Published in final edited form as:

Biomech Model Mechanobiol. 2016 April ; 15(2): 259–278. doi:10.1007/s10237-015-0684-y.

A Mixture Approach to Investigate Interstitial Growth in Engineering Scaffolds

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Abstract

Controlling biological growth within a cell-laden polymeric scaffold is a critical challenge in the tissue engineering community. Indeed, construct growth must often be balanced with scaffold degradation and is often coupled to varying degrees of deformation that originate from swelling, external forces and the effects of confinement. These factors have been shown to affect growth in many ways, but to date, our understanding is mostly qualitative. While cell sensing, molecular transport and scaffold/tissue interactions are believed to be important players, it will be critical to quantify, predict and control these effects in order to eventually optimize tissue growth in the laboratory. The aim of this paper is thus to provide a theoretical framework, to better understand how the scaffold-mediated mechanisms of transport, deposition (and possibly degradation) and elasticity affect the overall growth of a tissue subjected to finite deformations. We propose a formulation in which the macroscopic evolutions in tissue size, density as well as the appearance of residual stresses can be directly related to changes in internal composition by considering three fundamental principles: mechanical equilibrium, chemical equilibrium and molecular incompressibility. The resulting model allows us to pay particular attention to features that are critical to the interaction between growth and deformation: osmotic pressure and swelling, the strain mismatch between old and newly deposited material as well as the mechano-sensitive cell-mediated production. We show that all of these phenomena may indeed strongly affect the overall growth of a construct under finite deformations.

1 Introduction

Biological growth is a well-controlled phenomenon that relies on both biological and physical mechanisms occurring simultaneously from the cellular scale (micron) to the macroscale. On the biological side, cell activity is driven by epigenetic mechanisms [9] which involve changes in both the physical and chemical nature of their environment. For instance, external loading affect the way a tissue changes its structure, density and shape [32]. On the physical side, the evolution of a tissue's composition and shape is eventually determined by transport, assembly and possible degradation of building blocks through a material "scaffold" that is subjected to finite deformation and possess everchanging chemical and mechanical properties [32]. An accurate and quantitative understanding of these phenomena is becoming increasingly critical in medicine and bio-engineering, particularly to guide and control the growth of engineered tissues in the laboratory [15, 19].

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In this context, the present paper introduces a formulation that aims at connecting the dynamics of interstitial tissue growth to the underlying mechanisms (synthesis, transport, deposition) that are dictated by scaffold design.

Mathematical models of growth date back to the early 1900s with the pioneering work of Darcy-Thomson [33] who emphasized the important role of mechanics in these biological processes. It was however not until the early 1980's that more accurate formulations based on continuum mechanics were introduced by Skalak et al. in [28], in which growth was described in terms of both volume and density changes inducing tissue deformation. A generalization of this concept was then provided by Rodriguez et al. [26] and later Klisch et al. [21, 20] in order to account for cases where growth is not necessary isotropic and can result from the presence of several constituents. These considerations have motivated the introduction of a so-called growth tensor, that is analogous to the classical deformation gradient tensor, and which characterizes the change in shape and volume of an elementary particle due to the addition of new material. Interestingly, this formulation can, via a multiplicative decomposition of an elastic and growth deformation, describe the appearance of residual stresses that result from the incompatibility of deformation between different constituents.

Beyond macroscopic models, recent efforts have focused on establishing a link between microscopic processes and the overall growth dynamics of tissues and constructs [2]. For instance, Treweek et al. [34] proposed a multispecies model of cell-mediated growth in cartilage constructs, pointing out the distinct roles of advection of diffusion fluxes at the microscopic level. A link between transport and mechanics can further be found in refined formulations based on the theory of mixture [18] and poro-elasticity [8], within which tissue are seen as a mixture of interacting solid and fluid phases. For the past decades, the literature has shown that such formulations, through their ability to couple mechanics, transport and chemical reactions within a single consistent framework [4, 3, 14] were ideal to investigate the homeostasis and growth of biological tissues at a fundamental level. The effect of small scale phenomena such as nutrients transport [31], cell division [5], the presence of charged constituents [4], cell-mediated tissue production, deposition, as well as degradation and turnover of older material. From a purely mechanical stand point, mixture theories, can also be used to investigate the appearance of residual stresses when distinct solid constituents experience different levels of elastic strains. In this context, Klisch et al. [20] considered a situation in which each phase is associated with its own growth tensor, enabling the investigation of the mechanical interactions between constituents and their overall effect on interstitial growth. Athesian further showed that such reactive mixtures could describe similar physics without the need to introduce a second order growth tensor [4].

Finite deformation are indeed inherent in tissue engineering [24] due to scaffold degradation [25], swelling [11] or the application of external loads. While the effect of large strain on growth can be partially explained by the fact that the deformation of soft porous media affect the diffusion (and further deposition) of matrix molecules [29], other mechanical factors, such as scaffold and tissue mechanics may also play an important role [7]. The aim of this paper is therefore to build on the existing mixture theories to better understand *how the coupled mechanisms of transport, deposition (and possibly degradation) and elasticity can*

affect the overall growth of a tissue construct subjected to finite deformations. We propose three key contributions. First, the model is based on thermodynamical principles that accounts for both the elastic deformation of solid constituents and their mixing with fluid phases. The later naturally enables the considerations of osmotic pressure and swelling, which could be particularly important in hydrogel-based tissue constructs [23, 41] and does not rely on the definition of a growth tensor for each solid specie. Second, it enables a natural coupling between the mechanical deformation of each phase and the overall permeability of the tissue. The elastic deformation of tissues and particularly their volumetric component, such as observed during swelling, has been shown to affect the transport of matrix molecules within the porous space [10, 11]. For instance, the swelling of a tissue engineering scaffold may help increase the effective pore size and accelerate growth by easing the diffusion of matrix molecules. Third and finally, when finite deformation occur during growth, the configuration at which new particle are deposited matters. We therefore introduce theoretical treatment in the same spirit as Valentin et al. [35] and Ateshian [6] within the concept of “multigenerational interstitial growth” that allows us to better understand the effect of various deposition assumptions on the growth process. We particularly show that this phenomenon can lead to non-negligible build-up of residual stresses within a growing tissue.

With this formulation, we propose to investigate the role of the mechanical properties of distinct solid constituents, their mechanical state at the time of deposition as well as the presence of osmotic pressure on the overall interstitial growth of a hydrogel-based tissue construct. This provides further motivations for the use of such mixture models to better understand and design tissue scaffolds for functional tissue growth. The manuscript is organized as follows. In the next section, we give a description of the kinematics and mass transfer within a growing multi-phasic material. In section 3, we develop the fundamental equations governing the dynamics of a material’s evolution, which include the coupled mechanical, transport and growth mechanisms. In section 4, we then use the new formulation to investigate the growth behavior of cartilage tissue within a hydrogel scaffold. We investigate a number of different growth assumptions and analyze their effects on the development of residual stresses, molecular transport and growth dynamics.

2 Kinematics of growth in engineering scaffolds

2.1 Continuum description of a growing multi-phasic medium

Let us consider the situation of a deformable body, originally contained in a closed domain Ω_0 delimited by a boundary Γ_0 , undergoing isotropic growth via the secretion, transport and deposition of extra-cellular matrix (ECM) molecules within an existing hydrated porous structure. Let us further assume that the characteristic length-scale of each constituent (cells, pore size) is infinitesimally small relative to the size of a tissue so that the latter can be viewed as a continuum, and more specifically, as a deformable (fluid-solid) multi-phasic medium. In Ω_0 , a material particle P (with position vector $\mathbf{X}$ in an appropriate Cartesian coordinate system) is assumed to be composed of n different fluid or solid phases, each characterized by their nominal concentration C_α , i.e., by the number of moles of α –

constituent per reference volume of mixture. One can alternatively use the nominal volume fraction, i.e. the volume of a constituent per reference volume, given as:

$$\Phi_{\alpha}(\mathbf{X}, t) = \nu_{\alpha} C_{\alpha}(\mathbf{X}, t) \quad (1)$$

where ν_{α} is the true molar volume of the constituent. For simplicity, we assume here that all constituents are made of incompressible matter, that is, the specific (molar) volume ν_{α} does not change over time, regardless of their solid or fluid state. Note that this concept is to be understood within the context of homogenized equivalent constituents which enables us to avoid complications associated with incompressible constituents in their natural state [18]. To characterize the physical state of the mixture, it is convenient to decompose these volume fractions into contributions from solid and fluid phases. Omitting the arguments $(\mathbf{X}, t)$ for

clarity, we write $\Phi^* = \sum_{\alpha=1}^n \Phi_{\alpha}^*$ and $\Phi^f = \sum_{\alpha=1}^n \Phi_{\alpha}^f$ where a superscript $*$ denotes the solid state while no superscripts are used for fluid phases. Assuming that the mixture is saturated, it can be shown that the nominal volume fractions must verify, at any time:

$$\sum_{\alpha=1}^n (\Phi_{\alpha}^* + \Phi_{\alpha}) = J. \quad (2)$$

where we introduced $J = V/V_0$ as the volumetric deformation of a material particle (V and V_0 being the current and initial infinitesimal volumes of a particle, respectively). From (2), it can be inferred that at the reference (or initial) time $t = 0$, the volumetric deformation

verifies $J = 1$ and we obtain $\sum_{\alpha=1}^n (\Phi_{\alpha}^*(\mathbf{X}, 0) + \Phi_{\alpha}(\mathbf{X}, 0)) = 1$.

2.2 Kinematics of deformation during growth

We now focus on characterizing the deformation of solid constituents. It is clear here that the notion of a physical particle is questionable since material is constantly added or deleted in time. Nevertheless, if growth is a continuous function of time, one can define such a point as long as the solid concentrations do not vanish at all times. Adopting a constrained mixture approach [18], the motion of all solid constituents is described by a unique continuous and differentiable function $\chi(\mathbf{X}, t)$ that maps the reference position vector $\mathbf{X}$ of a particle into its current configuration $\mathbf{x}$. The overall deformation of a point, relative to its reference state is thus represented by the deformation gradient:

$$\mathbf{F}(\mathbf{X}, t) = \partial \chi(\mathbf{X}, t) / \partial \mathbf{X} \quad (3)$$

Deformation in a growing body generally occurs due to the actions of several types of forces amongst which are (a) the existence of external loading which may exist regardless of the growth process, (b) the hydrostatic pressure caused by the interstitial fluid phases (for instance, osmotic pressure causes swelling) and (c) the presence of residual stresses that result from inhomogeneous growth. For a growing multi-phasic body, one can therefore conclude that different constituents occupying the same location can experience different

states of strain and therefore, that the deformation gradient (3) is not sufficient to fully capture the kinematics of growth. To enrich our description, let us consider a situation in which growth occurs via the deposition (or more precisely, conversion) of an active constituent on an underlying porous scaffold whose deformation changes in time (Fig. 1). In this context, we make three assumptions:

1. At the time of deposition, the underlying scaffold undergoes a deformation $\mathbf{F}(\mathbf{X}, \bar{t}) = \mathbf{R}(\mathbf{X}, \bar{t}) \mathbf{U}(\mathbf{X}, \bar{t})$ where $\mathbf{U}$ is the right stretch tensor and $\mathbf{R}$ is the orthogonal tensor representing the rotation of the material at time $\bar{t}$.
2. The active constituent (referred to by subscript α) is deposited with its own natural configuration, represented by a symmetric stretch tensor $\bar{\mathbf{U}}_\alpha$ at the time $\bar{t}$ of deposition. To ensure the compatibility of rotation between the underlying scaffold and the newly added particles, the natural configuration at deposition may be rewritten in terms of a full deformation gradient $\bar{\mathbf{F}}_\alpha$ such that:

$$\bar{\mathbf{F}}_\alpha(\mathbf{X}, \bar{t}) = \mathbf{R}(\mathbf{X}, \bar{t}) \bar{\mathbf{U}}_\alpha(\mathbf{X}, \bar{t}) \quad (4)$$

In other words, a natural stretch $\bar{\mathbf{U}}_\alpha$ is first applied to the new constituent in the unrotated bases $\mathbf{e}_j$ such that an infinitesimal $d\mathbf{X}$ on the particle is transformed into a vector $d\bar{\mathbf{X}}' = \bar{\mathbf{U}}_\alpha d\mathbf{X}$. The new particle is then rotated by the same amount $\mathbf{R}(\mathbf{X}, \bar{t})$ as that experienced by the underlying scaffold at the time of deposition to ensure compatibility between the two material units.

3. Once deposited, a solid constituent is fully connected to other solid phases, and thus follows the same motion.

In this case, the deformation gradient $\mathbf{F}_\alpha(t, \bar{t})$ (we omit here the argument $\mathbf{X}$ for clarity) of a constituent α deposited at time $\bar{t}$ and evaluated at subsequent time $t > \bar{t}$ can be written:

$$\mathbf{F}_\alpha(t, \bar{t}) = \mathbf{F}(t) [\mathbf{F}(\bar{t})]^{-1} \bar{\mathbf{F}}_\alpha(\bar{t}) = \mathbf{F}(t) [\mathbf{U}(\bar{t})]^{-1} \bar{\mathbf{U}}_\alpha(\bar{t}) \quad (5)$$

where the last equality was obtained with the help of (4). For instance, in the case of a constituent deposited in a stress-free configuration, it is reasonable to write $\bar{\mathbf{U}}_\alpha(\bar{t}) = \mathbf{I}$ and the deformation $\mathbf{F}_\alpha(t; \bar{t})$ changes as a function of its time of deposition. This idea is illustrated in a one-dimensional setting in Fig. 1 for which the deformation gradient is replaced by the stretch λ of a material line. In this example, a constituent, represented by an elastic spring, is deposited with a natural configuration characterized by $\bar{\lambda}$, at three discrete times (t_0, t_1, t_2) over an underlying scaffold that deforms in time. For clarity, the deposited material is shown at different locations, but belongs to the same material point. It can be seen that as the underlying material is stretched, the constituents deposited at earlier times experience more deformation than those deposited at later times. Equation (5) captures this idea for the general case of a continuous rate of deposition in multiple dimensions.

Rather than the deformation gradient, it is generally more convenient to work with the objective, rotation-independent right Green-Lagrange deformation tensor in the form:

$$\mathbf{E}_\alpha(t; \bar{t}) = \frac{1}{2} \left[(\mathbf{F}_\alpha(t; \bar{t}))^T \mathbf{F}_\alpha(t; \bar{t}) - \mathbf{I} \right] = \frac{1}{2} \left[\mathbf{H}_\alpha^T(\bar{t}) (\mathbf{F}^T \mathbf{F}) \mathbf{H}_\alpha(\bar{t}) - \mathbf{I} \right] \quad (6)$$

where we omitted the argument t whenever a function is solely a function of the current time ($\mathbf{F} = \mathbf{F}(t)$). Furthermore, using (5), one can show that the symmetric “growth history” tensor $\mathbf{H}_\alpha$ used in (6) can be introduced as:

$$\mathbf{H}_\alpha(\bar{t}) = [\mathbf{F}(\bar{t})]^{-1} \bar{\mathbf{F}}_\alpha(\bar{t}) = [\mathbf{U}(\bar{t})]^{-1} \bar{\mathbf{U}}_\alpha(\bar{t}). \quad (7)$$

Several comments can be made. First, one can see that the tensor $\mathbf{H}_\alpha$ is only a function of $\bar{t}$ and thus represents the past history of the material deformation at the time of deposition.

Second, when a constituent is deposited in a stress-free configuration (i.e., $\bar{\mathbf{U}}_\alpha(\bar{t}) = \mathbf{I}$) at the initial time (for which $\mathbf{U}(0) = \mathbf{I}$), the growth history tensor becomes unity. In this case, its deformation is measured by the conventional Green-Lagrange tensor:

$$\mathbf{E}_\alpha(t, 0) = \mathbf{E}(t). \quad (8)$$

In other words, when no growth occurs over time ($t > 0$), the kinematics of deformation degenerates to conventional theories.

2.3 Mass balance and growth law

To keep track of mass fluxes within a growing body, one first needs to introduce the velocity of each constituent in the form $\mathbf{v}_\alpha = \mathbf{x}_\alpha / t$ where $\mathbf{x}_\alpha$ is the current coordinate of a particle α . In deformable porous media, it is often more convenient to track the transport of fluid phases with their velocity $\tilde{\mathbf{v}}_\alpha = \mathbf{v}_\alpha - \mathbf{v}^*$ relative to the solid velocity $\mathbf{v}^*$, or alternatively, by the relative molar fluxes $\mathbf{q}_\alpha = c_\alpha \tilde{\mathbf{v}}_\alpha$ in which $c_\alpha = C_\alpha / J$ is the current concentration of phase α . These definitions ensure that both $\tilde{\mathbf{v}}_\alpha$ and $\mathbf{q}_\alpha$ vanish when fluid and solid constituents follow the same motion. Finally, within the context of finite deformations, it is preferable to express these fluxes per cross-sectional area of material in its underformed configuration. Such nominal fluxes are related to the current fluxes by:

$$\mathbf{Q}_\alpha = J \mathbf{F}^{-1} \cdot \mathbf{q}_\alpha \quad (9)$$

In this work, the process of growth (depletion) is then defined as *the increase (decrease) in either volume or mass density of the solid constituents within the mixture*. This means that any fluid phase that do not convert into solid, can be thought of as an “inactive” constituent. For instance, water can induce volumetric deformation during swelling but it is not directly involved in the growth by converting into a solid phase. In contrast, constituents such as collagen and proteoglycans actively participate to the growth process by depositing and

becoming part of the solid phases over time. In the model, we therefore distinguish constituents in relation to their active (1 α m) and inactive (m α n) contributions to growth. The change in composition of an active constituent α thus arises from two main mechanisms: (a) the production rate P_α in its free (or fluid) state and (b) its conversion into solid with rate Γ_α , where it is clear that rate constants are measured in units of moles per time per reference volume. From the knowledge of these two quantities, it is straightforward to write the mass conservation in a reference elementary volume and obtain the following two equations:

$$\frac{DC_\alpha}{Dt} + \nabla \mathbf{x} \cdot \mathbf{Q}_\alpha = P_\alpha - \Gamma_\alpha \quad (10)$$

for fluid species, and

$$\frac{DC_\alpha^*}{Dt} = \Gamma_\alpha \quad (11)$$

for solid species. We have also introduced $\nabla_{\mathbf{x}}$ as the gradient operator in the reference configuration and $D/Dt = D^*/Dt$ as the material time derivative relative to solid phases. The above equations show that the knowledge of the production and conversion functions are enough to characterize the change in nominal concentrations of each phase of a growing body, and subsequently to deduce its change of mass. We therefore denote the knowledge of P_α and Γ_α as the “growth law” for which a specific example is given in section 3. Note that $P_\alpha = \Gamma_\alpha = 0$ for inactive constituents (m α n).

3 Mechanical equilibrium and transport

3.1 Elastic and mixing energies in a soft multi-phasic body

In the present framework, we concentrate on material systems that satisfy two assumptions. First, the interactions between fluid and solid constituents occurs through mixing and possible physical interactions (such as hydrophilic/hydrophobic forces). The effect of other types of interactions, including electrostatic forces in charged tissues [30] are not considered for the sake of clarity. Second, the mechanical behavior of the growing tissue (i.e., the solid phase) remains exclusively in the elastic range. Other, more complex behaviors, such as visco-elasticity or plasticity may be incorporated at later stages of the model development. In these conditions and following [17], it is possible to explicitly write the free energy of a unit reference volume of materials in terms of two contributions as:

$$\Delta G = \Delta G^{el} + \Delta G^{mix}. \quad (12)$$

Here, the first term arises from the elastic energy stored in the solid phases while the second term contains both an entropic term resulting from the mixing of fluid and solid constituents as well as from possible enthalpic interactions amongst constituents. In the following, we

discuss the specific form of each term and their relation to the physical state of the mixture (volume fractions and deformations).

Elastic energy—The elastic energy stored in a multi-phasic mixture arises from the respective deformation of all its phases, both fluid and solid. However, considering that fluid phases are incompressible and inelastic, their elastic energies may be neglected. Following the theory of mixtures, it is then convenient to additively decompose the energy G^{el} according to the contribution of each individual solid constituent as:

$$\Delta G^{\text{el}} = \sum_{\alpha=1}^n \Delta G_{\alpha}^{\text{el}} \quad (13)$$

where $\Delta G_{\alpha}^{\text{el}}$ is the elastic energy stored in solid constituent α per reference volume of mixture. As discussed above, a single solid constituent may possess an infinite number of natural configurations depending on the history of its deposition and the overall deformation $\mathbf{F}$. To evaluate $\Delta G_{\alpha}^{\text{el}}$, it is therefore appropriate to first express the infinitesimal elastic energy $\delta \Delta G_{\alpha}^{\text{el}}$ that is associated with the small fraction $\delta \Phi_{\alpha}^*(\bar{t})$ of material deposited at time $\bar{t}$ as follows:

$$\delta \Delta G_{\alpha}^{\text{el}} = \delta \Phi_{\alpha}^*(\bar{t}) \psi_{\alpha}(\mathbf{E}_{\alpha}(t; \bar{t})). \quad (14)$$

Here, we introduced the elastic potential ψ_{α} that characterizes the energy stored in a unit volume of solid constituent α if it was to be tested independently from the surrounding mixture. Using (1), one can show that $\delta \Phi_{\alpha}^* = \nu_{\alpha} \Gamma_{\alpha} \delta \bar{t}$ where $\delta \bar{t}$ is an infinitesimal time increment around the deposition time. Now integrating the contributions of the material deposited at all times, the partial elastic energy $\Delta G_{\alpha}^{\text{el}}$ can be expressed in terms of the following time integral:

$$\Delta G_{\alpha}^{\text{el}} = \Phi_{\alpha}^*(0) \psi_{\alpha}(\mathbf{E}) + \int_0^t \{ \nu_{\alpha} \Gamma_{\alpha}(\bar{t}) \psi_{\alpha}(\mathbf{E}_{\alpha}(t; \bar{t})) \} dt^*. \quad (15)$$

Note that the first term on the right hand side was found by invoking (8) and represents the contribution of the material that is present at the initial time ($t=0$). We also wish to point out that the argument $\mathbf{E}_{\alpha}$ indirectly depends on the total strain $\mathbf{E}$ through relation (6).

Mixing energy—In contrast to elastic contributions, the mixing energy mainly concerns fluid constituents as they are driven by thermal fluctuations. By essence, this energy is independent of elastic deformation and we can generally write:

$$\Delta G^{\text{mix}} = \Delta G^{\text{mix}}(C_{\alpha}) \quad \alpha=1, \dots, n \quad (16)$$

where we recall that C_{α} is the nominal concentration of constituent α in its fluid state.

Total energy with incompressibility constraint—In general, a solution to the growth problem may be found by minimizing the total energy (12) of the system at any time, while ensuring the saturation condition stated in (2). To satisfy both conditions within a simplified framework, we choose to use the Lagrange multiplier method that consists of modifying the total energy of the system by adding constraint (2) to the total energy as follows:

$$\Delta \hat{G} = \Delta G - p \left(J - \sum_{\alpha=1}^n (\Phi_{\alpha}^* + \Phi_{\alpha}) \right). \quad (17)$$

We introduced here the Lagrange multiplier p as the energy conjugate to the incompressibility conditions. This quantity may therefore be interpreted as the energy penalty that results from adding solid or fluid constituents in the system and is generally denoted as the hydrostatic pressure. As a summary, the modified energy functional is written:

$$\Delta \hat{G}(\mathbf{E}, C_{\alpha}) = \sum_{\alpha} \Phi_{\alpha}^*(0) \psi_{\alpha}(\mathbf{E}) + \sum_{\alpha} \left(\int_0^t \nu^{\alpha} \Gamma_a(\bar{t}) \psi_{\alpha}(\mathbf{E}_{\alpha}^e(t; \bar{t})) d\bar{t} \right) + \Delta G^{\text{mix}}(C_{\alpha}) - p \left(J - \sum_{\alpha=1}^n \nu_{\alpha} (C_{\alpha}^* + C_{\alpha}) \right) \quad (18)$$

where $J = \det(\mathbf{F})$. We can see here that although the elastic and mixing energies are only functions of the deformation and concentration, respectively, they are coupled through the incompressibility conditions. This ensures that changes of concentration properly induce the changes in volumetric deformations.

3.2 Stress and force balance in solid species

Let us now express the balance of linear momentum in our growing multi-phasic mixture. For this, it should first be noted that phenomena of growth, swelling and degradation occur over relatively long time scales such that inertial effects are negligible. In this context, one can assume quasi-static conditions, which implies that the balance of momentum can be expressed in terms of the nominal stress $\mathbf{P}$ as [14]:

$$\nabla_{\mathbf{x}} \cdot \mathbf{P} = \mathbf{b} \quad \text{where} \quad \mathbf{P} = \frac{\partial \Delta \hat{G}}{\partial \mathbf{F}} \Big|_t \quad (19)$$

and $\mathbf{b}$ is a vector that characterizes a body force per unit reference volume. Because of the non-symmetry of the nominal stress, it is often more convenient to work with the second Piola-Kirchhoff stress $\mathbf{S} = \mathbf{F}^{-1} \mathbf{P}$, that can equivalently be expressed in terms of the energy functional $\hat{G}$ as:

$$\mathbf{S}(t) = \frac{\partial \Delta \hat{G}}{\partial \mathbf{E}} \Big|_t = \sum_{\alpha=1}^n \mathbf{S}_{\alpha}(\mathbf{E}_{\alpha}, t) - pJ\mathbf{C}^{-1} \quad (20)$$

where $\mathbf{C} = \mathbf{F}^T \mathbf{F}$. We note here that the last equality was obtained by substituting the explicit form (12) of the energy functional and defining the partial solid stresses $\mathbf{S}_{\alpha}$ as:

$$\mathbf{S}_{\alpha} = \Phi_{\alpha}^{*}(0) \zeta_{\alpha}(t, 0) + \int_0^t \nu_{\alpha} \Gamma_{\alpha}(\bar{t}) \zeta_{\alpha}(t, \bar{t}) d\bar{t} \quad (21)$$

in which we defined the symmetric tensor $\zeta_{\alpha}(t, \bar{t})$ as the partial stress in the solid constituent α that was deposited at time $\bar{t}$. It reads:

$$\zeta_{\alpha}(t, \bar{t}) = \mathbf{H}_{\alpha}(\bar{t}) \left(\frac{\partial \psi_{\alpha}}{\partial \mathbf{E}_{\alpha}}(t, \bar{t}) \right) \mathbf{H}_{\alpha}^T(\bar{t}). \quad (22)$$

A few remarks can be made on the above stress decomposition. First, (20) shows that the stress in the mixture does not only arise from the presence of solid and elastic components, but also from the pressure p of the interstitial fluid constituents. We note here that osmotic pressure does not follow the same convention as other stress components: a positive pressure p may be interpreted as a state of compression within the fluid. Second, it can be seen in (21) that the partial stress $\mathbf{S}_{\alpha}$ arises from (a) the presence of the original material at the initial time (whose quantity is $\Phi_{\alpha}(0)$) and (b) the accumulation of new material deposited over time at rate Γ_{α} . Indeed, realizing that $\zeta_{\alpha}(t, 0) = \psi_{\alpha}/\mathbf{E}$, it can be appreciated that the first component in (21) is completely independent of the deposition history. On the other hand, the second is clearly dependent on the growth history due to the presence of the tensor $\mathbf{H}_{\alpha}$ in (22). It is finally important to note that in the absence of growth ($\Gamma_{\alpha} = 0 \forall \alpha = 1, m$) the integral in (21) vanishes and we recover the classical definition of the Second Piola-Kirchhoff stress. Finally, noting that the Cauchy stress is related to the first Piola-Kirchhoff stress by $\mathbf{T} = J^{-1} \mathbf{F} \mathbf{S} \mathbf{F}^T$, (20) can be rewritten in the current configuration as:

$$\mathbf{T} = \sum_{\alpha} \mathbf{T}_{\alpha} - p\mathbf{I} \quad \text{where} \quad \mathbf{T}_{\alpha} = \frac{1}{J} \mathbf{F} \mathbf{S}_{\alpha} \mathbf{F}^T$$

which is consistent with the classical stress decomposition in poromechanics [8].

3.3 Transport of fluid species

When transport is considered, one needs to establish a relation between the flux $\mathbf{q}_{\alpha}$ and its associated driving force $\zeta^{\alpha} = \nabla \mu_{\alpha}$ caused by a gradient in chemical potential $\mu_{\alpha} = \hat{G}/\Phi_{\alpha}$ [36, 37]. The fluid velocity can then be expressed in terms of the solid permeability κ and fluid viscosity η as:

$$\mathbf{q}_w(\mathbf{X}, t) = -\frac{\kappa}{\nu_w \eta} \nabla \mu_w \quad (23)$$

This expression is a generalization of Darcy's law for the transport of a solution (solute/solvent) in porous media. The transport of phase α is then governed by a diffusion term, related to the gradient of its chemical potential and a convection term governed by solvent velocity as:

$$\mathbf{q}_\alpha(\mathbf{X}, t) = c_\alpha \left(\tilde{\mathbf{v}}_w - \frac{\nu_\alpha D_\alpha}{RT} \nabla \mu_\alpha \right) \quad (24)$$

where $D_\alpha > 0$ is the diffusivity of specie α . During growth and remodeling, this parameter can be affected by many factors, including strain, the deposition of new material or degradation. This relationship enters the constitutive equations discussed in section 4. By making the proper pull-back transformations, and using equation (9), the above expressions can be written in the undeformed configuration as:

$$\mathbf{Q}_w = -\frac{\kappa}{\nu_w \eta} \nabla_{\mathbf{x}} (\mu_w) \quad (25)$$

$$\mathbf{Q}_\alpha = C_\alpha \tilde{\mathbf{V}}_w - \frac{\nu_\alpha c_\alpha}{RT} \bar{\mathbf{D}}_\alpha \nabla_{\mathbf{x}} (\mu_\alpha) \quad (26)$$

where $\nabla_{\mathbf{x}}$ is the gradient operator in the undeformed configuration, $\bar{\kappa} = J \mathbf{F}^{-1} \kappa \mathbf{F}^{-T}$ and $\bar{\mathbf{D}}_\alpha = J \mathbf{F}^{-1} D_\alpha \mathbf{F}^{-T}$ are the pullback permeability and diffusivity tensors, respectively and $\tilde{\mathbf{V}}_w = \mathbf{F}^{-1} \tilde{\mathbf{v}}_w$ is the pull-back velocity vector of the water-constituent.

4 Constitutive relations

In this section, we highlight the different components of the constitutive relations that are necessary to fully describe the growth of an elastic body within the context of the proposed formulation. For clarity, we decompose these relations into three main components: (a) the definition of the mixing and elastic potential to describe the mechanical behavior of the mixture, (b) the definition of the production, transport and deposition of new material and (c) the definition of the natural configuration at which the new material deposits within the growing body. To illustrate these relations and without loss of generality, we choose to concentrate on a particular system that consists of the growth of a tissue into a pre-existing hydrogel scaffold made of a mixture of cross-linked polymer and water. Three main phases must therefore be considered (Fig. 2): (a) the polymer network (solid), denoted by subscript p , (b) the growing matrix (in its free and solid state), denoted by subscript m and (c) the

interstitial water (fluid), denoted by subscript w . Note that in this example, only the matrix constituent is an active contributor to growth.

4.1 Mixing energy

The free energy of mixing of a fluid-polymer mixture can usually be decomposed into two terms, the enthalpy of mixing H^{mix} and the entropy of mixing S^{mix} such that $G^{mix} = H^{mix} - T S^{mix}$, T being the absolute temperature. The entropy of mixing can be determined by quantifying the number of physical states each species can take in a lattice model [11], leading to the conventional expression:

$$\Delta S^{mix} = -k_B \sum_{\alpha} C_{\alpha} \ln \phi_{\alpha} \quad (27)$$

where k_B is the Boltzmann constant and $\phi_{\alpha} = \Phi_{\alpha}/J$ is the volume fraction of constituent α . The enthalpy of mixing then accounts for physical interactions between fluid and solid phases. Considering prevalent interactions between solvent (water) and the scaffold polymer, it can be shown that [11]:

$$\Delta H^{mix} = k_B T \chi C^f \phi^* \quad (28)$$

where χ is the binary (polymer-fluid interaction) Flory-Huggins parameter and we recall that ϕ^* is the current volume fraction of all solid phases. A positive value of χ implies that polymer-polymer and solvent-solvent contacts are more energetically favorable than polymer-solvent contacts. The final form of the mixing energy, expressed by reference volume of mixture, is thus:

$$\Delta G_{mix} = RT (C_w \ln(\phi_w) + C_m \ln(\phi_m) + \chi C_w (1 - \phi_w)) \quad (29)$$

where $R = N_A k_B$ is the gas constant (N_A is the Avogadro constant). We also note that due to their restricted motion, we neglected the entropy of the solid phases compared to that of fluid constituents.

4.2 Matrix production, transport and deposition

From a microscale perspective, biological growth originates from the synthesis, transport and linkage of molecular units from the membrane of cells to the final site of deposition. For clarity, we here model these processes from a macroscopic viewpoint in which cell-mediated production is modeled by a continuous mass source $P_{\alpha}(\mathbf{X}, t)$ within the existing scaffold. If microscopic growth is of interest, however, the presented models can be adapted accordingly as can be seen in section 5.2 of this paper. The form of the source term depends on two fundamental micro-mechanisms as shown in Fig. 3 and studied in details in previous studies including [27] and [10] for instance. The first mechanism relates to the capacity of cells to produce molecular building blocks at their membrane while the second depends on the ability of these molecules to diffuse into the surrounding tissue. Indeed, if the matrix is

totally impermeable to these building blocks, no growth can occur. The overall rate of tissue production (introduced in (10)) of unattached (or free) matrix molecules ($\alpha = m$ here) is therefore decomposed into two terms (a) the synthesis of these molecules at the level of the cells' membrane, denoted by the function $S_\alpha(t)$ and (b) the ability of these molecules to diffuse through the existing porous material, characterized here by the function $D_\alpha(t)$. Since these two processes occur in series, it is reasonable to assume a multiplicative decomposition in the form:

$$P_\alpha(t) = S_\alpha(t) D_\alpha(t). \quad (30)$$

Cell-mediated Matrix production—Modeling cell-mediated matrix synthesis involves a deep knowledge of cell mechano-biology and sensing, which is beyond the scope of this paper. However, from a physical viewpoint, it is reasonable to assume that matrix production is driven by the capacity of cells to overcome the resistance of the surrounding medium to the addition of new finite-sized molecular units. This resisting force is measured by the change of free energy of the system when a cell produces one mole of free matrix molecules, or, in other words, by the osmotic pressure p . A first-order model of matrix synthesis may therefore be cast in the form:

$$S_\alpha(\pi) = d^c S_\alpha^0 \beta \left(1 - \frac{\pi}{\pi_c}\right) \quad (31)$$

where $\beta = 1$ if $\pi \leq \pi_c$ and $\beta = 0$ if $\pi > \pi_c$. Here the parameter d^c represents the cell density (i.e., the number of cells per initial volume) and S_α^0 denotes the average production of a single cell in an unconstrained medium (the osmotic pressure vanishes). Finally, the quantity π_c represents a threshold value of the osmotic pressure at which matrix production totally ceases. A linear relationship is assumed in-between these two extreme cases. While this assumption is based on a physical, rather than biological basis, it can readily be improved to yield a more realistic behavior such as presented by Haider et al. in [16].

Transport—In contrast to production, the phenomenon of matrix transport is directly related to the physical state of the surrounding medium, and more specifically its permeability. For a low permeability, transport is totally hindered while the opposite holds for high permeability. Without losing generality, permeability can be related to the porosity $\phi_f = \Phi_f/J$ of the mixture [22], the radius of gyration r_s of the diffusing molecule as well as the characteristic pore size χ [29]:

$$D_\beta = D_\beta(\phi_f, r_s/\chi). \quad (32)$$

For instance, for a fibrous network, Nabovati et al. [22] have shown a non-linear relationship between permeability and porosity in the form:

$$D_{\alpha}(\phi_f) = \alpha \left(\sqrt{\frac{1 - \phi_f^c}{1 - \phi_f}} - 1 \right)^b \quad (33)$$

where ϕ_f^c is a critical value at which the network becomes totally impermeable ($D_{\alpha} = 0$). For a random fibrous network, the parameters a and b have been estimated to be 0.491 and 2.31, respectively, using numerical simulations. We note here that this model describes the permeability of a network for infinitely small fluid particles and may change when the pore size becomes comparable to the size of the free matrix molecules. In this case, a correction to this function should be made in terms of the ratio r_a/χ where r_a and χ are the sizes of the molecules and the pores, respectively. Readers are referred to [29, 11] for a more detailed explanation of such a correction.

Deposition—The deposition of free macro-molecules onto an existing scaffold as well as their increasing participations to the elastic properties of the new tissue are the result of complex bio-chemical processes [1]. The rate of deposition Γ_{α} may therefore be a function of variables such as concentrations, stress, strain or osmotic pressure. As such processes are beyond the scope of the current work, we propose here a simplistic model based on first order kinetics reaction. More specifically, we assume that deposition can be approximated as a conversion process of a fluid solution with concentration c_{α} into a solid medium with concentration c_{α}^* . Introducing k_{α}^f and k_{α}^d as the rate of conversion and dissociation, respectively, we write the rate of deposition originally introduced in (10) and (11) as:

$$\Gamma_{\alpha} = k_{\alpha}^f c_{\alpha} - k_{\alpha}^d c_{\alpha}^*. \quad (34)$$

We note here that the concentration are expressed per units of current volume, and are thus related to nominal concentrations by $c_{\alpha} = C_{\alpha}/J$.

4.3 Material's configuration at deposition

An important aspect of the constitutive relation is the assumption regarding the configuration α at which new material is deposited (see equation (4)). Realistic models should be such that this deformation is independent of the current state of deformation $\mathbf{F}$ of the surrounding material, since it is unlikely that free molecules can sense this state and adjust their deformation accordingly as they deposit. Assuming here an isotropic deposition, the deformation gradient can be represented as a diagonal tensor of the form $\bar{\mathbf{U}}_{\alpha} = \text{diag}(\bar{J}_{\alpha}^{1/3})$ where $\bar{J}_{\alpha}$ is the Jacobian of the deformation. We can then consider several situations:

$$\begin{aligned} \bar{J}_{\alpha} < 1 & \quad \text{Deposition in a compressive state} \\ \bar{J}_{\alpha} = 1 & \quad \text{Stress- free deposition} \\ \bar{J}_{\alpha} > 1 & \quad \text{Deposition in a tensile state.} \end{aligned} \quad (35)$$

In all of these cases, it is clear that the natural configuration of deposited material depends on its time t^* of deposition. It is however interesting to investigate two special cases for which it does not hold.

The case of degradation—Material's growth and degradation may be seen as complementary processes wherein the first arise from the deposition of new material while the second occurs through the loss of existing material. In other words, when growth of a material phase occurs, Γ_α is positive while when degradation occurs, Γ_α becomes negative. Although these processes may at first seem very similar, there are some fundamental differences from a mechanical perspective. Let us first investigate the case of degradation and for this, consider a material phase α undergoing an elastic deformation $\mathbf{F}_\alpha = \mathbf{F}$. Let us further consider that a fraction of this material dissolves at time $\bar{t}$ and write its state of deformation at the time of dissolution as:

$$\bar{\mathbf{F}}_\alpha(\bar{t}) = \mathbf{F}(\bar{t}) \quad \forall \bar{t}. \quad (36)$$

In this case, one can show from (7) that $\mathbf{H}_\alpha(\bar{t}) = \mathbf{I}$ and that the Green-Lagrange strain tensor is independent of previous times $\bar{t}$, that is, $\mathbf{E}_\alpha(t; \bar{t}) = \mathbf{E}(t)$. The stress can then be computed from (21) as:

$$\mathbf{S}_\alpha = \Phi_\alpha^* \zeta_\alpha = \Phi_\alpha^* \frac{\partial \psi_\alpha}{\partial \mathbf{E}}. \quad (37)$$

Mechanically, the constituent therefore responds like a conventional Cauchy continuum and its degradation is only felt via the decrease of the nominal volume fraction Φ_α^* .

Link to existing growth models—Here, we aim to provide a link between existing growth models derived in the literature and the proposed formulation. We specifically concentrate on the model of Klisch and al. [20] for cartilage explants, in which growing constituents deposit in a way to keep their mass density (or nominal concentrations) constant and equal to that of the material in its natural state (or natural concentration) as depicted in Fig. 4. Within the context of this work, this situation is modeled as follows. First of all, we need to assume that the new constituent, at any stage of growth, is deposited in the reference (or undeformed) material configuration ($J(\bar{t}) = 1$). In this condition, the history function becomes:

$$H_\alpha = \bar{J}_\alpha / J(\bar{t}) = \bar{J}_\alpha. \quad (38)$$

Once again, it is interesting to see that in this case, the function H_α becomes independent of the deposition time t^* . Note that while questionable in the context of growth, this assumption is similar to the case of degradation studied above. Assumptions for the natural configuration of the new constituent during deposition are then dictated by the following rules.

- In the case where the nominal solid concentration C_α^* of the new constituent is lower than its natural density C_α^n , deposition occurs in a stress-free configuration within the porous space of the host material. This means that:

$$\bar{J}_\alpha(t) = 1 \quad \text{with} \quad C_\alpha^*(t) \leq C_\alpha^n. \quad (39)$$

- In the case where the nominal solid concentration C_α^* of the new constituent α is larger than its natural density C_α^n , the volume taken by N_α is given by $V_\alpha^n = N_\alpha / C_\alpha^n$. The volumetric deformation $\bar{J}_\alpha$ needed to bring this volume back to the initial volume V_0 is then:

$$\bar{J}_\alpha(t) = \frac{V_0}{V_\alpha^N} = \frac{C_\alpha^N}{C_\alpha^*(t)} \quad \text{with} \quad C_\alpha^*(t) > C_\alpha^n \quad (40)$$

where we used the fact that $C_\alpha^* = N_\alpha / V_0$. Since $C_\alpha^*(t) > C_\alpha^n$, it is clear that $\bar{J}_\alpha < 1$ and the new constituent is deposited in a state of compression. This compression will subsequently create a state of residual stress in other phases as will be discussed in the examples of section 5.

With these assumptions, the volumetric part of the right Cauchy-Green deformation tensor

introduced in (6) takes the form $E_\alpha(t) = 1/2 \left(\left(H_\alpha(t) J^{1/3}(t) \right)^2 - 1 \right)$. Using (39) and (40), one obtains:

$$E_\alpha = 1/2 \left(J^{2/3} - 1 \right) \quad \text{when} \quad C_\alpha^*(t) \leq C_\alpha^n \quad (41)$$

$$= \frac{1}{2} \left(\left[\frac{C_\alpha^N J^{1/3}}{C_\alpha^*} \right]^2 - 1 \right) \quad \text{when} \quad C_\alpha^*(t) > C_\alpha^n. \quad (42)$$

The stress ζ_α from (22) then becomes a function of the current time of the form

$\zeta_\alpha(t) = H_\alpha^2(t) \partial \psi_\alpha / \partial E_\alpha$ and the partial (volumetric) stress S_α , becomes, according to (21):

$$S_\alpha = \Phi_\alpha^* \frac{\partial \psi_\alpha}{\partial E_\alpha} \quad \text{when} \quad C_\alpha^*(t) \leq C_\alpha^n \quad (43)$$

$$= \Phi_\alpha^* \left[\frac{C_\alpha^n}{C_\alpha^*} \right]^2 \frac{\partial \psi_\alpha}{\partial E_\alpha} \quad \text{when} \quad C_\alpha^*(t) > C_\alpha^n. \quad (44)$$

The meaning of these findings may be clarified by considering the specific case of isochoric growth, for which the total volumetric deformation J remains equal to unity. In this situation, (41) and (44) imply that the states of stress and strain becomes negative since

$1/2 \left((C_\alpha^n / C_\alpha^*(t))^2 - 1 \right) < 0$ when $C_\alpha^*(t) > C_\alpha^n$. One therefore observes the appearance of compressive residual stresses, and a resulting change in mass density, as the material grows without volume change.

4.4 Elastic potentials

In equation (15), it was shown that the elastic energy stored of a growing body can be additively decomposed into contributions from its different solid phases, all possessing their own potential energy depending on deformations and mechanical properties. This decomposition requires the definition of elastic potentials ψ_α , defined per unit reference volume of pure constituent; two examples are given here for our polymer-matrix system.

Polymer scaffold elasticity—Following the classical Flory-Rehner model for the elastic energy of a hydrogel [12], the elastic potential of the polymer network, with reference in its dry state, reads:

$$\psi_p(\mathbf{E}_p^d) = \frac{\rho RT}{\nu_p} \left(\text{tr}(\mathbf{E}_p^d) - \ln(J_p^d) \right). \quad (45)$$

Here ρ represents the molar ratio of cross-links and polymer chains while ν_p is the molar volume of the polymer. We also note that the Green-Lagrange strain $\mathbf{E}_p^d$ is measured with respect to the dry (or unswollen) polymer state; this motivates the use of the upper-script d . For most applications, including tissue engineering, it is more practical to choose the reference state as the equilibrated swollen state, for which the Jacobian of the deformation is $J_p = J_0 = 1$. In this case, the relation between the deformation gradient measured from the dry and swollen states, respectively is $\mathbf{F}_p^d = J_0^{1/3} \mathbf{F}_p$. The elastic potential ψ_p can then be rewritten as:

$$\psi_p(\mathbf{E}_p) = \frac{\rho RT}{\nu_p} \left(J_0^{2/3} \text{tr}(\mathbf{E}_p) - \ln(J_p J_0) + \frac{2}{3} (J_0^{2/3} - 1) \right). \quad (46)$$

Tissue elasticity—In contrast to a hydrogel, the elasticity of the newly deposited matrix depends on the properties of the building blocks, such as collagen or proteoglycans as well as the physical links that form between them. In general, this will yield relationships that are currently poorly understood due to a lack of measurements of tissue properties during growth. As a first approximation, it is therefore reasonable to choose an extension of linear isotropic elasticity for large deformations (known as the Saint-Venant-Kirchhoff model) for its simplicity and generality. The elastic potential of the deposited matrix can then be written in terms of two Lamé constants λ and μ as:

$$\psi_m(\mathbf{E}_m) = \frac{\lambda}{2} (\text{tr}(\mathbf{E}_m))^2 + \mu \text{tr}(\mathbf{E}_m^2). \quad (47)$$

Remark: The above constitutive relations are for *compressible* elastic solids. While not obvious at first, this compressibility is compatible with the assumption of molecular incompressibility assumed throughout this work. Indeed, the elastic responses introduced above account for the presence of pores within the material, which by being compressed or stretched, generate an overall change in volume in the solid phase. These deformations, however, occur such that the volume of the intrinsic solid phases (between the pores) remain constant.

5 Role of constitutive assumptions on tissue growth: example of tissue engineering in a hydrogel scaffold

The objective of this section is to use our example of tissue growth in a polymer scaffold in order to assess the role of various constitutive assumptions on the dynamics of growth, the appearance of residual stresses, as well as the final composition of the growing tissue. In this example, we consider that growth is spatially uniform, which helps in reducing the original differential equations into algebraic ones. We furthermore assume that growth occurs in an isotropic fashion so that stress and deformation tensors can be represented by of scalar quantities.

5.1 Uniform and isotropic tissue growth in a hydrogel scaffold

Problem reduction: For isotropic growth, the deformation gradient and Green-Lagrange strain tensor become:

$$\mathbf{F}(t) = J^{1/3}(t) \mathbf{I}, \quad \mathbf{E}(t) = \frac{1}{2} (J^{2/3}(t) - 1) \mathbf{I} \quad (48)$$

where $\mathbf{I}$ is the second-order identity tensor. These relations are also true for the deformation of any solid phases $\mathbf{F}_\alpha$, $\mathbf{E}_\alpha$ or even $\overline{\mathbf{F}}_\alpha$. To simplify the formulation, it is therefore convenient to represent all deformations (and stresses) by their diagonal components.

Growth law: In the following examples, we assume that the scaffold (polymer) does not grow, nor degrade in time ($\Gamma_p = 0$). Its nominal volume fraction and concentration therefore remain constant throughout the growth process, i.e. $C_m^*(t) = C_m^*(0)$. The changes in matrix concentrations C_m and C_m^* are then determined by the production rate P_m and the deposition rate Γ_m . Furthermore, using the assumption of uniformity, we recognize that the spatial gradient of any field vanishes and the mass balance equations (10) and (11) can be rewritten, after time integration:

$$C_m(t) = \int_0^t [P_m(\bar{t}) - \Gamma_m(\bar{t})] d\bar{t} \quad \text{and} \quad C_m^*(t) = \int_0^t \Gamma_m(\bar{t}) d\bar{t}.$$

Invoking (30) and (34) and assuming that no dissociation occurs between solid and free matrix molecules ($k_m^d=0$), we write:

$$P_m(t) = S_m(t) D_m(t) \quad \text{and} \quad \Gamma_m = k_m^f C_m / J \quad (49)$$

where the functions S_m and D_m are described by the constitutive relations proposed in (31) and (33).

Chemical equilibrium: Once again invoking the assumption of uniformity and vanishing spatial gradients, one finds from (25) that all fluid fluxes vanish and that the chemical potentials μ_α do not vary (and remain null) throughout the solid. This yields the following equations:

$$\Delta \mu_\alpha = \partial \Delta G^{\text{mix}} / \partial \Phi_\alpha = 0 \quad \alpha = m, w.$$

where we recall that m (for dilute matrix molecules) and w (for water) denote the fluid phases of our system. Using the expression for the mixing energy expressed in (29) and assuming that the volume fraction of dissolved matrix molecules remains small $\phi_m \ll 1$, we obtain (see appendix) two equations that characterize (a) the chemical equilibrium of the matrix in its fluid state and (b) the chemical equilibrium of the solvent (water):

$$p = -RT/\nu_w \left(\ln(\phi_w) + (1 - \phi_w) + \chi(1 - \phi_w)^2 \right) \quad (50)$$

$$0 = p + \frac{RT}{\nu_m} (1 + \ln(\phi_m)) \quad (51)$$

where the right-hand side of (50) is usually denoted as the osmotic pressure π (see appendix). Solving these equations enable the determination of two unknowns, the nominal concentration $C_w = J\phi_m/\nu_m$ of solvent and the hydrostatic pressure p .

Mechanical equilibrium and residual stresses: For a body growing uniformly in a stress-free state, the momentum equation (19), combined with the stress decomposition (20) becomes:

$$S = S_p + S_m - J^{1/3} p = 0. \quad (52)$$

Since the polymer neither grows nor loses mass in time, the history function H_p vanishes. Furthermore, the fact that no matrix is present in the reference state translates into $\Phi_m^*(0) = 0$. Now invoking equation (7) to find the history function $H_m(\bar{t}) = \bar{J}_m(\bar{t}) / J(\bar{t})$ and substituting this result in (21), (46) and (47), one obtains:

$$S_p = \Phi_p^* \kappa_p \left[J_0^{2/3} - J_p^{-2/3} \right] \quad (53)$$

$$S_m = \kappa_m \left[J^{2/3} A_1(t) - A_2(t) \right] \quad (54)$$

where $\kappa_m = (3\lambda + 2\mu)$, $\kappa_p = RT\rho/\nu_p$ and

$$A_1(t) = \int_0^t \nu_m \Gamma_m(\bar{t}) \left(\frac{\bar{J}_m(\bar{t})}{J(\bar{t})} \right)^{4/3} d\bar{t}, \quad A_2(t) = \int_0^t \nu_m \Gamma_m(\bar{t}) \left(\frac{\bar{J}_m(\bar{t})}{J(\bar{t})} \right)^{2/3} d\bar{t}. \quad (55)$$

We recall that the polymer deformation is $J_p = 1$ in the initially swollen configuration. This means that it is in a pre-stressed state at $t = 0$ (since $S_p > 0$ in (53)) due to the presence of the solvent exerting a hydrostatic (or osmotic) pressure in its interstitial space. We also clearly see from (55) that the natural configuration $\bar{J}_m$ at deposition plays a role in the build-up of residual stress in the polymer phase. This aspect will be investigated below.

Solution: The above set of equations consists of an initial value problem that has to be solved in time for three unknowns: the Jacobian $J(t)$ of the mixture deformation, the solvent concentration $C_w(t)$ and the osmotic pressure $\pi(t)$. At each time, these variables can be found by simultaneously solving (73), (74) and (52). Other variables, such as stresses and matrix concentrations can then be found by time integration appearing in (49) and (55). In this study, we use a backward Euler numerical integration scheme and a nonlinear algebraic solver to derive a solution for stress, concentrations and deformations at all times during the growth process. Results are reported below.

Role of the natural matrix configuration at deposition—One of the key novelties of the proposed formulation is that one can consider the role of the natural configuration of a constituent at the time of deposition on the growth dynamics of a biological tissue. We here propose to emphasize its role on both growth and the build-up of residual stresses within the material. Referring to section 4.3, we consider three main types of depositions:

- Case 1: The deposition strain $\bar{J}$ is independent of the time of deposition. In this context, we investigate situations in which the matrix deposits in (a) a stress-free configuration, i.e., $\bar{J}=1$ and (b) a pre-existing compressive state, i.e., $\bar{J}=0.6$. The second situation could occur when a building block unfolds at the time of deposition, for instance.
- Case 2: The deposition strain is equal to the strain of the underlying material ($\bar{J}=J$). This assumption, which is implicitly made by most growth models, can also be interpreted by stating that deposition occurs in a stress-free configuration

with respect with the undeformed (or reference) material. In this case, it is straightforward to show that the stress (54) in the matrix is:

$$S_m = \kappa_m \Phi_m^* [J - 1]. \quad (56)$$

- Case 3: The deposition occurs at constant density ($C_m^* = C_m^n$). As discussed in section (4.3), we assume that when the nominal density of the new matrix exceeds a critical value, it applies a compressive stress state to the surrounding material, and according to (44), the matrix stress becomes:

$$S_m = \kappa_m \Phi_m^* \left(\frac{C_\alpha^n}{C_\alpha^*} \right)^{\frac{2}{3}} \left[\left(J \frac{C_\alpha^n}{C_\alpha^*} \right)^{\frac{2}{3}} - 1 \right] \quad \text{if} \quad \frac{C_\alpha^n}{C_\alpha^*} > 1 \quad (57)$$

$$= \kappa_m \Phi_m^* [J - 1] \quad \text{if} \quad \frac{C_\alpha^n}{C_\alpha^*} \leq 1 \quad (58)$$

To investigate the appearance of residual stress, we first show in Fig. 5 (a,b,c) the temporal evolution of the Cauchy stress in the matrix, the polymer scaffold, as well as the osmotic pressure in the interstitial fluid. Note that the sum of all these contributions vanishes, consistent with our assumption of stress-free growth. It can first be noted that the stress in the matrix largely varies from a tensile to a compressive state depending on the assumption. When $\bar{J}=0.6$, we can initially observe a strong state of overall compression, which tends to decrease in time due to the additional tension that arises from adding more material within the interstices of the scaffold. In the long term, the third case (growth at constant density) actually leads to increasing compression since more growth means more matrix that needs to be compressed in order to fit within the scaffold material. Generally, the stress in the scaffold is much less affected than that in the matrix and remains in a state of tension in order to resist the insertion of new material. Similarly, the osmotic pressure rises for all cases, although the increase is less significant when the material deposits in a state of compression. This can be explained by the fact that, in such a situation, the new material participates in maintaining the state of compression, and thus decreases the contribution of osmotic pressure.

Let us now investigate how the appearance of residual stresses affect the overall growth of the tissue (Fig. 5 (d,e,f)). First, we note that the amount of free matrix molecules present in the material tends to decrease with growth. This observation can mainly explained by the fact that cells decrease their production rate due to a rise in osmotic pressure as depicted in Fig 3. Consequently, cases where the deposited matrix holds the most compressive stresses (case 1 for $\bar{J}=0.6$ and case 3) allow for the highest matrix production by cells. It is therefore not surprising that maximum tissue growth, both in terms of new matrix density C_m^* and volumetric expansion J , is also observed for those cases as seen in Fig. 5 (e,f). Results also highlight that when $\bar{J}=0.6$, the model predicts that the tissue can grow twice as much

compared to models based on traditional assumptions (case 2). This suggests that a considerable effort has to be made to accurately account for the configuration of deposited molecules in future models of growth.

Role of cell-mediated matrix production—We now assume that the matrix is deposited in a stress-free configuration $\bar{J}=1$ and investigate the effect of the strength of matrix-releasing cells as characterized by the critical pressure π_c appearing in eq. (31). For this, we vary the pressure around the reference value π_c^0 (we concentrate on $\pi_c=0.9\pi_c^0$, π_c^0 and $1.4\pi_c^0$, respectively) and explore the consequences of such changes on the evolution of internal stresses and overall growth. In this context, Fig. 6(d,e,f) show that as π_c increases, cells are capable of producing more free matrix under a given osmotic pressure, which explains the rise in concentration C_m with π_c . In turn, this translates into a larger conversion from free to solid matrix (Fig. 6 (d)) and an increase in volumetric growth (Fig. 6 (e)). Note that the trends are not necessarily linear since the material response, especially that of the polymer, displays an increased stiffness with de-formation. In other words, the effect of π_c on volumetric growth decreases with increasing values of π_c .

The internal mechanical forces in the material are also strongly affected by matrix production as can be observed in Fig. 6 (a,b,c). When cells are stronger (π_c is large), the matrix contribution σ_m to the overall stress (here tensile since $\bar{J}=1$) becomes more preponderant because more matrix is present. At the same time, because more matrix induces more volumetric expansion, an increased residual stress σ_p is felt by the surrounding material and a high osmotic pressure is observed.

Role of elasticity—In this section, we finally assess how growth dynamics is affected by the elastic properties of the active phase (here, the matrix), and more specifically the stiffness ratio κ_m/κ_p of the matrix and polymer materials. For clarity, we limit our study to the three following cases: (a) $\kappa_m/\kappa_p = 0.1$, (b) $\kappa_m/\kappa_p = 1$ and (c) $\kappa_m/\kappa_p = 4$ while keeping our assumption that the matrix is deposited in a stress-free configuration ($\bar{J}=1$). Results in Fig. 6 (a,b,c) show that a stiffer matrix results in a larger tensile residual stress σ_m , relative to the volumetric deformation. This translates into a higher resistance to deformation, reduced growth (Fig. 7f), and consequently a lower stress carried by the polymer scaffold. Since a stiff matrix yields a larger tension in the solid phases, a larger osmotic pressure quickly develops to keep the overall stress-free state of the material. It is therefore not surprising that the matrix production rate (and consequently the conversion rate) quickly drops in this situation. Overall, it can be concluded that when the active phase is stiff relative to its underlying scaffold, there is a rise in residual stresses and osmotic pressure in the construct, a feature that turns to be detrimental to the growth process.

5.2 Nonuniform tissue growth around a cell in a hydrogel scaffold

In the second example, we propose to investigate the microscopic growth dynamics around cartilage cells (or chondocytes) encapsulated in a hydrogel scaffold. Understanding how the scaffold design affects the local matrix deposition around cells is indeed an important aspect of finding new solutions for cartilage engineering [10, 11]. To simplify the problem, we

consider the case of low cell density which allows us to study a single, unit hydrogel sphere of initial radius R_g containing a chondrocyte of radius $R_c = 5\mu m$ at its center (Fig 8). Note that the ratio between these radii is dictated by the cell volume fraction $f_c = (R_c/R_g)^3$ which we take as $f_c = 0.01$ in the following. The synthesis and release of ECM molecules is then modeled in the form of surface fluxes Q_m^0 on the surface of the cell whose magnitude is dictated by (31); The released ECM is subsequently available for diffusion and deposition in the scaffold.

Problem reduction—Using a spherical coordinate system (R, Θ, Φ) and assuming central symmetry, it can be found that displacements only occur in the radial direction (Fig. 8). Denoting by r the coordinate of a point that was originally in R , one can derive the following expression for the deformation gradient:

$$\mathbf{F} = \text{diag} \left[\frac{\partial r}{\partial R}, \frac{r}{R}, \frac{r}{R} \right] \quad (59)$$

For simplicity, we assume here that the matrix deposits at a configuration $\bar{\mathbf{F}}_m = \mathbf{F}$, i.e., $\mathbf{F}_m = \mathbf{F}$ at all time. In other words, the Green-Lagrange strain in the polymer and solid matrix is the same and has the following non-zero components:

$$E_{RR} = \frac{1}{2} \left[\left(\frac{\partial r}{\partial R} \right)^2 - 1 \right] \quad E_{\Theta\Theta} = E_{\Phi\Phi} = \frac{1}{2} \left[\left(\frac{r}{R} \right)^2 - 1 \right] \quad (60)$$

in the radial and circumferential directions, respectively.

Mechanical equilibrium and residual stresses—When no body forces are considered, the momentum equation (19) becomes:

$$\frac{\partial P_{RR}}{\partial R} + \frac{2}{R} (P_{RR} - P_{\Theta\Theta}) = 0. \quad (61)$$

subjected to boundary conditions $r(R_c) = R_c$ and $P_{RR}(R_s) = 0$ for a scaffold under stress-free conditions. The decomposition of stresses then follows:

$$P_{RR} = F_{RR} \left[(S_m)_{RR} + (S_p)_{RR} \right] - pJ/F_{RR} \quad (62)$$

$$P_{\Theta\Theta} = F_{\Theta\Theta} \left[(S_m)_{\Theta\Theta} + (S_p)_{\Theta\Theta} \right] - pJ/F_{\Theta\Theta} \quad (63)$$

where the component of the second Piola-Kirchhoff stress in the matrix are:

$$(S_m)_{RR} = \Phi_m^*(t) \frac{\partial \Psi_m}{\partial E_{RR}} = \Phi_m^*(t) [(\lambda + 2\mu) E_{RR} + 2\lambda E_{\Theta\Theta}] \quad (64)$$

$$(S_m)_{\Theta\Theta} = \Phi_m^*(t) \frac{\partial \Psi_m}{\partial E_{\Theta\Theta}} = \Phi_m^*(t) [\lambda E_{RR} + 2(\lambda + \mu) E_{\Theta\Theta}] \quad (65)$$

and in the polymer:

$$(S_p)_{RR} = \Phi_p^* \frac{\partial \Psi_p}{\partial E_{RR}} = \frac{\rho \Phi_p^* RT}{\nu_p} \left(J_0^{2/3} - \frac{1}{F_{RR}^2} \right) \quad (66)$$

$$(S_p)_{\Theta\Theta} = \Phi_p^* \frac{\partial \Psi_p}{\partial E_{\Theta\Theta}} = \frac{2\rho \Phi_p^* RT}{\nu_p} \left(J_0^{2/3} - \frac{1}{F_{\Theta\Theta}^2} \right) \quad (67)$$

Note that we assume here that no matrix was present originally and that the scaffold did not degrade during the growth process.

Chemical equilibrium and Growth law—As in the previous example, we assume that the scaffold (polymer) does not grow, nor degrade in time ($\Gamma_p = 0$), i.e. $C_p^*(t) = C_p^*(0)$. The changes in matrix concentrations C_m and C_m^* however depend on the deposition rate Γ_m as seen below. For our centro-symmetric problem, the mass balance equations (10) and (11) for the matrix take the form:

$$\frac{DC_m}{Dt} + \frac{1}{R^2} \frac{\partial (R^2 Q_m)}{\partial R} = -\Gamma_m \quad \text{and} \quad \frac{DC_m^*}{Dt} = \Gamma_m \quad (68)$$

where no matrix is allowed to leave the domain, i.e. $Q_m(R_s) = 0$. The flux of fluid ECM is given, within our centro-symmetric assumptions, by

$$Q_m = -\bar{D}_m \frac{\partial}{\partial R} \left(\frac{C_m}{J} \right) \quad \text{with B.C.} \quad Q_m(R_c) = Q_m^0 \beta \left(1 - \frac{\pi}{\pi_c} \right) \quad (69)$$

While the flux boundary condition (B.C.) at the cell's surface follows the inhibitory model described in (31). Furthermore, following the framework of section 3.3, one can show that the diffusion coefficient depends on deformation as $\bar{D}_m = D_m F_{\Theta\Theta}^2 / F_{RR}$ while D_m is described by the constitutive relation shown in (33). Finally invoking (34) and assuming that no dissociation occurs between solid and free matrix molecules ($k_m^d = 0$), we write:

$$\Gamma_m = k_m^f C_m / J \quad (70)$$

Since growth occurs over large time scales, we assume here that the solvent (water) remains in chemical equilibrium, that is (50) is valid at all time ($p = \pi$).

Solution—The above set of equations consists of an initial boundary value problem that has to be solved in time for three unknowns: $J(R, t)$, $C_w(R, t)$ and the hydrostatic pressure $p(R, t)$. We use a nonlinear mixed finite element formulation as described in earlier studies [11]. More precisely, the solution is found via a Newton-Raphson procedure at each time step while a backward Euler numerical integration scheme is used to evolve each variable in time.

Results—We propose here to investigate how local tissue growth around a chondrocyte is affected by the ECM deposition kinetics and the scaffold deformation. For this, we choose a reference scaffold design, corresponding to $k_m^f = 0.001 \text{ (1/hr)}$, $D_m = 0.8 D_\infty$ (where D_∞ is the diffusion coefficient in a pure solvent), $\rho_x = 1.48 \text{ mole/Liter}$ and $Q_m^0 = 10^{-11} \text{ mole/m}^2/\text{hr}$ and investigate how the growth dynamics is altered by (a) an increase of the deposition rate k_m^f by a factor of 10 and (b) a state of volumetric compression. We are particularly interested in understanding the role of these conditions on the spatial profiles and overall time evolution of detached ECM concentration C_m , attached ECM concentration C_m^* and osmotic pressure at different times during the growth process.

First of all, we note that our reference case (Fig. 9a) displays relatively slow ECM deposition kinetics; this means that detached ECM can diffuse over large distances from the cell boundary before it becomes a solid constituent. Consequently, in the earlier stages of growth, the detached ECM displays a very inhomogeneous profile with a maximum concentration near the cell. This regime tends to locally increase the osmotic pressure in the pericellular region, which according to (31) induces an early inhibition of cell-mediated ECM production. The total amount of detached ECM in the system therefore reaches a maximum (inset in Fig. 9a) before dropping and relaxing to a diffusion-driven homogeneous distribution. Because of the slow deposition rate k_m^f , the ECM tends to deposit a later stages and therefore display a fairly homogeneous profile which steadily increases with time, until it depletes the existing fluid-ECM reservoir. We also note that during the growth process, the osmotic pressure steadily increases in order to compensate for the addition of new material in the pore space of the hydrogel scaffold. When the rate Γ_m of ECM deposition increases by a factor of 10 (Fig. 9b), the ECM quickly turns to its solid state as it is diffusing through the scaffold. This results in highly inhomogeneous distribution of solid-ECM and a very quick rise in osmotic pressure near the cell. For this reason, the rate of ECM release quickly drops in time and the growth process stops prematurely as seen in the insets of Fig. 9b. This situation is detrimental to growth as it yields to the formation of a pericellular matrix around chondrocyte without overall ECM production. We finally consider the effect of applying a confined compressive deformation, given by a radial stretch ratio with the Dirichlet boundary conditions $r(R_g) = 0.95 R_g$ to the scaffold throughout the growth process. Since this

compressive state naturally induces a rise in hydrostatic pressure, one also observe a rise in osmotic pressure (from (50)), which tends to inhibit ECM release at an early stage (once again, due to (31)). In other words, the growth dynamics follow a very similar trend as for the reference design (Fig. 9a) but experiences an early growth inhibition, which eventually translate into very little deposited ECM in the final state. This result is not surprising since applying a compressive state to a construct effectively reduces the space available for growth.

6 Conclusion and future work

To summarize, the present paper has introduced a formulation for the growth in engineering scaffold that permits the investigation of the effects of finite deformations (from swelling and applied loading) on the underlying production, transport and deposition mechanisms. Following the theory of reactive mixtures [4], growth is viewed as a change in material density, and possibly volume, via the transport and deposition of free “building blocks” in an existing scaffold. The consideration of these phenomena is possible by modeling a growing material as a multi-constituent solid-fluid mixture whose mechanical and chemical behaviors are dictated by the minimization of both the elastic and mixing energy of the system. This approach not only offers a flexible platform to describe the relationships between swelling, transport and material deposition, but it also enables one to consider the role of the natural configuration of active constituents at their time of deposition [18]. Another advantage of the approach is that it provides a bridge between the macroscopic growth of a material and the underlying mechanisms occurring at the micro-scale. To the benefit of applications such as tissue engineering, it therefore becomes possible to assess the role of material stiffness, chemistry and permeability as well a cell response on the overall evolution of a biological tissue. One of the inevitable consequences is that the model necessitates the introduction of an enriched set of constitutive relations in the form of (a) elastic and mixing energies of various constituents, (b) cell-mediated tissue production, (c) transport and deposition of building blocks and finally, (d) the natural configuration of these blocks at the time of deposition. We have proposed simple forms for these relationships and, when possible, compared them with existing models.

To investigate the predictions of the model, we have considered the particular case of tissue growth in a non-degradable polymeric scaffold, for both its relative simplicity and direct applications to tissue engineering. First considering the simple case of uniform, isotropic growth, we have shown how various constitutive assumptions could affect the dynamics of growth and the development of residual stresses. Generally, it was found that the natural configuration of building blocks at the time of deposition has a strong effect on all of the above. This finding is important since existing models do not account for this aspect. We also found that the strength of matrix-producing cells, as well as the elasticity of the tissue at deposition are strong players during growth. Generally, growth is promoted by strong cells (large π_c) and a soft matrix at the time of deposition (small κ_m). We then investigated how the rate of ECM deposition and the presence of a compressive deformation to the scaffold affected tissue growth around chondrocytes in a construct. The model shows that these factors could not only inhibit overall tissue growth (for fast deposition kinetics or large compressive strains) but could also drastically affect the homogeneity of the tissue structure.

We note here that the introduction of accurate and biologically motivated constitutive relations was beyond the scope of the study and future research should concentrate on these aspects with applications to specific tissues and materials. For instance, it is known that the presence of charged particles in tissues affect swelling and subsequent growth. Such physics may be accounted to the presented model by incorporating an electro-chemical potential such as that introduced in [30] to the free energy function. The case of non-uniform growth in which transport becomes predominant is also an important problem to address to better understand and eventually control the morphology and spatial growth of tissue constructs. Study of cell mechano-sensing [39, 40, 13] and the adjustment of their matrix release capabilities is also a critical area of investigation to explain the effect of load on isotropic and anisotropic growth [32, 38]. Finally, it is well known that active constituents usually comprises a myriad of building blocks of different sizes and chemistries; a question arises whether it is realistic to lump these phases into a single matrix constituent or rather into families of building blocks. It is clear that answering such questions will necessitate strong integrations between modeling and experimental efforts in the future.

Acknowledgments

The author would like to acknowledge the support of the National Science Foundation under the CAREER award 1350090 and the National Institute of Health under award 8265940. The help of Umut Akalp for generating the figures in section 5 is also deeply appreciated.

8 Appendix: Derivation of chemical potentials, osmotic pressure and fluxes for the triphasic tissue construct

The chemical potential is related to the mixing energy by:

$$\Delta\mu_\alpha = \frac{\partial\Delta G^{\text{mix}}}{\partial\Phi_\alpha} \quad \alpha = m, w.$$

where we recall that m (for dilute matrix molecules) and w (for water) denote the fluid phases of our system. Using the expression for the mixing energy expressed in (29), we obtain:

$$\Delta\mu_w = p + \frac{RT}{\nu_w} \left(\ln(\phi_w) + (1 - \phi_w) - \frac{C_m}{J} \nu_w + \chi(1 - \phi_w)^2 \right) \quad (71)$$

$$\Delta\mu_m = p + \frac{RT}{\nu_m} \left(\ln(\phi_m) + (1 - \phi_m) - \frac{C_w}{J} \nu_m + \chi \frac{C_w}{J} \phi_w \nu_m \right) \quad (72)$$

Note that to obtain the above equations, the volume fraction of water was expressed in terms of other variables in the form $\phi_w = (J_0 J - 1 - J_0 \nu_m C_m - J_0 \nu_m C_m^*) / (J_0 / J)$. Now realizing that the nominal concentration of dissolved matrix is typically much smaller than that of the solvent, i.e., $\phi_m \ll 1$, we obtain:

$$\Delta\mu_w \approx p + \frac{RT}{\nu_w} \left(\ln(\phi_w) + (1 - \phi_w) + \chi(1 - \phi_w)^2 \right) \quad (73)$$

$$\Delta\mu_m \approx p + \frac{RT}{\nu_m} (1 + \ln(\phi_m)) \quad (74)$$

Now noticing that the osmotic pressure is:

$$\pi = \frac{\partial \Delta G^{\text{mix}}}{\partial J} = - \frac{RT}{\nu_w} \left(\ln(\phi_w) + (1 - \phi_w) + \chi(1 - \phi_w)^2 \right) \quad (75)$$

The chemical potential of the solvent can be rewritten in the simpler form:

$$\Delta\mu_w = p - \pi \quad (76)$$

According to (23) and (25), the fluid velocity $\mathbf{v}_w$ and molar flux of matrix are thus expressed as:

$$\mathbf{q}_w = - \frac{\kappa}{\eta \nu_w} (\nabla p - \nabla \pi) \quad (77)$$

$$\mathbf{q}_m = c_m \tilde{\mathbf{v}}_w - D_m \nabla c_m \quad (78)$$

where $\tilde{\mathbf{v}}_w = \mathbf{q}_w / c_w$. We recover a more classical case of Darcy's law where fluid motion is governed by the gradient of hydrostatic and osmotic pressures while the flux of solute (matrix) has both a convective component and a Fickian diffusive component.

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Figure 1.

Decomposition of deformable particles deposited at different times on an underlying material that undergoes a deformation $\mathbf{F}(t) = \text{diag}(\lambda(t), 1, 1)$. In this illustration, we consider three particles depositing with a natural configuration $\bar{\lambda}$ at three different times, t_0 , t_1 and t_2 on a material that undergoes a stretch of $\lambda = 1, 1.5$ and 2 , respectively. The deformation at time t of a particle that deposited at time t_a is then described by the deformation $\lambda(t, t_a)$, whose value can be computed in terms of $\lambda(t)$ and the deposition strain at given times.

Figure 2.
Internal composition of a growing tissue in a polymeric scaffold.

Figure 3.

Microscale assumptions for the production of new matrix (in its detached state) in a growing tissue. Cells, represented here by circular shapes first release matrix molecules that are free to diffuse and subsequently deposit within the existing material. We assume here that (a) matrix synthesis decreases linearly with the osmotic pressure π in the surrounding material. When π reaches a critical value π_c , synthesis completely ceases. Using results from studies on the diffusion of species in a fibrous network, we then assume that (b) matrix transport is facilitated by a large porosity ϕ_f in a nonlinear fashion as expressed in (33).

Figure 4.

Model of growth previously proposed in the literature [20]. When the nominal concentration C_α of a growing phase is smaller than the natural concentration C_α^N in the absence of surrounding medium, growth occurs at constant volume. However, when the concentration C_α is equal to C_α^N , the mixture changes volume in order to accommodate the new material.

Figure 5.

Evolution of the normalized volumetric Cauchy stresses $\hat{\sigma}_\alpha = \sigma_\alpha / \pi(0)$, osmotic pressure $\hat{\pi} = \pi / \pi(0)$, matrix concentration $\hat{C} = C / C_{max}$ and overall volume change J for different cases of natural configurations $\bar{J}$ of the matrix at the time of deposition.

Figure 6.

Evolution of the volumetric Cauchy stresses $\hat{\sigma}_\alpha = \sigma_\alpha / \pi(0)$, osmotic pressure $\hat{\pi} = \pi / \pi(0)$, matrix concentration $\hat{C} = C / C_{max}$ and overall volume change J for different critical pressures for cell-mediated matrix production.

Figure 7.

Evolution of the volumetric Cauchy stress $\hat{\sigma}_\alpha = \sigma_\alpha / \pi(0)$, osmotic pressure $\hat{\pi} = \pi / \pi(0)$, matrix concentration $\hat{C} = C / C_{max}$ and overall volume change J for different matrix stiffness.

Figure 8.
Schematic and variable definition for the non-uniform growth around a chondrocytes

Figure 9.

Evolution of the normalized fluid ECM, solid ECM and osmotic pressure distribution along the distance r from the cell surface for three different times. The insets show the volume average of the above quantities in time and symbols denote time points where each of the spatial distribution are plotted. In (a), we show the case of slow deposition kinetics, in (b) we show the effect of fast deposition rate and in (c) we show the effect of imposing confined compressive strain to the construct.