ plays the role of the “conventional yield stress”^{[44]3}, while
542 $Z_v > 0$ is a model parameter defining the purely dissipative part of $H_\varepsilon^{(i,d)}$. By doing this, the Authors rewrite the balance
543 equation $H_\varepsilon^{(i)} = H_\varepsilon^{(e)}$ in terms of a yield function of the type $\tilde{f} = J_\gamma \sqrt{\frac{3}{2}} \|\tilde{\Sigma}_v\|_\eta - (J \sigma_{th} + J_\gamma (A_v + Z_v) [\varepsilon_p - e_p])$. In particular,
544 according to the theory of Anand et al.^[44], it occurs that $\dot{\varepsilon}_p = 0$, if $\tilde{f} < 0$, and $\dot{\varepsilon}_p > 0$, if $\tilde{f} = 0$. This approach is equivalent to the

³Note that, differently from what is assumed here, Anand et al.^[44] hypothesise that the conventional yield stress is a monotonically decreasing function of ε_p , because they are interested in studying the phenomenon of *strain-softening*.

545 elasto-plastic problem in the Karush-Kuhn-Tucker form, i.e.,

$$\mathbf{f} \leq 0, \quad \dot{\varepsilon}_p \geq 0, \quad \mathbf{f} \dot{\varepsilon}_p = 0, \quad (64)$$

546 where $\dot{\varepsilon}_p$ is determined by means of the consistency condition $\dot{\varepsilon}_p \mathbf{f} = 0$, when $\mathbf{f} = 0$. If, in our work, we had followed the approach
 547 outlined by Anand et al.^[44], we would have found a very complicated evolution law for ε_p , especially from the computational
 548 point of view. To circumvent this technical difficulty, we have proposed a modification to the model, i.e., we have assumed
 549 $H_\varepsilon^{(i)} = H_\varepsilon^{(e)} \neq 0$ and, in order to obtain an evolution law for ε_p of the type $J \tau_p \dot{\varepsilon}_p = \mathbf{f}$ (cf. Equation (57)), with \mathbf{f} defined as done
 550 by Anand et al.^[44], we have exploited the “freedom” we have to express $H_\varepsilon^{(e)}$ as in (58). A last comment pertains to the terms
 551 λ_p/J and $J \sigma_{th}$ featuring in Equation (59): if λ_p and σ_{th} are such that $\lambda_p/J_e \equiv \Lambda_p$ and $J_e \sigma_{th} \equiv \Sigma_{th}$ are constants, then it holds
 552 that $\lambda_p/J = \Lambda_p/J_\gamma$ and $J \sigma_{th} = J_\gamma \Sigma_{th}$. In this case, J_γ does not feature explicitly in Equation (59), which becomes $\dot{\varepsilon}_p = \Lambda_p \tilde{\mathbf{f}}$,
 553 where we have set $\tilde{\mathbf{f}} \equiv \mathbf{f}/J_\gamma$. In this case, Σ_{th} acquires the meaning of the yield stress that is used in the yield criteria formulated
 554 in terms of the norm of the Mandel stress tensor (see e.g.^[43]). We remark, however, that solving $\dot{\varepsilon}_p = \Lambda_p \tilde{\mathbf{f}}$ in lieu of (59) leads,
 555 in our work, to no appreciable differences in the simulation results.

556 5 | MODEL EQUATIONS AND BENCHMARK TEST

557 In this section, we summarise all the model equations and their corresponding unknowns, we highlight the fundamental
 558 hypotheses adopted to simplify our simulations, and we describe the benchmark problem used for testing our model.

559 5.1 | Summary of the model equations

560 The first equation of the problem is given by (56a), i.e., the momentum balance law for the mixture as a whole, and its associated
 561 unknown is given by the solid phase motion, χ . The second equation determines the pressure, p , and is supplied by the mass
 562 balance law (8d), in which, coherently with (56b), \mathbf{Q} is expressed as $\mathbf{Q} = -\mathbf{K} \text{Grad} p$. The right-hand-side of (8d) is set equal
 563 to zero on the basis of the assumption that, in tumours, the mass densities ρ_{s0} and ρ_{f0} are approximately the same. The third
 564 equation is the mass balance of the proliferating cells (8a), and its corresponding unknown is the mass fraction ω_p . The fourth
 565 equation is in the mass fraction of the nutrients, ω_N , and is obtained from (8c) by using the identities $\Phi_f = \mathbf{J} - J_\gamma \Phi_{sv}$ and
 566 $Y_N = -\rho_{f0} \mathbf{D} \text{Grad} \omega_N$. The fifth equation descends for the mass balance law of the solid phase and, by assigning the mass source
 567 R_s phenomenologically, it puts a constraint on the growth parameter, γ , which is thus bound to comply with (23). Except for the
 568 sources and sinks of mass, which are defined in a slightly different way in our work, the five equations mentioned so far are the
 569 same as those studied by Mascheroni et al.^[24] and Di Stefano et al.^[54].

570 The evolution of the plastic distortions is described by the dynamic equation (59), which determines ε_p , and by the constraint
 571 on \mathbf{F}_p placed by (20). These add two more equations to the previous five. Finally, the equation for the micro-scale “plasticity”
 572 variable, \mathbf{e}_p , is supplied by (62).

573 In conclusion, by putting together all the laws enumerated up to now, we obtain

$$\text{Div}(\mathbf{P}_f + \mathbf{P}_s) = \mathbf{0}, \quad (65a)$$

$$\text{Div}(\mathbf{K} \text{Grad} p) = \mathbf{J}, \quad (65b)$$

$$\rho_{s0} J_\gamma \Phi_{sv} \dot{\omega}_p = R_{pn} + R_{fp} - R_s \omega_p, \quad (65c)$$

$$\rho_{f0} [J - J_\gamma \Phi_{sv}] \dot{\omega}_N + \rho_{f0} \mathbf{Q} \text{Grad} \omega_N = \text{Div}(\rho_{f0} \mathbf{D} \text{Grad} \omega_N) + R_{Np} + R_s \omega_N, \quad (65d)$$

$$\dot{\gamma} = \frac{R_s}{3 \rho_{s0} \Phi_{sv} \gamma^2}, \quad (65e)$$

$$\dot{\varepsilon}_p = \frac{\lambda_p}{J} \left\{ \left(J_\gamma \sqrt{\frac{3}{2}} \|\tilde{\Sigma}_v\|_\eta - J \sigma_{th} \right) - J_\gamma (A_v + Z_v) [\varepsilon_p - \mathbf{e}_p] \right\}, \quad (65f)$$

$$\dot{\mathbf{F}}_p = \left(\sqrt{\frac{3}{2}} \dot{\varepsilon}_p \boldsymbol{\eta}^{-1} \mathbf{N}_v \right) \mathbf{F}_p, \quad (65g)$$

$$\text{Div}(\gamma \mathbf{B}_v \mathbf{B}_p \text{Grade}_p) - \gamma^3 A_v \mathbf{e}_p = -\gamma^3 A_v \varepsilon_p, \quad (65h)$$

574 which constitutes a system of 18 scalar equations in the 18 unknowns

$$\mathcal{U} = \{\chi, p, \omega_p, \omega_N, \gamma, \varepsilon_p, \mathbf{F}_p, \mathbf{e}_p\}. \quad (66)$$

575 For ensuring the non-negativity of $\dot{\epsilon}_p$ at all times and at all points, we solve (65f) numerically by taking the positive part of its
576 right-hand-side. Moreover, to close the problem, we prescribe the permeability tensor and the diffusion tensor^[54,59,74,75],

$$\mathbf{K} = Jk_0\mathbf{C}^{-1}, \quad k_0 = k_{0R} \left[\frac{J - J_\gamma \Phi_{sv}}{J_\gamma \varphi_{f0}} \right]^{m_0} \exp \left(\frac{m_1}{2} \left[\frac{J^2 - J_\gamma^2}{J_\gamma^2} \right] \right), \quad (67a)$$

$$\mathbf{D} = Jd_0\mathbf{C}^{-1}, \quad d_0 = \frac{J - J_\gamma \Phi_{sv}}{J} d_{0R}, \quad (67b)$$

577 as well as the sources and sinks of mass^[24,54], i.e.,

$$R_{pn} = -J\zeta_{pn} \left\langle 1 - \frac{\omega_N}{\omega_{Ncr}} \right\rangle_+ \frac{J_\gamma \Phi_{sv}}{J} \omega_p, \quad (68a)$$

$$R_{fp} = J\zeta_{fp} \left\langle \frac{\omega_N - \omega_{Ncr}}{\omega_{Nenv} - \omega_{Ncr}} \right\rangle_+ \left[1 - \frac{\delta_1 \langle \varphi \rangle_+}{\delta_2 + \langle \varphi \rangle_+} \right] \frac{J - J_\gamma \Phi_{sv}}{J \varphi_{f0}} \frac{J_\gamma \Phi_{sv}}{J} \omega_p, \quad (68b)$$

$$R_s = R_{fp} + R_{nf}, \quad (68c)$$

$$R_{nf} = -J\zeta_{nf} [1 - \omega_p] \frac{J_\gamma \Phi_{sv}}{J}, \quad (68d)$$

$$R_{Np} = -J\zeta_{Np} \frac{\omega_N}{\omega_N + \omega_{N0}} \frac{J_\gamma \Phi_{sv}}{J} \omega_p. \quad (68e)$$

578 Since the expressions of R_{pn} , R_{fp} , R_{nf} , and R_{Np} have been already commented in previous works^[24,54], we do not spend any
579 more words here on their derivation. We recall, however, that the operator $\langle \cdot \rangle_+$ returns the positive part of its argument, and
580 that ω_{Ncr} denotes a critical value of the mass fraction of the nutrients, below which the proliferating cells tend to be necrotic
581 (that is, $R_{pn} < 0$), whereas ω_{Nenv} represents the mass fraction of the nutrients in the ‘‘environment’’. Both ω_{Nenv} and ω_{Ncr} are
582 regarded as constant parameters in our work, and it is assumed that the condition $\omega_{Nenv} > \omega_{Ncr}$ is always respected, so that
583 also R_{fp} is deactivated, i.e., $R_{fp} = 0$, for $\omega_N < \omega_{Ncr}$. Moreover, looking at the definition of R_{fp} , and bearing in mind that, for
584 $\omega_N > \omega_{Ncr}$, R_{fp} describes the positive variation of mass of the tissue’s solid phase, we notice that the factor

$$\left[1 - \frac{\delta_1 \langle \varphi \rangle_+}{\delta_2 + \langle \varphi \rangle_+} \right]$$

585 accounts for mechanotransduction through the action of the stress $\langle \varphi \rangle_+$. Comparing this result with the works of Mascheroni
586 et al.^[24] and Di Stefano et al.^[54], we notice that our model suggests a slightly different interpretation of mechanotransduction.
587 Indeed, while Mascheroni et al.^[24] and Di Stefano et al.^[54] prescribe φ as $\varphi = -(1/3)\text{tr}(\mathbf{g}\boldsymbol{\sigma}_{sc})$, where $\boldsymbol{\sigma}_{sc} = J^{-1}\mathbf{P}_{sc}\mathbf{F}^T$ is the
588 constitutive part of the solid phase Cauchy stress, and, accordingly, \mathbf{P}_{sc} is defined by

$$\mathbf{P}_{sc} = J_\gamma \left(\rho_{s0} \Phi_{sv} \mathbf{g}^{-1} \frac{\partial \hat{\Psi}_s^{(st)}}{\partial \mathbf{F}_e} (\mathbf{F} \mathbf{F}_\gamma^{-1} \mathbf{F}_p^{-1}) \mathbf{F}_p^{-T} \mathbf{F}_\gamma^{-T} \right) \equiv \mathcal{P}_{sc}(\mathbf{F}, \mathbf{F}_\gamma, \mathbf{F}_p), \quad (69)$$

589 in our approach φ is taken as $\varphi = -(1/3)\text{tr}(\mathbf{g}\boldsymbol{\sigma}_{eff})$ (see also^[19]), with

$$\begin{aligned} \boldsymbol{\sigma}_{eff} &= \boldsymbol{\sigma}_{sc} + \frac{1}{J_e} \mathbf{g}^{-1} \mathbf{F}_e^{-T} \boldsymbol{\eta} \boldsymbol{\Sigma}_v^{(n-st)} \mathbf{F}_e^T = \frac{1}{J_e} \mathbf{g}^{-1} \mathbf{F}_e^{-T} \boldsymbol{\eta} \boldsymbol{\Sigma}_v^{(st)} \mathbf{F}_e^T + \frac{1}{J_e} \mathbf{g}^{-1} \mathbf{F}_e^{-T} \boldsymbol{\eta} \boldsymbol{\Sigma}_v^{(n-st)} \mathbf{F}_e^T \\ &= \frac{1}{J_e} \mathbf{g}^{-1} \mathbf{F}_e^{-T} \boldsymbol{\eta} \boldsymbol{\Sigma}_v \mathbf{F}_e^T. \end{aligned} \quad (70)$$

590 In other words, while the works done by Mascheroni et al.^[24] and Di Stefano et al.^[54] the stress used to express the mechan-
591 otransduction is the classical $\boldsymbol{\sigma}_{sc}$, we propose here to adopt the *effective Cauchy stress*, $\boldsymbol{\sigma}_{eff}$, which captures both $\boldsymbol{\sigma}_{sc}$ and the
592 non-standard, purely configurational contribution $\boldsymbol{\Sigma}_v^{(n-st)}$. Our point is that, since in our approach $\boldsymbol{\Sigma}_v$ is (power-)conjugate to the
593 growth rate $\dot{\gamma}/\gamma$ (through R_s) and to $\dot{\epsilon}_p$ (see (37)), it might be a more natural representative of the stress responsible for mod-
594 ulating growth. This consideration notwithstanding, for the parameters chosen in our simulations, the contribution of $\boldsymbol{\Sigma}_v^{(n-st)}$ is
595 very marginal with respect to the standard measures of stress, and its contribution is thus not much appreciable.

596 5.2 | Benchmark problem

597 The benchmark problem is essentially the same as the one computed in Di Stefano et al.^[54], with the major difference that we
598 are now considering also plastic distortions and the role of micro-plasticity. Hence, by adapting a study originally designed

599 by Ambrosi and Mollica^[53], we consider the case of volumetric growth in a cylindrical sample of isotropic material. For this
 600 purpose, we introduce the systems of cylindrical coordinates (R, Θ, Z) and (r, θ, z) , which cover the reference and current
 601 configuration, respectively. For both systems, the first coordinate is radial, the second one is circumferential, and the third one
 602 is axial.

603 We assume that the radius of the specimen is preserved, and that only its length varies along the axial direction. Hence, we
 604 eliminate any rigid rotation about the principal axis. These restrictions imply that the momentum balance law (65a) reduces to
 605 a scalar equation in Z , and that the deformation gradient tensor becomes $F = e_r \otimes E^R + e_\theta \otimes E^\Theta + (1 + \frac{\partial u}{\partial Z})e_z \otimes E^Z$, where
 606 u is the field of axial displacements. We note that $\{E^R, E^\Theta, E^Z\}$ and $\{e_r, e_\theta, e_z\}$ are the co-vector and vector bases associated
 607 with the system of cylindrical coordinates (R, Θ, Z) and (r, θ, z) , respectively.

608 We impose the following boundary conditions on Equations (65a)–(65h)

$$(-Jp\mathbf{g}^{-1}F^{-T} + \mathbf{P}_{sc}).\mathbf{N}_A = \mathbf{0}, \quad \text{on } (\partial\mathcal{B})_{\text{Left}} \text{ and } (\partial\mathcal{B})_{\text{Right}}, \quad (71a)$$

$$p = 0, \quad \text{on } (\partial\mathcal{B})_{\text{Left}} \text{ and } (\partial\mathcal{B})_{\text{Right}}, \quad (71b)$$

$$(-\mathbf{K}\text{Grad } p).\mathbf{N}_C = 0, \quad \text{on } (\partial\mathcal{B})_C, \quad (71c)$$

$$(-\rho_f \mathbf{D}\text{Grad } \omega_N).\mathbf{N}_C = 0, \quad \text{on } (\partial\mathcal{B})_C, \quad (71d)$$

$$\omega_N = \omega_{\text{Nenv}}, \quad \text{on } (\partial\mathcal{B})_{\text{Left}} \text{ and } (\partial\mathcal{B})_{\text{Right}}, \quad (71e)$$

$$(\gamma \mathbf{B}_v \mathbf{B}_p \text{Grad}_p).\mathbf{N} = 0, \quad \text{on } \partial\mathcal{B}, \quad (71f)$$

609 where $\partial\mathcal{B} = (\partial\mathcal{B})_{\text{Left}} \cup (\partial\mathcal{B})_C \cup (\partial\mathcal{B})_{\text{Right}}$, $(\partial\mathcal{B})_C$ is the lateral boundary of the cylinder, $(\partial\mathcal{B})_{\text{Left}}$ and $(\partial\mathcal{B})_{\text{Right}}$ are the left
 610 and right surface cross-sections at $Z = -L/2$ and $Z = L/2$, respectively, and L is the initial length of the cylinder. Moreover,
 611 \mathbf{N}_A , \mathbf{N}_C , and \mathbf{N} are fields of unit vectors normal to $(\partial\mathcal{B})_{\text{Left}}$ and $(\partial\mathcal{B})_{\text{Right}}$, $(\partial\mathcal{B})_C$, and $\partial\mathcal{B}$, respectively.

612 Equations (71a) and (71b) mean that the left and right ends of the cylinder are free boundaries. The relations (71c) and (71d)
 613 are enforced to express that $(\partial\mathcal{B})_C$ is undeformable and impermeable to the fluid and to the nutrients, respectively. Equation
 614 (71e) is a Dirichlet condition specifying that there always exists a constant availability of nutrients on the boundaries $(\partial\mathcal{B})_{\text{Left}}$
 615 and $(\partial\mathcal{B})_{\text{Right}}$. Finally, the boundary condition (71f) is introduced following Anand et al.^[44].

616 To complete the mathematical formulation of the problem, we prescribe the initial conditions,

$$\chi^r(R, \Theta, Z, 0) = R, \quad (72a)$$

$$\chi^\theta(R, \Theta, Z, 0) = \Theta, \quad (72b)$$

$$\chi^z(R, \Theta, Z, 0) = Z, \quad (72c)$$

$$p(R, \Theta, Z, 0) = 0, \quad (72d)$$

$$\omega_N(R, \Theta, Z, 0) = \omega_{\text{Nenv}}, \quad (72e)$$

$$\gamma(R, \Theta, Z, 0) = 1, \quad (72f)$$

$$\omega_p(R, \Theta, Z, 0) = 1, \quad (72g)$$

$$\varepsilon_p(R, \Theta, Z, 0) = 0, \quad (72h)$$

$$\mathbf{e}_p(R, \Theta, Z, 0) = \mathbf{0}, \quad (72i)$$

617 with $R \in [0, R_b]$, $\Theta \in [0, 2\pi[$ and $Z \in [-L/2, L/2]$. The conditions (72a)–(72i) have to be valid in the whole domain \mathcal{B} .

618 The material parameters k_{0R} , m_0 , m_1 , and d_{0R} , the coefficients ζ_{pn} , ζ_{fp} , ζ_{nf} , and ζ_{Np} as well as the constants ω_{Nenv} , ω_{Ncr} , ω_{N0} ,
 619 δ_1 , δ_2 , σ_{th} , and λ_p are given in Table 1 .

620 In Table 1 , the length of the cylindric specimen, L , and the radius of its cross section, R_b , are chosen within a plausible phys-
 621 ical range. However, it is necessary to motivate the choice of the parameters ω_{Nenv} , ω_{Ncr} , and ω_{N0} , which are all taken from Di
 622 Stefano et al.^[54]. These quantities are adapted from^[24], where they were set equal to $\omega_{\text{Nenv}} = 7.0 \cdot 10^{-6}$, $\omega_{\text{Ncr}} = 2.0 \cdot 10^{-6}$, and
 623 $\omega_{\text{N0}} = 4.2 \cdot 10^{-6}$, respectively. With the exception of ω_{Ncr} ⁴, in the work of Mascheroni et al.^[24] these values come from exper-
 624 iments performed on tumour spheroids and associated with geometry, size, diffusion length scales and nutrients' characteristic
 625 mass fractions that are very different from those considered in our work. Indeed, an essential feature of the benchmark problem
 626 investigated by Mascheroni et al.^[24] is that, because of the spherical geometry of the tumour, and because of the nutrients being
 627 distributed homogeneously on the tumour's surface, the diffusion of the nutrients occurs isotropically, from the boundary to the

⁴Note that the values attributed to ω_{Ncr} Mascheroni et al.^[24] for all the considered studies are never referenced, the only exception being the growth of a tumour spheroid. In this case, however, the reference is a typographical error.

center of the spheroid, in radial direction. In our problem, instead, the nutrients can diffuse only along the axial direction of the tumour, and they have to travel the length L , which is much larger than the radius, of about $20 \mu\text{m}$, of the spheroids considered Mascheroni et al.^[24]. Due to these geometric and size aspects, if we used the values of ω_{Nenv} , ω_{Ncr} and ω_{N0} suggested Mascheroni et al., we would generate a situation in which the replenishment of the nutrients “eaten” by the cells would be too slow for the tumour to grow. Indeed, especially in the middle of the tumour, the nutrients’ mass fraction would go below the threshold value, ω_{Ncr} , after few hours. Therefore, to avoid a fast inhibition of growth, we have increased the value of ω_{Nenv} of three orders of magnitude in our experiment *in silico*. Note that there is a certain freedom in the choice of ω_{Nenv} , since prescribing its value amounts to preparing the bath of nutrients in which the tumour is immersed. This freedom notwithstanding, the value assigned to ω_{Nenv} should take into account the characteristic length of the tumour—in our case, L —in order to ensure that the effects of growth remain active over a sufficiently long time scale. In principle, ω_{Ncr} and ω_{N0} should be determined experimentally. Still, since we are not aware of any experimental value of ω_{Ncr} , we have calibrated it so that ω_{Ncr} be smaller than ω_{Nenv} , but big enough to allow for a transition from the stage of tumour growth, for $\omega_{\text{Ncr}} < \omega_{\text{N}} \leq \omega_{\text{Nenv}}$, to the stage of no growth, for $\omega_{\text{N}} \leq \omega_{\text{Ncr}} < \omega_{\text{Nenv}}$. This reasoning has led us to choose ω_{Ncr} three orders of magnitude greater than the value assigned Mascheroni et al.^[24]. Finally, the value given to ω_{N0} in our work (see Table 1) is two orders of magnitude greater than the one prescribed by Mascheroni et al.^[24]. This choice allows us to be consistent with the scale of the nutrients’ mass fraction imposed in our work.

6 | SOME COMPUTATIONAL ASPECTS

The system (65a)–(65h) features both ordinary differential equations (ODEs) in time, and partial differential equations (PDEs). All the ODEs of our model, including those obtained after that the finite element discretisation of the PDEs is performed, have been discretised adaptively in time, and have been solved by means of a four-step Backward Differentiation Formula (BDF4). This is an implicit linear multistep method, which generalises the implicit Euler method. Since the BDF4 is implicit, it requires in general the solution of nonlinear equations at each time integration step. The BDF4 is available in COMSOL Multiphysics[®], which has been used to run our simulations.

The PDEs have been put in weak form and solved by means of Finite Element techniques. In particular, classical methods have been used for (65b), (65d), and (65h), while a “special treatment” has been reserved to the momentum balance law (65a), for which the Hu-Washizu method^[76] has been employed.

Looking more closely at the PDEs (65b), (65d), and (65h), we notice that (65b) is a generalised Poisson equation in the pressure, p , with a time-dependent right-hand-side, \dot{J} , which represents the volume change of the solid phase due to the changes in porosity accompanying the flow of the fluid. Equation (65d), instead, is a nonlinear diffusion-advection-reaction equation in the mass fraction of the nutrients, ω_{N} , with the nonlinearity being nested in the reaction terms, R_{Np} and R_{Ns} . Both for (65b) and for (65d), the Finite Element Method leads to a set of ODEs in which the unknowns are the nodal pressures and the nodal mass fractions of the nutrients, respectively. Finally, Equation (65h) is an equation of Helmholtz type and, in this case, the Finite Element method yields a set of algebraic equations in the nodal values of e_{p} , which are anyway time-dependent. In the following, we do not fuss over the procedure for obtaining the set of nodal equations associated with (65b), (65d), and (65h), since such procedure is rather standard.

To sketch the formulation of the Hu-Washizu method, we add together the expressions of the stress tensors \mathbf{P}_{f} and \mathbf{P}_{s} , and we notice that the weak form of the momentum balance law (65a) admits the compact form

$$\int_{\mathcal{B}} (\mathbf{P}_{\text{f}} + \mathbf{P}_{\text{s}}) : \mathbf{g} \text{Grad } \mathbf{U}_{\text{s}} = \int_{\mathcal{B}} (-Jp \mathbf{g}^{-1} \mathbf{F}^{-\text{T}} + \mathbf{P}_{\text{sc}}) : \mathbf{g} \text{Grad } \mathbf{U}_{\text{s}} = 0, \quad (73)$$

where \mathbf{U}_{s} is the virtual velocity of the solid, expressed as a function of the points X of \mathcal{B} .

One of the main drawbacks of this formulation is that, once a Finite Element scheme is used for solving (73), the “limitations” of the interpolations adopted for χ ^[76], \mathbf{F} , and \mathbf{F}_{p} are transferred to \mathbf{P}_{sc} through its constitutive representation, $\mathbf{P}_{\text{sc}}(\mathbf{F}, \mathbf{F}_{\gamma}, \mathbf{F}_{\text{p}})$. This ill behaviour persists even increasing the order of the basis functions used for the discretisation of χ , and may lead to a remarkable deterioration of the resolution of \mathbf{P}_{sc} , with consequent loss of accuracy of the employed numerical method. A possible way to contain the occurrence of the just depicted numerical phenomenon is supplied by the Hu-Washizu method^[76], which we implement for our purposes in its three-field-formulation. Although the Hu-Washizu method is well known in the computational community, we briefly explain here how we adapt it to the case under investigation in this work.

673 Together with the motion, χ , which is an unknown of the model, we introduce two tensor-valued auxiliary variables, which
 674 we regard as additional independent fields of our model: these are an auxiliary “deformation gradient tensor”, \mathbf{F}^{HW} , and an
 675 auxiliary first Piola-Kirchhoff stress tensor, $\mathbf{P}_{\text{sc}}^{\text{HW}}$ (note that the superscript “HW” stands for “Hu-Washizu”). Although being
 676 independent, \mathbf{F}^{HW} and $\mathbf{P}_{\text{sc}}^{\text{HW}}$ must be consistent with the *true* deformation gradient tensor and with the *true* first Piola-Kirchhoff
 677 stress tensor, respectively, and are thus bound to satisfy the constraints

$$\mathbf{F}^{\text{HW}} = \mathbf{F}, \quad (74a)$$

$$\mathbf{P}_{\text{sc}}^{\text{HW}} = \mathcal{P}_{\text{sc}}(\mathbf{F}^{\text{HW}}, \mathbf{F}_\gamma, \mathbf{F}_p). \quad (74b)$$

678 To proceed with the Hu-Washizu method, we rephrase Equations (74a) and (74b) in weak form. Hence, we write

$$\int_{\mathcal{B}} \{ [\mathbf{F} - \mathbf{F}^{\text{HW}}] : \mathbf{\Pi} + [\mathcal{P}_{\text{sc}}(\mathbf{F}^{\text{HW}}, \mathbf{F}_\gamma, \mathbf{F}_p) - \mathbf{P}_{\text{sc}}^{\text{HW}}] : \mathbf{\Lambda} \} = 0, \quad (75)$$

679 where $\mathbf{\Pi}$ and $\mathbf{\Lambda}$ denote the virtual variations of $\mathbf{P}_{\text{sc}}^{\text{HW}}$ and \mathbf{F}^{HW} , respectively, and represent a virtual stress rate and a virtual
 680 velocity gradient. Equation (75) is now appended to (73), which has to be reformulated in terms of the Hu-Washizu auxiliary
 681 fields, thereby obtaining

$$\int_{\mathcal{B}} \{ [\mathbf{P}_{\text{sc}}^{\text{HW}} - (\det \mathbf{F}^{\text{HW}}) p \mathbf{g}^{-1} (\mathbf{F}^{\text{HW}})^{-\text{T}}] : \mathbf{g} \text{Grad } U_s + [\mathbf{F} - \mathbf{F}^{\text{HW}}] : \mathbf{\Pi} + [\mathcal{P}_{\text{sc}}(\mathbf{F}^{\text{HW}}, \mathbf{F}_\gamma, \mathbf{F}_p) - \mathbf{P}_{\text{sc}}^{\text{HW}}] : \mathbf{\Lambda} \} = 0. \quad (76)$$

682 After performing the interpolation of all the fields introduced so far, the algebraic form of (76) consists of a block system, in
 683 which one block corresponds to the balance of momentum, one block is associated with (74a), and one with (74b).

684 7 | RESULTS

685 To weigh the effects of the non-local theory of remodelling on the benchmark problem presented in Section 5.2, we perform
 686 two different simulations: one is done by excluding micro-plasticity, and is thus said to be “standard”; the other one, instead,
 687 accounts for micro-plasticity, and refers to the “non-standard” model.

688 The standard model (ST) is obtained by setting A_v , B_v , and Z_v equal to zero, so that Equation (65h) is always satisfied and
 689 the evolution law for ε_p only takes into account the first term of the right-hand-side of (65f), with $\mathbf{\Sigma}_v \equiv \mathbf{\Sigma}_v^{(\text{st})}$. In the non-standard
 690 model (NST), the parameters A_v , B_v , and Z_v are different from zero (see Table 2), and the full system of equations (65a)–(65h)
 691 has to be solved.

692 Since, to the best of our knowledge, no measurements for A_v , B_v , and Z_v are available in the scientific literature on soft
 693 tissues, we have chosen such parameters after several trials. For this reason, the values used to obtain Figures 2 –5 may be
 694 unrealistic for describing a true biological situation. Moreover, we remark that the convergence of the system (65a)–(65h) was
 695 achieved only for $Z_v \leq 1$ and $A_v > B_v$, whereas our computations never converged for $Z_v > 1$, regardless of the tested values
 696 of A_v and B_v . We also emphasise that, for the cases in which the model converged, the results of the simulations featured no
 697 remarkable difference.

698 To report the results of our model, we display the numerical solutions of the displacement, the growth parameter, γ , the mass
 699 fraction of the proliferating cells, ω_p , the pressure, p , and the axial component of the effective Cauchy stress tensor, σ_{eff}^{zz} . We plot
 700 all these quantities versus the axial coordinate of the specimen, and at the times $t = 10$ d and $t = 20$ d.

701 Figure 2 shows the displacement of the tumour (left panel) and the growth parameter, γ (right panel). Both quantities are
 702 computed only for the case of growth without “plasticity” (remodelling) (NP), i.e., for $\mathbf{F}_p = \mathbf{I}$, $\varepsilon_p = 0$, $e_p = 0$, and for the case
 703 in which “plasticity” (remodelling) is active. Moreover, “plasticity” is accounted for as prescribed by the non-standard model
 704 (NST). In fact, we could have also used the standard one (ST), but it would have led to imperceptible differences with respect to
 705 the non-standard model. As expected, both the displacement and the growth parameter increase as time goes by, but we observe
 706 a drastic reduction of their spatiotemporal evolution when remodelling is active. The results presented in Figure 2 confirm the
 707 ones obtained by Mascheroni et al.^[24] and Di Stefano et al.^[54], and have been re-computed with the purpose of highlighting the
 708 important role that remodelling may play on growth.

709 To further investigate the possible role of remodelling on growth and, in particular, the switch from the standard to the
 710 non-standard approach, we study the evolution of ω_p (Figure 3), p (Figure 4), and σ_{eff}^{zz} (Figure 5).

TABLE 1 Numerical values of the parameters used both for the standard and for the non-standard model.

Parameter	Unit	Value	Equation	Reference
L	[cm]	1.000	—	[54]
R_b	[cm]	$1.000 \cdot 10^{-2}$	—	[54]
k_{0R}	[mm ⁴ /(N s)]	0.4875	(67a)	[59]
m_0	[—]	0.0848	(67a)	[59]
m_1	[—]	4.6380	(67a)	[59]
d_{0R}	[m ² /s]	$3.200 \cdot 10^{-9}$	(67b)	[59]
σ_{th}	[Pa]	$1.000 \cdot 10^{-7}$	(58)	[32]
λ_p	[m s/kg]	$7.000 \cdot 10^{-7}$	(59)	[32]
λ	[Pa]	$1.333 \cdot 10^4$	(47)	[77]
μ	[Pa]	$1.999 \cdot 10^4$	(47)	[77]
ω_{Ncr}	[—]	$1.000 \cdot 10^{-3}$	(68a)	[54]
ω_{Nenv}	[—]	$7.000 \cdot 10^{-3}$	(68b)	[54]
ω_{N0}	[—]	$1.480 \cdot 10^{-4}$	(68e)	[54]
δ_1	[—]	$7.138 \cdot 10^{-1}$	(68b)	[78]
δ_2	[Pa]	$1.541 \cdot 10^3$	(68b)	[78]
ζ_{pn}	[kg/(m ³ s)]	$1.500 \cdot 10^{-3}$	(68a)	[79]
ζ_{fp}	[kg/(m ³ s)]	$1.343 \cdot 10^{-3}$	(68b)	[79]
ζ_{nf}	[kg/(m ³ s)]	$1.150 \cdot 10^{-5}$	(68d)	[79]
ζ_{Np}	[kg/(m ³ s)]	$3.000 \cdot 10^{-4}$	(68e)	[80]

Figure 3 displays, in the left panel, the progression of the mass fraction of the proliferating cells, ω_p , and, in the right panel, the absolute value of the difference between ω_p^{ST} and ω_p^{NST} , which denote the mass fractions of the proliferating cells computed with the standard model (ST) and the non-standard model (NST), respectively. In the left panel, we notice that, at time $t = 10$ d, the differences between ω_p^{ST} and ω_p^{NST} are irrelevant. However, at $t = 20$ d, a slight, yet appreciable, difference starts to appear. We visualise this difference in the right panel of Figure 3. Here, we notice that, due to the Dirichlet boundary condition imposed on ω_p at $Z = L/2$, such difference cannot be pronounced for values of the axial coordinate tending to $L/2$. On the other hand, $|\omega_p^{ST} - \omega_p^{NST}|$ becomes relatively more visible in the portion of the specimen in which growth is inhibited (see Figure 2 (right)). This is due to a limited availability of nutrients (data not shown).

In the left panel of Figure 4, we show the pressure, p , both for the ST model and for the NST one. For both models, the same behaviour is attained, i.e., the pressure drops from the tumour boundary towards its centre, where it takes negative values. In the right panel of Figure 4, we report the absolute value of the difference, at time $t = 20$ d, between p^{ST} and p^{NST} , i.e., the pressures computed with the ST model and the NST model, respectively. The differences between p^{ST} and p^{NST} are relatively small, but visible, in almost all of the half domain and at both times. They are clearly zero at the Dirichlet boundary $Z = L/2$ and, at $t = 20$ d, the maximum of $|p^{ST} - p^{NST}|$ is reached at a point between 0.4 cm and 0.5 cm.

Moreover, in Figure 5, the axial component of the constitutive part of the Cauchy stress tensor, σ_{sc}^{zz} , is shown. Indeed, due to the imposed boundary conditions and the symmetry restrictions of the considered problem, the balance of momentum (65a) amounts to requiring $-p + \sigma_{sc}^{zz} = 0$ everywhere in the specimen. Hence, it holds that $\sigma_{sc}^{zz} = p$. In addition, the axial component of the stress used to model the mechanotransduction, σ_{eff}^{zz} , is different from σ_{sc}^{zz} , as it features $\partial e_p / \partial Z$ (see Equation (70)). However, since this derivative is very small, it occurs that σ_{eff}^{zz} can be safely approximated with σ_{sc}^{zz} and, thus, with p .

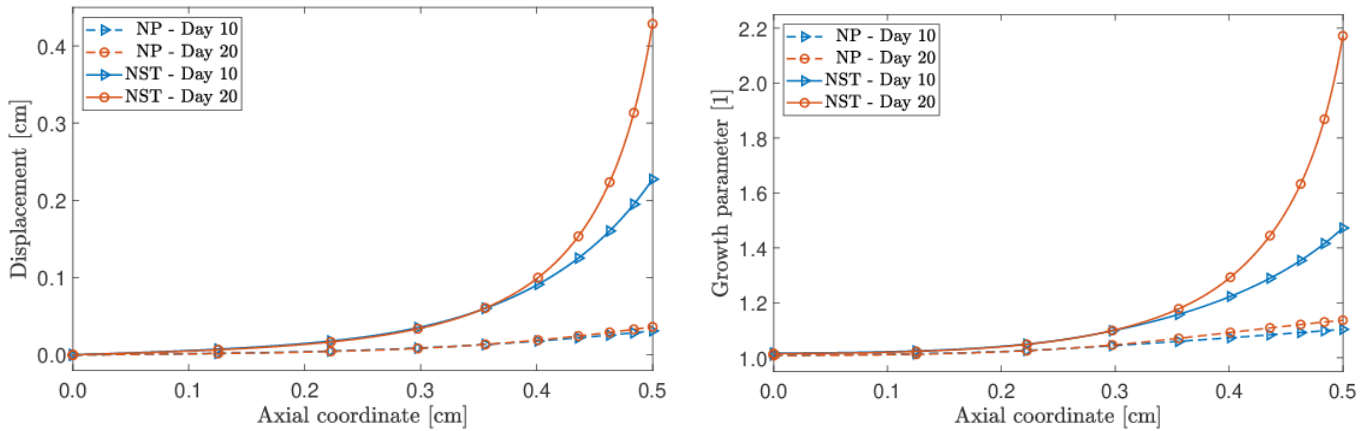
A last comment concerns the evolution of e_p and ε_p . As reported in Figure 6, both e_p and ε_p are increasing functions of time and space. If we focus on ε_p , we note that, as time goes by, the remodelling strains augment and accumulate in a neighbourhood of the boundaries of the specimen. This is highlighted by the fact that the slope of the curves corresponding to ε_p tends to raise when it approaches the edge. However, as predicted by the theory, e_p plays a smoothing role on the remodelling distortions and, in fact, it distributes itself more uniformly along the specimen. A relevant aspect of this result is that, while the curves corresponding to ε_p at $t = 10$ d and $t = 20$ d are almost coincident at the centre of the specimen, the curves determining e_p are distinguishable from one another.

TABLE 2 Numerical values of the parameters A_v , B_v and Z_v for the non-standard model.

Parameter	Unit	Value	Equation
A_v	[Pa]	$1.0 \cdot 10^{-9}$	(38c)
B_v	[Pa m ²]	$1.0 \cdot 10^{-14}$	(38d)
Z_v	[Pa]	$1.0 \cdot 10^{-2}$	(65f)

737

738

**FIGURE 2** *Left panel:* spatial profile of the displacement. *Right panel:* spatial profile of the growth parameter, γ . Since the problem is symmetric, in both panels only the half $[0, L/2]$ of the domain is shown.

739 8 | CONCLUSIONS

740 In this work, we study an idealised biological tissue that grows and remodels. As tissue we consider a tumour in avascular stage,
 741 and we assume that its remodelling —or structural reorganisation— occurs through a two-scale plasticity-like phenomenon.
 742 Following^[44], we distinguish a coarse and a fine scale, and we resolve this phenomenon, at the coarse scale, by means of the
 743 accumulated remodelling strain, ε_p , and, at the fine scale, by means of e_p . The latter is the representative of the so-called *micro-*
 744 “*plasticity*” and, being related to ε_p through a Helmholtz-like equation, it makes ε_p non-local^[44]. Within this framework, we
 745 have set ourselves the scope of evaluating if, how, and to what extent the micro-“*plasticity*” influences the growth of the tumour.
 746 In our approach, such influence can occur both directly and indirectly. The direct way is due to the fact that the *effective* Cauchy
 747 stress, σ_{eff} , modulates the source of mass R_{fp} , and thus also R_s , by giving rise to mechanotransduction. The indirect way, instead,
 748 manifests itself through the slight, and to a certain extent visible, changes that the non-local plastic-like distortions induce in
 749 some of the physical quantities that characterise the growth of the tumour, as reported in Section 7.

750 It is important to emphasise that the results shown in this work (see Figures 2 –5) are obtained for numerical values of the
 751 “non-standard” parameters A_v , B_v , and Z_v (see Table 2), which could be far beyond the physical range. Therefore, for the time
 752 being, our results aim at being a qualitative contribution to a unified strain-gradient theory of growth and remodelling. However,
 753 they are quantitative in evaluating the impact of the considered theory on growth.

754 We remark that, following an idea put forward by Epstein^[81], Di Stefano et al.^[54] proposed a model of strain-gradient growth,
 755 in which the evolution of γ is governed by a generalised diffusion-reaction equation. Such equation was obtained by accounting

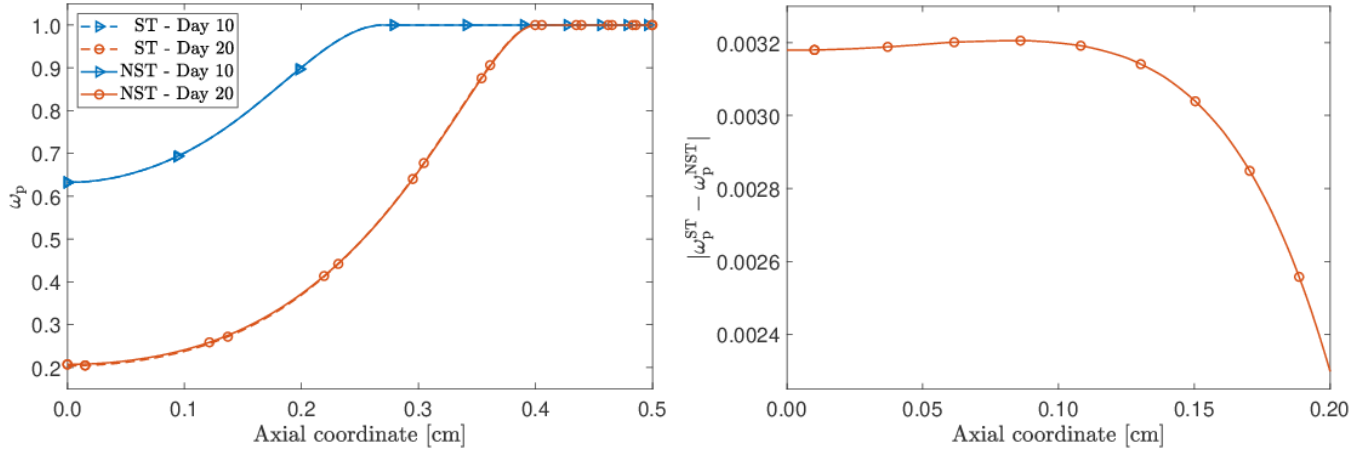


FIGURE 3 *Left panel:* spatial profile of the mass fraction of the proliferating cells, ω_p . Since the problem is symmetric, only the half $[0, L/2]$ of the domain is shown. *Right panel:* spatial profile of the absolute value of the difference between ω_p^{ST} and ω_p^{NST} , i.e., the mass fractions of the proliferating cells computed with the standard model (ST) and the non-standard model (NST), respectively. The picture refers to the portion of the half domain in which $|\omega_p^{ST} - \omega_p^{NST}|$ is greater than, approximately, $2.25 \cdot 10^{-3}$, and is computed at time $t = 20$ day.

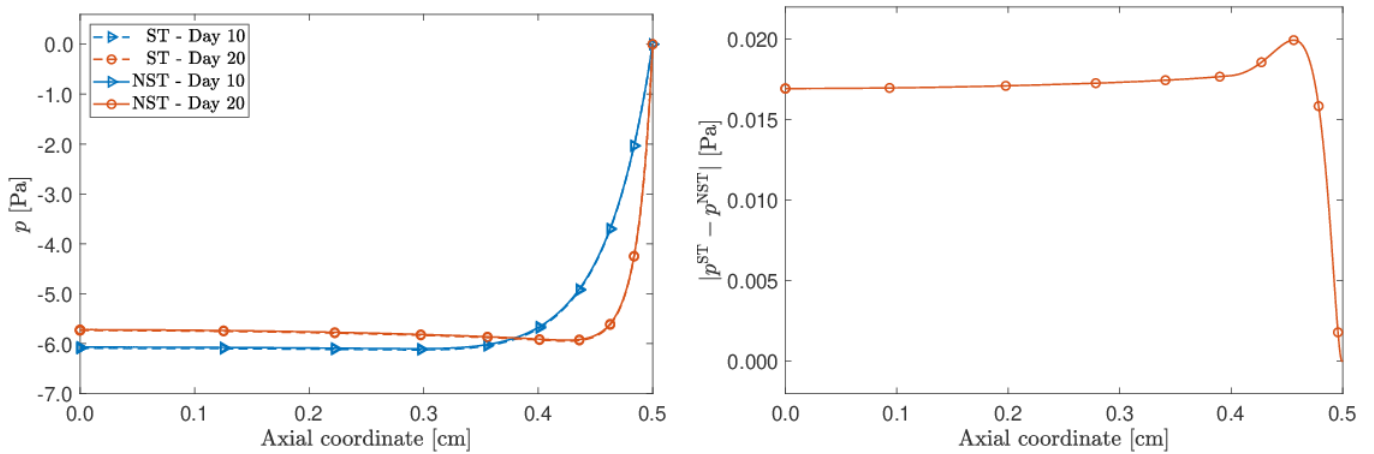


FIGURE 4 *Left panel:* spatial profile of the pressure, p . *Right panel:* spatial profile of the absolute value of the difference between p^{ST} and p^{NST} , which denote the pressure computed with the standard model (ST) and the pressure computed with the non-standard model (NST). The picture is computed at time $t = 20$ day. Since the problem is symmetric, in both panels only the half $[0, L/2]$ of the domain is shown.

756 for the growth-induced scalar curvature, κ_γ^5 , which features the spatial derivatives of γ up to the second order. However, in that
 757 that model we considered no remodelling. In the present work, instead, we have neglected the role of κ_γ , but we have focussed our
 758 attention on strain-gradient remodelling in order to quantify its effect on growth. The role of κ_γ in the current framework can
 759 be recovered by simply re-activating $r_{p\gamma}$ and $r_{n\gamma}$ in (2a) and (2b) (see Di Stefano et al.^[54] for the definition of these terms as
 760 functions of κ_γ).

761 Apart from the obvious fact that the topics under study necessitate further investigations from our side, two comments are
 762 in order: firstly, we have not hypothesised a strain-softening behaviour of the considered material, and no formation of shear

⁵The growth distortions, $F_\gamma = \gamma I$, induce the Riemannian metric tensor $C_\gamma = \gamma^2 G$, which yields Christoffel symbols that allow to determine a Levi-Civita connection with nontrivial fourth-order curvature tensor^[61,66] and, thus, with nontrivial associated Ricci curvature tensor, \mathfrak{R}_γ . Hence, it is possible to define the scalar curvature as $\kappa_\gamma := \mathfrak{R}_\gamma : C_\gamma^{-1}$ (see^[54] for details).

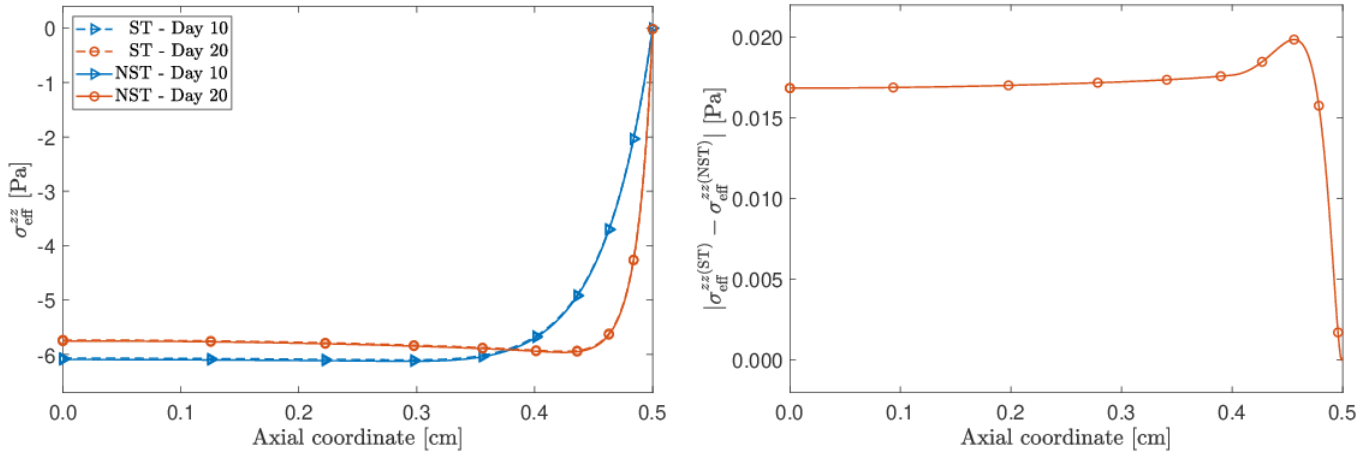


FIGURE 5 *Left panel:* spatial profile of the axial component of the effective Cauchy stress tensor, σ_{eff}^{zz} . *Right panel:* spatial profile of the absolute value of the difference between $\sigma_{\text{eff}}^{zz(\text{ST})}$ and $\sigma_{\text{eff}}^{zz(\text{NST})}$, which denote the stress computed with the standard model (ST) and the non-standard model (NST), respectively. The picture is computed at time $t = 20$ day. Since the problem is symmetric, in both panels only the half $[0, L/2]$ of the domain is shown.

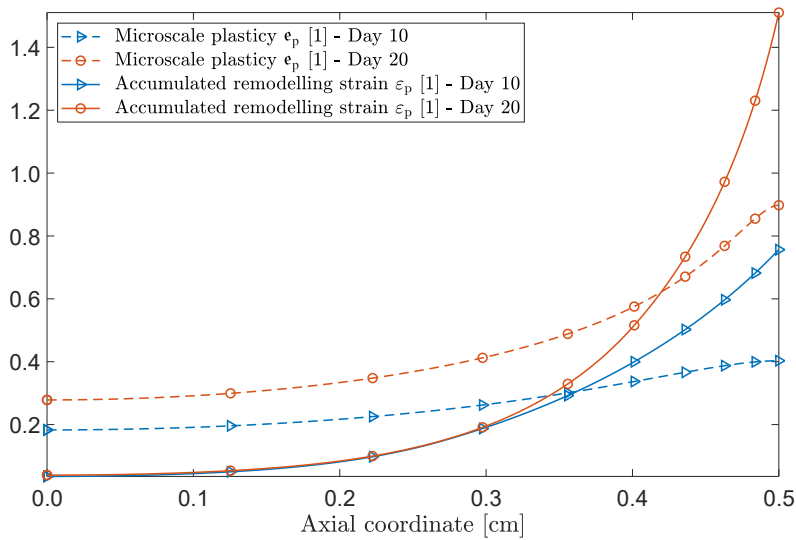


FIGURE 6 Spatial profiles of the accumulated remodelling strain ε_p and of the microscale plasticity e_p . Since the problem is symmetric, only the half $[0, L/2]$ of the domain is shown.

763 bands can be observed that justifies from the outset the use of a strain-gradient regularisation; secondly, the benchmark problem
 764 adopted in this work might be inappropriate, since it does not produce the desired/expected localisation of the accumulated
 765 plastic strain, ε_p , which calls for the employment of a strain-gradient theory. Nevertheless, our model is able to capture the
 766 regularising effect that the microscale descriptor e_p has on the accumulated remodelling distortions (cf. Figure 6).

767 It is known that the internal structural changes occurring in heterogeneous materials influence their overall macroscopic
 768 behaviour. For example, in bones, the change of orientation of the lamellae's collagen fibres modifies the bone's longitudinal
 769 effective Young's modulus^[82,83]. In the present work, we attempt to know how, and to what extent, the microscopic plastic-
 770 like (remodelling) effects are significant for the macroscopic evolution of the tissue. To the best of our knowledge, there are no
 771 experimental studies showing the influence of the microscopic plastic effects on the tissue behaviour. However, one can think of
 772 an experiment where, at some level, there can be a relatively strong localisation of the accumulated "plastic" strain, e_p , because
 773 of the presence of constraints (e.g. contact of the tissue with much stiffer materials). In this respect, we hope that our work

774 contributes to understand the interactions between growth and remodelling by merging the theories of multiphase materials
775 and of strain-gradient plasticity.

776 To the best of our understanding, another important difference between our work and previous publications (see e.g.^[39–41])
777 resides in the definition of the internal and external mechanical powers. Indeed, looking for instance at^[40], these powers feature
778 only the generalised velocities associated with the “classical” degrees of freedom of a body⁶, while the time derivatives of the
779 tensors associated with the body’s structural changes appear in the study of the dissipation inequality through the derivative of
780 the body’s Helmholtz free energy density. In our case, instead, following a philosophy outlined in other papers^[29,44,45,52,64], we
781 introduce the structural kinematic descriptors both constitutively, i.e., as arguments of the solid phase Helmholtz free energy
782 density, and in the formulation of the overall virtual powers of the problem, that is, jointly with the “classical” ones.

783 In our work, the tensor $\tilde{\Sigma}_v$ is entirely determined by mechanical quantities (cf. Equation (38a)) and this property is inherited
784 by its associated direction tensor, $\mathbf{N}_v = \tilde{\Sigma}_v / \|\tilde{\Sigma}_v\|_q$. Consequently, the hypothesis of co-directionality of $\tilde{\mathbf{D}}_p$ and $\tilde{\Sigma}_v$ implies that
785 the direction of the plastic flow is exclusively dictated by mechanical stress, the latter being augmented by the non-standard
786 contribution $\tilde{\Sigma}_v^{(n-st)}$. However, in more general situations, it is possible to define generalised Mandel stress tensors featuring bio-
787 chemical contributions, i.e., depending explicitly on the mass fraction of the nutrients (and on its gradient). In such cases, tensor
788 \mathbf{N}_v defines the direction of the plastic flow on the basis of chemo-mechanical guidance.

789 A last comment is on the design of an adequate benchmark problem. Indeed, when Anand et al.^[44] developed their theory,
790 they wrote that e_p “is introduced for the purpose of regularisation of numerical simulations of shear band formation under strain
791 softening conditions”. To achieve this objective, they called for the concept of micro-scale plasticity, and admitted a physics
792 described by ε_p , e_p , and Grade_p . Then, in order to determine these quantities, they established a thermodynamically consistent
793 framework, rather than simply improving the equations that were problematic from the numerical point of view. In our work,
794 we have extended such thermodynamic set-up to a growth problem, by admitting that its physical meaning goes beyond the
795 necessity of solving numerical issues. Nevertheless, we have seen only a very marginal impact of this modelling choice on our
796 results and we argue that it is of fundamental importance to design benchmark problems capable of capturing the physics behind
797 it. This is part of our ongoing research.

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804 Author contributions

805 All Authors have equally contributed to this work.

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810 Conflict of interest

811 The authors declare no potential conflict of interests.

⁶These are the body velocity, \mathbf{V} , the time derivative of the deformation gradient tensor, $\dot{\mathbf{F}}$, and the time derivative of the second gradient of the deformation, i.e., $\text{Grad}\dot{\mathbf{F}}$ ^[40].

SUPPORTING INFORMATION

None.

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