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Mass transport in morphogenetic processes: a second gradient theory for volumetric growth and material remodeling

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Abstract

In this work, we derive a novel thermomechanical theory for growth and remodeling of biological materials in morphogenetic processes. This second gradient hyperelastic theory is the first attempt to describe both volumetric growth and mass transport phenomena in a single-phase continuum model, where both stress- and shape-dependent growth regulations can be investigated. The diffusion of biochemical species (e.g. morphogens, growth factors, migration signals) inside the material is driven by configurational forces, enforced in the balance equations and in the set of constitutive relations. Mass transport is found to depend both on first- and on second-order material connections, possibly withstanding a chemotactic behavior with respect to diffusing molecules. We find that the driving forces of mass diffusion can be written in terms of covariant material derivatives reflecting, in a purely geometrical manner, the presence of a (first-order) torsion and a (second-order) curvature. Thermodynamical arguments show that the Eshelby stress and hyperstress tensors drive the

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rearrangement of the first- and second-order material inhomogeneities, respectively. In particular, an evolution law is proposed for the first-order transplant, extending a well-known result for inelastic materials. Moreover, we define the first stress-driven evolution law of the second-order transplant in function of the completely material Eshelby hyperstress.
The theory is applied to two biomechanical examples, showing how an Eshelbian coupling can coordinate volumetric growth, mass transport and internal stress state, both in physiological and pathological conditions. Finally, possible applications of the proposed model are discussed for studying the unknown regulation mechanisms in morphogenetic processes, as well as for an optimizing scaffold architecture in regenerative medicine and tissue engineering.

Keywords: Volumetric growth, Remodeling, Mass transport, Morphogenesis, Configurational forces, Mechanobiology

1 Introduction

Morphogenesis in contemporary sciences is commonly intended as the study of all developmental processes which intervene in the creation of the shape of living objects. This statement has *in se* an implicit definition, referring to the etymological meaning of the word itself[1] in Aristotle's Physics books. The Greek philosopher considered the essence ($o\acute{\upsilon}\sigma\iota\alpha$- ousía) of a living being as an indissoluble combination of matter ($\acute{\upsilon}\lambda\eta$-hylé [2]) and shape ($\mu o\rho\phi\acute{\eta}$-morphé), which is its manifestation in the sensible universe. In this connotation, the morphogenetic science has a much wider sense than that of pattern (corresponding to the greek concept of $\sigma\chi\acute{\eta}\mu\alpha$-schéma) generation. If the latter is oriented to the quest of the mechanisms regulating the physical appearance of biological matter, morphogenesis considers the emergence of shape as an intrinsic characteristic of a living being, dynamically revealed during evolution. In biomechanical terms, morphogenetic events do not only include pattern and template formation, but may also actively interact with other dynamic processes (see the extensive reviews of Taber (1995) and

[1]The word *morphé* was earlier employed by Homer in the Odyssey, books II and VIII, with a meaning of "outward appearance"

[2]the mass unit of 1 *hyle*=1 s^3VA/cm^2 was proposed in 1910 by Gustav Mie in the definition of his VACS system of units

Cowin (2004)). For example, morphogenesis can involve simultaneous changes in mass and material properties, here referred as growth and remodeling, respectively.

In this respect, a considerable amount of modeling research has been performed to accommodate the evolution law of mass variation inside a material, written as a volumetric change of bulk material or an accretion/resorption at a surface (see Ambrosi et al. (2011) and Ganghoffer (2010) and references therein). Volumetric growth in continuum theories can occur at the expense of the material porosity (Cowin and Hegedus, 1976), or as a smooth change in a single-phase material. A seminal idea has been to assume a separability principle between growth and elastic deformation (Skalak et al., 1982; Rodriguez et al., 1994). Modeling approaches based on such a decomposition hypothesis have shown how complex biological patterns can arise from the loss of elastic stability due to geometrical incompatibilities of the growth processes (Dervaux and Ben Amar, 2008; Dervaux et al., 2009; Ben Amar and Ciarletta, 2010). As discussed by Epstein and Maugin (2000), continuum theories of growth and remodeling often exclude *ab-initio* the possibility to include a diffusive mass flow inside the body, as their driving forces would involve the second gradient of the elastic deformation. In order to avoid this difficulty, theories of mixtures are often employed to couple growth and mass transport phenomena of the fluid and solid components of the material (Ateshian, 2009). Although multiphase theories of reactive mixtures can extend the continuum models with the thermodynamic potentials of biochemical factors diffusing inside the body, major drawbacks consist in dealing with partial stresses and with mass exchanges between the single phases (Ambrosi et al., 2010).

In this work we propose a morphogenetic theory of a growing continuum accounting both for volumetric growth and for mass transport inside the body. Our viewpoint reflects the definition given by Bard (1990) of a 'middle view': both genetic information and epigenetic processes contribute to the creation of the final shape. In other words, we assume that genes carry specific biochemical instructions for the creation of biological matter, while the biomechanical and biochemical interactions with the environment generate the shape emergence. Our constitutive growth model of a hyperelastic second-gradient material includes mass transport

phenomena, and we use the theory of configurational forces (Maugin, 2011) to account for some open problems in the continuum treatment of growth and remodeling in morphogenetic processes. With this aim, we include the role of diffusing morphogens in the determination of spatial patterns of cell differentiation, a very active research area of developmental biology in the last decades (Wolpert, 1969; Kondo and Miura, 2010). Furthermore, our theory provides a thermodynamically-based coupling for modeling the stress-driven feedback mechanisms that regulate growth and orchestrate shape during morphogenetic events (Lecuit and Le Goff, 2007). A second gradient morphoelastic model provides, in this sense, a rich theoretical framework, where both mechanical and shape-dependent effects on growth can be considered.

The work is organized as follows. In Section 2, we state the kinematic theory for motion and deformation of a single-phase continuum. In Section 3, a thermo-mechanical theory of growth for a second gradient continuum is introduced, deriving the balance equations and the thermodynamical laws. In Section 4, the bases of a second gradient theory of growth and material remodeling are established. In particular, we define a constitutive equation for the diffusive mass transport inside the body, and we obtain the evolution laws for the first- and the second-order material inhomogeneities. In Section 5, we apply the proposed theory to model two biomechanical examples of growing materials. Finally, our results are summarized in Section 6, with a discussion about the effectiveness and the limitations of the proposed theory for modeling morphogenetic events.

2 Theory of motion and deformation

Let us consider a mapping $\mathbf{x} = \chi(\mathbf{X}, t)$ that describes the deformation of a continuous body from the reference to the actual configuration. Let $\mathbf{F} = \text{Grad } \mathbf{x} = \nabla_R \mathbf{x} = \{F^i_K \equiv F_{iK}\}$ (the upward or downward position of the lower Latin indices is irrelevant when choosing a Cartesian representation in the current configuration) and $\nabla_R \mathbf{F} = \text{Grad Grad } \mathbf{x} = \nabla_R \nabla_R \mathbf{x}$ be the deformation gradient tensor and the second gradient of the deformation, respectively. It is useful to remind that the gradient operators in current and reference configurations are linked

by the relation $\nabla = \mathbf{F}^{-T}.\nabla_R$. As a notation rule, in the following we will make use of n dots (n=1,2,3) to indicate the contraction of n inner indices in the product between tensor fields (e.g. $(\mathbf{T} : \nabla_R \mathbf{F})_k = \mathbf{T}_{ji}(\nabla_R \mathbf{F})_{ijk}$, assuming Einstein's summation rule on repeated indexes).

The elastic problem can be formulated in two different space time parameterizations, using the so-called direct and inverse kinematics (Maugin, 2003). The direct kinematics considers the variables $(\mathbf{X}, t)$ belonging to the physical space. Its formulation of the elastic problem is based on the following fields:

$$\begin{cases} \mathbf{x} = \chi(\mathbf{X}, t); & \mathbf{F} = \nabla_R\ \mathbf{x}; & \nabla_R \mathbf{F} = \nabla_R \nabla_R \mathbf{x}; \\ \mathbf{v} = \frac{\partial \mathbf{x}}{\partial t}|_X & \mathbf{l} = \nabla_{\mathrm{R}}\ \mathbf{v} = \dot{\mathbf{F}}\ |_X & \mathbf{L} = \nabla\ \mathbf{v} = \dot{\mathbf{F}}\ |_X\ .\mathbf{F}^{-1} \\ K = \frac{1}{2}\rho_0 \mathbf{v}^2 : & \mathbf{p} = \frac{\partial K}{\partial \mathbf{v}} = \rho_0 \mathbf{v} & \end{cases} \tag{1}$$

where $\mathbf{v}$ is the spatial velocity, and $\mathbf{l}, \mathbf{L}$ are the material, spatial velocity gradients, respectively. Being K the kinetic energy density of the continuum body, $\mathbf{p}$ represents the physical linear momentum density.

On the other hand, the inverse kinematics considers the motion $\chi^{-1}(\mathbf{x}, t)$, and it is an intrinsic formulation where the domain changes over time and the range is fixed. The inverse formulation of the elastic problem is based on the following variables:

$$\begin{cases} \mathbf{X} = \chi^{-1}(\mathbf{x}, t); & \mathbf{F}^{-1} = \nabla\ \mathbf{X}; \qquad \nabla \mathbf{F^{-1}} = \nabla \nabla \mathbf{X}; \\ \mathbf{V} = \frac{\partial \mathbf{X}}{\partial t}|_x = -\mathbf{F}^{-1}.\mathbf{v} & \nabla_{\mathrm{R}}\ \mathbf{V} = \dot{\mathbf{F}}^{-1}\ |_x\ \mathbf{F} = -\mathbf{F}^{-1}.\mathbf{L}.\mathbf{F} - \nabla_{\mathrm{R}} \mathbf{F}^{-1}.\ \mathbf{v} \\ K = \frac{1}{2}\rho_0 \mathbf{V}.\mathbf{C}.\mathbf{V} & \mathbf{P}_m = \frac{\partial K}{\partial \mathbf{V}} = \rho_0 \mathbf{F}^T.\mathbf{F}.\mathbf{V} = \rho_0 \mathbf{C}.\mathbf{V} = -\mathbf{F}^T.\mathbf{p} = -\mathbf{p}.\mathbf{F} \end{cases} \tag{2}$$

where $\mathbf{V}$ is the inverse motion velocity, i.e. the material velocity field, and $\mathbf{C} = \mathbf{F}^T\mathbf{F}$. The material covector $\mathbf{P}_m$ is the true conjugate of the material velocity, and it is often referred to as pseudomomentum density or canonical momentum density. The balance law of $\mathbf{P}_m$ in the material framework accounts for the momentum associated to all the degrees of freedom of the deformation field, while the balance of $\mathbf{p}$ involves only the translational momentum (Maugin and Trimarco, 1992). This is why the balance of pseudomomentum density must be considered when

there are inhomogeneities in the material set. Moreover, as previously discussed in Epstein and Maugin (2000), the transformation law of the material gradient of the inverse motion velocity, expressed in the second line of Eq.(2), involves the second gradient of the deformation and the direct velocity gradient. A second gradient morphoelastic theory is therefore necessary to state a constitutive equation for the mass transport, as well as to define thermodynamically compatible evolution equations for mass remodeling during the morphogenetic processes.

3 Thermo-mechanics of growing second gradient continua

The aim of this section is to define the balance principles characterizing a thermo-mechanical theory for coupling volumetric growth processes and mass transport phenomena inside a second gradient continuous body.

3.1 Balance equations for mass and morphogens/nutrients concentration

Let us consider a growing body, whose density in the reference and actual configurations is indicated with $\rho_0(\mathbf{X}, t)$ and $\rho(\mathbf{x}, t)$, respectively. The following relations hold:

$$\rho_0 = J\ \rho : \qquad \dot{J} = J\ \mathrm{tr}\mathbf{L} \tag{3}$$

where $J(\mathbf{X}, t)$ is the determinant of $\mathbf{F}$, and the upper dot indicates time derivative. We define the mass production rates Γ, γ and the mass flux vectors $\mathbf{M}, \mathbf{m}$ in the reference and actual configurations, respectively. The mass balance equation in material coordinates can be expressed as:

$$\dot{\rho_0} = \Gamma\rho_0 + \nabla_{\mathrm{R}}.\ \mathbf{M} \tag{4}$$

while its expression in spatial form reads:

$$\dot{\rho} + \rho\ \nabla.\ \mathbf{v} = \gamma\rho + \nabla.\ \mathbf{m} \tag{5}$$

where $J\ \gamma = \Gamma$, and $\mathbf{M} = J\mathbf{F}^{-1}\mathbf{m}$ is the material contravector of mass flux, obtained through a Piola transformation. The following identity relates the material and spatial divergence:

$\nabla_R.\mathbf{M} = J\nabla.\mathbf{m}$. The rates γ, Γ have the physical dimension of the inverse of a characteristic time.

The morphogenetic processes in biological materials are characterized by the concentration of passive scalars driving both growth (e.g. nutrients, growth factor) and mass transport phenomena (e.g. migration signals, morphogens) which are dispersed in the extracellular matter. Indicating with $c_i(\mathbf{x}, t)$ the concentration of the generic $i-th$ species per unit volume, its balance equation can be written in the material form as:

$$\dot{c}_i - \nabla_{\mathrm{R}}.\ \mathbf{J}_{ci} = \xi_i(\mathbf{F}, \nabla_R\mathbf{F}) \tag{6}$$

where ξ_i is the absorption rate of the $i-th$ species. In the following, its value is assumed to depend both on the first and on the second gradient of the deformation field, reproducing, for example, curvature-dependent effects in the absorption of angiogenetic factors (Levine et al., 2001). The diffusion of a morphogen from the source through the extracellular matter, with a sink function possibly regulated by receptor endocytosis, has been proved to describe the morphogens gradient in multicellular embryonic tissues (Yu et al., 2009). In Ambrosi and Mollica (2002), a simple expression for the material flux of nutrients $\mathbf{J}_c$ has been proposed for a reaction-diffusion evolution equation as:

$$\mathbf{J}_{ci} = D(c_i)J\mathbf{C}^{-1}.\nabla_R c_i \tag{7}$$

where $D(c_i)$ represents a diffusion coefficient, whose positiveness and monotonicity on c_i ensure the stability of the solution (e.g. shocks for nonlinear diffusive problems). The thermodynamical admissibility of the constitutive laws for both mass and biochemical transport processes is one of the issues to be addressed in this work.

3.2 Balance of mechanical energy

Let Ω_0 be the volume occupied by the continuous body in the reference configuration and let $\partial\Omega_0$ be its boundary. For the sake of simplicity we assume $\partial\Omega_0$ to be twice continuously differentiable

almost everywhere, with outward normal $\mathbf{N}$ and local curvature (possibly having jumps on the e-th edge curve $\partial\partial\Omega_e$). The equilibrium state of the body is provided by the balance of mechanical energy (the kinetic energy theorem):

$$\frac{d}{dt}\int_{\Omega 0} K(t)dV = P_{ext}(t) + P_{int}(t) \tag{8}$$

where $P_{int}(t), P_{ext}(t)$ are the internal and the external rates of mechanical work, respectively. Following Germain (1973), we postulate an expression for the internal mechanical power to deduce the boundary actions on the body. The mechanical powers read as follows:

$$P_{int} = \int_{\Omega 0} p_{int}(t)dV = -\int_{\Omega 0} (\mathbf{T}_f : \dot{\mathbf{F}} + \mathbf{T}_s \vdots \nabla_R \dot{\mathbf{F}})dV \tag{9}$$

$$P_{ext} = \int_{\Omega 0} \mathbf{f}_0.\mathbf{v} + \frac{\rho_0 \Gamma \mathbf{v}^2}{2}dV + \int_{\partial\Omega 0} (\mathbf{t}.\mathbf{v} + \boldsymbol{\tau}_f.\dot{\mathbf{F}}.\mathbf{N} + \mathbf{N}.\mathbf{M}\frac{\mathbf{v}^2}{2})dS + \sum_e \int_{\partial\partial\Omega e} \mathbf{f}_e.\mathbf{v}dl \tag{10}$$

where $\mathbf{f}_0$ are volume forces, and $\mathbf{t}, \boldsymbol{\tau}_f$ are surface traction and surface double forces, respectively, and $\mathbf{f}_e$ are forces acting on the $e-th$ edge of the boundary. In Eq.(9), $\mathbf{T}_f$ is the Piola-Kirchhoff stress tensor and $\mathbf{T}_s$ is the Piola-Kirchhoff hyperstress, the energy conjugates of the first and the second deformation gradients, respectively. Applying the Gauss divergence theorem in Eq.(9), the following expression can be derived:

$$\begin{aligned} P_{int} = \; & \int_{\Omega 0} (\nabla_R.(\mathbf{T}_f - \nabla_{\mathrm{R}}.\, \mathbf{T}_s)\mathbf{v}dV \\ & - \int_{\partial\Omega 0} ([\mathbf{N}.(\mathbf{T}_f - \nabla_{\mathrm{R}}.\, \mathbf{T}_s) + (\nabla^{\mathrm{t}}_{\mathrm{R}}\mathbf{N} : \mathbf{I}_R)\mathbf{N}\otimes\mathbf{N} : \mathbf{T}_s - \nabla^{\mathrm{t}}_{\mathrm{R}}(\mathbf{N}.\mathbf{T}_s) : \mathbf{I}_R].\mathbf{v} \\ & - \mathbf{N}.[(\mathbf{N}\otimes\mathbf{N}) : \mathbf{T}_s].\nabla_R\mathbf{v})dS \end{aligned} \tag{11}$$

where $\nabla^t_R(\cdot) = \nabla_R(\cdot)(\mathbf{I}_R - \mathbf{N}\otimes\mathbf{N})$ is the material tangential gradient, and $\mathbf{I}_R$ is the unit dyadic in reference configuration. From Eqs.(1,4), the time variation of the kinetic energy can be written as:

$$\frac{dK(t)}{dt} = \frac{\dot{\rho_0}}{2}\mathbf{v}^2 + \rho_0\dot{\mathbf{v}}.\mathbf{v} = \frac{\rho_0\Gamma + \nabla_R.\mathbf{M}}{2}\mathbf{v}^2 + \rho_0\dot{\mathbf{v}}.\mathbf{v} \tag{12}$$

Substituting Eqs.(10,11,12) in the mechanical balance of Eq.(8), considering arbitrary velocity fields and exploiting the principle of virtual power, we derive the following balance equation in material form:

$$\frac{d}{dt}(\rho_0\mathbf{v}) = \frac{d\mathbf{p}}{dt} = \mathbf{f}_0 + \Gamma\rho_0\mathbf{v} + \nabla_{\mathrm{R}}.\,(\mathbf{T}_f - \nabla_{\mathrm{R}}.\,\mathbf{T}_s + \mathbf{M}\otimes\mathbf{v}) \tag{13}$$

with the following boundary conditions at the loaded surface:

$$\mathbf{N}.(\mathbf{T}_f - \nabla_{\mathrm{R}}.\ \mathbf{T}_s) + (\nabla^{\mathrm{t}}_{\mathrm{R}}\mathbf{N} : \mathbf{I}_R)\mathbf{N}\otimes\mathbf{N} : \mathbf{T}_s - \nabla^{\mathrm{t}}_{\mathrm{R}}(\mathbf{N}.\mathbf{T}_s) : \mathbf{I}_R = \mathbf{t} \quad \text{on } \partial\Omega_0 \tag{14}$$

$$[(\mathbf{N}\otimes\mathbf{N}) : \mathbf{T}_s] = \boldsymbol{\tau}_f \quad \text{on } \partial\Omega_0 \tag{15}$$

Finally, the following jump conditions must be imposed at the e-th edge:

$$\boldsymbol{\epsilon} : [\![(\mathbf{N}\otimes\mathbf{N}) : \mathbf{T}_s]\!] \otimes \mathbf{e}_{Te} = \mathbf{f}_e \quad \text{on } \partial\partial\Omega_{\mathrm{e}} \tag{16}$$

where $\boldsymbol{\epsilon}$ is the Levi-Civita permutation tensor, $\mathbf{e}_{Te}$ is the unit tangential vector at the $e-th$ edge, and $[\![\cdot]\!]$ indicates the jump across the faces of the edge. As discussed by dell'Isola and Seppecher (1995), only the edges of a gradient material are can account for the effect of the hyperstress in an independent way. A weaker formulation of the principle of virtual power has been proposed to avoid this problem (Lazar and Maugin, 2005).

The spatial form of the motion equation in Eq.(13) can be written using Eq.(5) and the Piola transformations on second and third order tensors:

$$\rho\frac{d\mathbf{v}}{dt} = J^{-1}\mathbf{f}_0 + \nabla.\left(J^{-1}(\mathbf{F}.\mathbf{T}_f + \nabla_R\mathbf{F} : \mathbf{T}_s) + \nabla.\ (J^{-1}\mathbf{T}_s^T : [\mathbf{F}^T, \mathbf{F}^T])\right) + (\mathbf{m}\cdot\nabla)\ \mathbf{v} \tag{17}$$

where all the divergence operators are taken on the left of the tensorial objects, and the product rule for third-order tensors has been defined by $(\mathbb{C} : [A, B])_{ijk} = \mathbb{C}_{i\alpha\beta}A_{\alpha j}B_{\beta k}$.

3.3 Balance of internal energy and entropy inequality

Indicating with ε the internal energy per unit mass and with μ_i a scalar function representing the source of internal energy associated with the $i-th$ solute c_i, the first law of thermodynamics can be expressed as follows:

$$\frac{d}{dt}\int_{\Omega_0}(\rho_0\varepsilon + K)dV = P_{ext}(t) + \int_{\Omega_0}[\Gamma\rho_0\varepsilon + \xi_i c_i\mu_i + r_0]dV + \int_{\partial\Omega_0}\mathbf{N}.(\mathbf{M}\varepsilon + \mu_i\mathbf{J}_{ci} - \mathbf{Q})dS \tag{18}$$

Here r_0 is the external heat supply per unit of volume, $\mathbf{Q}$ is the heat flux, μ_i is minus the chemical potential of the i-th species and represents the increase of internal energy of the continuum by

physical absorption of the diffusing chemicals. Irreversible terms might be accounted in Eq.(18), and a temperature gradient dependence could be included (Forest et al., 2002): nevertheless both effects have been neglected for the sake of simplicity. Substituting Eqs.(4,6,8,9) in the local form of Eq.(18), we obtain the following balance law in local form for the internal energy of a growing second-gradient hyperelastic continuum:

$$\rho_0 \dot{\varepsilon} = \mathbf{T}_f : \dot{\mathbf{F}} + \mathbf{T}_s \vdots \nabla_R \dot{\mathbf{F}} + \mu_i \dot{c}_i - \nabla_{\mathrm{R}} . \mathbf{Q} + r_0 + \mathbf{M} . \nabla_R \varepsilon + \mathbf{J}_{ci} . \nabla_R \mu_i \tag{19}$$

which shows how the internal energy rate, due to mass transport and to biochemical fluxes, is coupled with the second gradient of the deformation.

The entropy inequality in the Clausius-Duhem form can be written as:

$$\frac{d}{dt} \int_{\Omega_0} \rho_0 \eta \, dV \geq \int_{\Omega_0} \left[\Gamma \rho_0 \eta + \eta_i \xi_i \dot{c}_i + \frac{r_0}{\Theta} \right] dV + \int_{\partial \Omega_0} \mathbf{N} . \left[\mathbf{M} \eta + \mathbf{J}_{ci} \eta_i - \frac{\mathbf{Q}}{\Theta} \right] dS \tag{20}$$

where η, η_i are the entropy density per unit mass and per unit of solvent concentration, respectively. The local form of the entropy inequality, substituting Eq.(4) in Eq.(20), reads:

$$\rho_0 \dot{\eta} \ \geq \eta_i \dot{c}_i + \mathbf{M} . \nabla_R \eta + \mathbf{J}_{ci} . \nabla_R \eta_i + \frac{r_0}{\Theta} - \nabla_{\mathrm{R}} . \left(\frac{\mathbf{Q}}{\Theta} \right) \tag{21}$$

Recalling the expression of the Helmholtz free energy per unit of mass, $\Psi = \varepsilon - \Theta \eta$, and per unit of solvent concentration, $\Psi_i = \mu_i - \Theta \eta_i$, we can put together Eqs.(19, 21) in order to obtain an equivalent form of the entropy inequality for a second gradient continuum:

$$\rho_0 (\dot{\Psi} + \dot{\Theta} \eta) \ \leq \mathbf{T}_f : \dot{\mathbf{F}} + \mathbf{T}_s \vdots \nabla_R \dot{\mathbf{F}} + \Psi_i \dot{c}_i + \mathbf{M} \cdot (\nabla_R \Psi + \eta \nabla_R \Theta) + \mathbf{J}_{ci} \cdot (\nabla_R \Psi_i + \eta_i \nabla_R \Theta) - \frac{\mathbf{Q}}{\Theta} \cdot \nabla_R \Theta \tag{22}$$

The latter relation describes the thermodynamical consistency for the energy dissipation inside a growing second gradient hyperelastic continuum, accounting both for mass transport and for the diffusion of the biochemical species.

3.4 Balance of pseudomomentum

We postulate a functional form of the Helmholtz free energy Ψ for a second gradient material as follows:

$$\Psi = \Psi(\mathbf{F}, \nabla_R \mathbf{F}, c_i, \Theta; \mathbf{X}, t) \tag{23}$$

We apply the chain rule on Ψ in the Clausius-Duhem inequality in Eq.(22), following the methodology of Coleman and Noll (1963), and we obtain the following set of constitutive equations for a thermo-elastic continuum:

$$\mathbf{T}_f = \rho_0 \frac{\partial \Psi}{\partial \mathbf{F}} \tag{24}$$

$$\mathbf{T}_s = \rho_0 \frac{\partial \Psi}{\partial (\nabla_R \mathbf{F})} \tag{25}$$

$$\Psi_i = \rho_0 \frac{\partial \Psi}{\partial c_i} \tag{26}$$

$$\eta = -\frac{\partial \Psi}{\partial \Theta} \tag{27}$$

Note that the third order tensor $\mathbf{T}_s$ inherits the symmetry properties of $\nabla_R \mathbf{F}$, expressed in index terms as $(\mathbf{T}_s)_k^{IJ} \equiv (\mathbf{T}_s)_k^{JI}$. With such constitutive identifications, the Clausius-Duhem inequality reduces to:

$$\mathbf{M} \cdot (\nabla_R \Psi + \eta \nabla_R \Theta) + \mathbf{J}_{ci} \cdot (\nabla_R \Psi_i + \eta_i \nabla_R \Theta) - \rho_0 \frac{\partial \Psi}{\partial t}|_{expl} - \frac{\mathbf{Q}}{\Theta} \cdot \nabla_R \Theta \geq 0 \tag{28}$$

where the explicit derivative over time accounts for possible dissipation due to ageing phenomena (Maugin, 2009). The canonical projection of the linear momentum in the material setting yields the balance of the pseudomomentum. Let us perform a right-multiplication of Eq.(13) times .$\mathbf{F}$, as follows:

$$\frac{d}{dt}(\rho_0 \mathbf{v}).\mathbf{F} = -\frac{d\mathbf{P}_m}{dt} - \rho_0 \mathbf{v}.\dot{\mathbf{F}} = \mathbf{f}_0.\mathbf{F} - \Gamma \mathbf{P}_m + \nabla_{\mathrm{R}}.(\mathbf{T} + \mathbf{M} \otimes \mathbf{v}) \ .\mathbf{F} \tag{29}$$

where $\mathbf{T} = \mathbf{T}_f - \nabla_{\mathrm{R}}.\mathbf{T}_s$. Recalling the following identities:

$$\nabla_{\mathrm{R}}. \ (\mathbf{M} \otimes \mathbf{v}) = \nabla_R \mathbf{v} \ .\mathbf{M} + \mathbf{v}(\nabla_{\mathrm{R}}.\mathbf{M}) \tag{30}$$

$$(\nabla_{\mathrm{R}}. \ \mathbf{T}) \ .\mathbf{F} = \nabla_{\mathrm{R}}. \ (\mathbf{T}.\mathbf{F}) - \mathbf{T} : (\nabla_R \mathbf{F}) \tag{31}$$

we can substitute Eqs.(30, 31) in Eq.(29), and the following relation holds:

$$\frac{d\mathbf{P}_m}{dt} = -\mathbf{f}_0.\mathbf{F} + \Gamma\mathbf{P}_m - \nabla_{\mathrm{R}}.\ (\mathbf{T}.\mathbf{F}) + \mathbf{T} : (\nabla_R\mathbf{F}) - \nabla_R\mathbf{v}\ \mathbf{M}.\mathbf{F} + \frac{\mathbf{P}_m}{\rho_0}\nabla_{\mathrm{R}}.\mathbf{M} - \rho_0\mathbf{v}.\dot{\mathbf{F}} \tag{32}$$

Substituting Eq.(4) in the latter, we find the equivalent form:

$$\frac{d\mathbf{P}_m}{dt} = -\mathbf{f}_0.\mathbf{F} + \frac{\dot{\rho_0}}{\rho_0}\mathbf{P}_m - \nabla_{\mathrm{R}}.\ (\mathbf{T}.\mathbf{F}) + \mathbf{T} : (\nabla_R\mathbf{F}) - (\nabla_R\mathbf{v}.\mathbf{M}).\mathbf{F} - \rho_0\mathbf{v}.\dot{\mathbf{F}} \tag{33}$$

Eq.(33) represents the canonical balance of pseudomomentum density in the material framework. Using the constitutive assumptions in Eqs.(23-27), the following identities hold:

$$\mathbf{T}_f : (\nabla_R\mathbf{F}) = \nabla_{\mathrm{R}}.\ (\rho_0\Psi\mathbf{I}_R) - \mathbf{T}_s \vdots (\nabla_R\nabla_R\mathbf{F}) - \frac{\partial(\rho\Psi)}{\partial\mathbf{X}}|_{expl} - \mu_i\nabla_R c_i + \eta\nabla_R\Theta \tag{34}$$

$$\rho_0\mathbf{v}.\dot{\mathbf{F}} = \nabla_{\mathrm{R}}.\ (K\mathbf{I}_R) - \frac{\partial K}{\partial\mathbf{X}}|_{expl} = \nabla_R.K - \frac{1}{2}\mathbf{v}^2(\nabla_R.\rho_0) \tag{35}$$

$$-(\nabla_{\mathrm{R}}.\ \mathbf{T}_s) : (\nabla_R\mathbf{F}) - \mathbf{T}_s \vdots (\nabla_R\nabla_R\mathbf{F}) = -\nabla_{\mathrm{R}}.\ (\mathbf{T}_s : (\nabla_R\mathbf{F})) \tag{36}$$

Substituting Eqs.(34, 35, 36) in Eq.(33), we obtain the canonical balance of pseudomomentum for a growing material in gradient hyperelasticity:

$$\frac{d\mathbf{P}_m}{dt} = \mathbf{f}^{ext} + \mathbf{f}^{g} + \mathbf{f}^{inh} + \mathbf{f}^{c} + \mathbf{f}^{\Theta} + \nabla_{\mathrm{R}}.\ \mathbf{b} \tag{37}$$

The conservation of the pseudo-momentum in eq.(37) states that there are five sources of material inhomogeneities: the convection of the body forces in $\mathbf{f}^{ext}$, the volumetric growth and the mass transport in $\mathbf{f}^{g}$, the true material inhomogeneities in $\mathbf{f}^{inh}$, the internal variables in $\mathbf{f}^{c}$, and the temperature in $\mathbf{f}^{\Theta}$. They are defined as:

$$\begin{cases} \mathbf{f}^{ext} = -\mathbf{f}_0.\mathbf{F} \\ \mathbf{f}^{g} = \frac{\dot{\rho_0}}{\rho_0}\mathbf{P}_m - (\nabla_R\mathbf{v}.\mathbf{M})\ .\mathbf{F} \\ \mathbf{f}^{inh} = \frac{\partial(K-\rho_0\Psi)}{\partial\mathbf{X}}|_{expl} \\ \mathbf{f}^{c} = -\mu_i\nabla_R c_i \\ \mathbf{f}^{\Theta} = \rho_0\eta\nabla_R\Theta \end{cases} \tag{38}$$

Accordingly, the Eshelby tensor in a second gradient material reads:

$$\mathbf{b} = -[(K - \rho_0\Psi)\mathbf{I}_R + \mathbf{T}.\mathbf{F} + \mathbf{T}_s : \nabla_R\mathbf{F}] \tag{39}$$

Eq.(37) states that the Eshelby stress tensor $\mathbf{b}$, defined in Eq.(39), is the stress measure that drives the evolution of material inhomogeneities. Two components can be devised in $\mathbf{b}$ as:

$$\mathbf{b} = -(K - \rho_0\Psi)\mathbf{I}_R - \mathbf{T}_f.\mathbf{F} - 2\mathbf{T}_s : (\nabla_R\mathbf{F}) + \nabla_{\mathrm{R}}.(\mathbf{T}_s.\mathbf{F}) = \mathbf{b}_f + \nabla_{\mathrm{R}}.\mathbf{b}_s \tag{40}$$

where it has been used the relation $\nabla_{\mathrm{R}}.(\mathbf{T}_s\mathbf{F}) = (\nabla_{\mathrm{R}}.\mathbf{T}_s) + \mathbf{T}_s : (\nabla_R\mathbf{F})$. Such an expression of the Eshelby stress can be found in Epstein (1999): the decomposition into a first gradient component $\mathbf{b}_f$ and an Eshelby hyperstress $\mathbf{b}_s$ will be useful in the description of material evolution laws.

Finally, frame indifference of the Helmholtz free energy in Eqs.(24, 25) must hold for arbitrary rotations of the actual configuration (Kirchner and Steinmann, 2007). This condition can be written as:

$$\mathbf{F}.\mathbf{T}_f + \nabla_R\ \mathbf{F} : \mathbf{T}_s = (\mathbf{F}.\mathbf{T}_f + \nabla_R\ \mathbf{F} : \mathbf{T}_s)^T \tag{41}$$

stating that the generalized first gradient Cauchy stress in Eq.(17) must be a symmetric tensor.

4 A second gradient theory for volumetric growth and material remodeling

The aim of this section is to define the constitutive aspects of a morphoelastic theory of volumetric growth and material remodeling for second gradient continua, accounting for the effects of mass transport inside the body.

4.1 Definition of a second order material isomorphism

As discussed in the previous sections, the extension of the growth theory to second order continua is necessary to include the driving force in the theory of internal mass transport. In a second gradient theory, it is necessary to consider second-order equivalence classes, also known as 2-jets, at each material point. In practice, each point of the body in the reference configuration is linked

to an intermediate grown state by means of a first order transplant (linear map of the tangent spaces) of second-order tensorial components $\mathbf{F}_g$, and a second order transplant of third-order tensorial components $\mathbf{Q}_g$, as schematically shown in Figure 1.

We generalize the form of the strain energy function introduced in Eq.(23), introducing a second

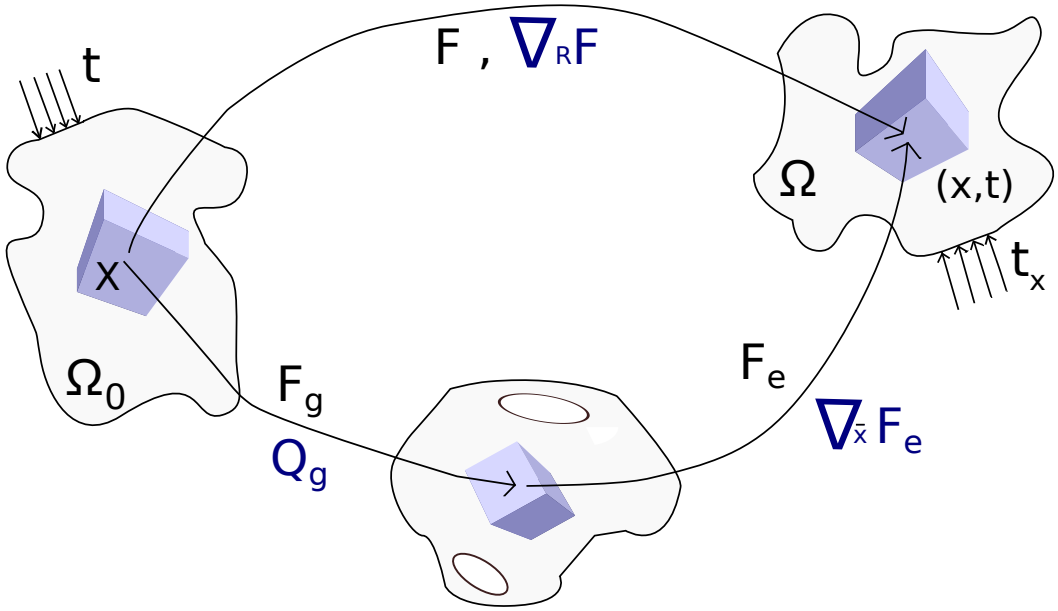

Figure 1: Illustration of the material isomorphism involving the first-order transplant $\mathbf{F}_g$ and the second-order transplant $\mathbf{Q}_g$ in the intermediate grown state.

order material isomorphism for Ψ. This is a natural extension to growing gradient continua of the first-order multiplicative decomposition of the deformation gradient:

$$\Psi(\mathbf{F}, \nabla_R\mathbf{F}, \mathbf{F}_g(\mathbf{X}), \mathbf{Q}_g(\mathbf{X}), c_i, \Theta) = (det\mathbf{F}_g) \cdot \Psi_0(\mathbf{F}_e, \mathbf{Q}_e, c_i, \Theta) \tag{42}$$

where no explicit dependence of the free energy on time is included. The proposed material isomorphism can be seen as a symmetry group of the strain energy Ψ, so that the terms $\mathbf{F}_e, \mathbf{Q}_e$ in Eq.(42) transform according to the following composition laws for first and second derivatives:

$$\begin{cases} \mathbf{F}_e = \mathbf{F}.\mathbf{F}_g^{-1} \\ \mathbf{Q}_e = \nabla_R\mathbf{F} : [\mathbf{F}_g^{-1}, \mathbf{F}_g^{-1}] - \mathbf{F}_e.\mathbf{Q}_g : [\mathbf{F}_g^{-1}, \mathbf{F}_g^{-1}] \end{cases} \tag{43}$$

Note that, for the symmetry properties of $\nabla_R\mathbf{F}$, the material isomorphism requires that $(\mathbf{Q}_g)_{iJK} = (\mathbf{Q}_g)_{iKJ}$, representing the local deformation gradient imposed by growth.

We remark that $\mathbf{Q}_g$ is a measure of the differential deformation of the local grown state, and it is independent on the material gradient of $\mathbf{F}_g$, because the intermediate state is not a configuration, and a growth map cannot be defined.

It is useful to compare the proposed material isomorphism to the transformation law reported in Epstein and Maugin (2000). They consider an implant $(\mathbf{K}, \mathbf{Q}_k)$ from the archetype in the intermediate state to the material point $\mathbf{X}$, so that their corresponding transformation law (indicated with $\circ$) reads:

$$(\mathbf{F}, \nabla_R \mathbf{F}) \circ (\mathbf{K}, \mathbf{Q}_k) := (\mathbf{F}\mathbf{K}, \mathbf{F}\mathbf{Q}_k + \nabla_R \mathbf{F} : [\mathbf{K}, \mathbf{K}]) \tag{44}$$

Such a composition law has a unit element, it is associative and it has a unique inverse operator defined as:

$$(\mathbf{K}, \mathbf{Q}_k)^{-1} := (\mathbf{K}^{-1}, -\mathbf{K}^{-1}.\mathbf{Q}_k : [\mathbf{K}^{-1}, \mathbf{K}^{-1}]) \tag{45}$$

Recalling that we have defined an implant from the material point to the intermediate grown configuration, we can check that setting $(\mathbf{F}_g, \mathbf{Q}_g) := (\mathbf{K}, \mathbf{Q}_k)^{-1}$ we find that the proposed material isomorphism corresponds to the same transformation law.

Finally, it might be useful to note that if $\mathbf{Q}_g = \nabla_R \mathbf{F}_g$ (i.e. growth can be described by a smooth differentiable mapping), the transformation law for second derivatives is $\mathbf{Q}_e = \nabla_R \mathbf{F}_e.\mathbf{F}_g^{-1}$, which represents in this case the gradient of $\mathbf{F}_e$ with respect to the intermediate configuration. In mechanical terms, a second gradient growth theory considers both the effects of volumetric growth, through $\mathbf{F}_g$, and of density gradients generated by elastic deformation, through the dependence on $\mathbf{Q}_g$. In fact, we can consider that the material in the intermediate grown state has a constant density ρ_g, so that the material density can be expressed as $\rho_0 = \rho_g \ (det\mathbf{F}_g) = \rho_g \ J$. A isochoric elastic deformation, expressed by $\mathbf{F}_e$, will not change the spatial density, given by $\rho = \rho_g \ (det\mathbf{F}_e)^{-1} = \rho_g$, but will determine a spatial density gradient in the second order transplant, as follows:

$$\nabla_{\bar{X}} \rho = -\mathbf{F}_e^{-1} : \mathbf{Q}_e \tag{46}$$

Giving a simple geometrical interpretation, a first-gradient growth theory only includes the torsional effects of the material connection, while a second order transplant allows to account

for the curvature-dependent evolution of the material inhomogeneities, which are involved in mass diffusion processes.

Finally, a second-order material isomorphism can be used to define a constitutive equation for the mass transport:

$$\mathbf{M}(\mathbf{F}, \nabla_R \mathbf{F}, c_i, \Theta; \mathbf{X}) = (det\mathbf{F}_g)\ \mathbf{F}_g^{-1}.\mathbf{M}_0(\mathbf{F}_e, \mathbf{Q}_e, c_i, \Theta) \tag{47}$$

Eqs.(42, 47) represent the two material isomorphisms for the second gradient free energy of the continuum and the mass transport phenomena, respectively.

4.2 Thermodynamical compatibility in isothermal conditions

Let us consider the Clausius-Duhem inequality for a second gradient material, as expressed in Eq.(21), in the case of isothermal processes:

$$\rho_0 \dot{\Psi} \leq \mathbf{T}_f : \dot{\mathbf{F}} + \mathbf{T}_s \ \vdots\ \nabla_R \dot{\mathbf{F}} + \Psi_i \dot{c}_i + \mathbf{M}.\nabla_R \Psi + \mathbf{J}_{ci}.\nabla_{\mathrm{R}} \Psi_{ci} \tag{48}$$

Using the constitutive relation in Eq.(42) and the tensorial transformation rules in Eq.(43), we can develop the terms involved in Eq.(48) as follows:

$$\dot{\Psi} = J\Psi_0 \mathbf{F}_g^{-1} : \dot{\mathbf{F}}_g + J\frac{\partial \Psi_0}{\partial \mathbf{F}_e} : \dot{\mathbf{F}}_e + J\frac{\partial \Psi_0}{\partial \mathbf{Q}_e} \vdots \dot{\mathbf{Q}}_e + J\frac{\partial \Psi_0}{\partial c_i} \cdot \dot{c}_i \tag{49}$$

$$\mathbf{T}_f : \dot{\mathbf{F}} = \mathbf{T}_f : (\dot{\mathbf{F}}_e \mathbf{F}_g + \mathbf{F}_e \dot{\mathbf{F}}_g) = \mathbf{F}_g.\mathbf{T}_f : \dot{\mathbf{F}}_e + \mathbf{T}_f.\mathbf{F}_e : \dot{\mathbf{F}}_g \tag{50}$$

$$\nabla_R \dot{\mathbf{F}} = \dot{\mathbf{Q}}_e : [\mathbf{F}_g, \mathbf{F}_g] + \mathbf{Q}_e : [\dot{\mathbf{F}}_g, \mathbf{F}_g] + \mathbf{Q}_e : [\mathbf{F}_g, \dot{\mathbf{F}}_g] + \dot{\mathbf{F}}_e.\mathbf{Q}_g + \mathbf{F}_e.\dot{\mathbf{Q}}_g \tag{51}$$

$$\begin{aligned} \mathbf{T}_s \vdots \nabla_R \dot{\mathbf{F}} = \ & \left(\mathbf{T}_s{}^T : [\mathbf{F}_g^T, \mathbf{F}_g^T]\right)^T \vdots \dot{\mathbf{Q}}_e + 2\left(\mathbf{T}_s{}^T : [\mathbf{F}_g^T, \mathbf{F}_g^T]\right)^T : (\mathbf{Q}_e) : (\dot{\mathbf{F}}_g.\mathbf{F}_g^{-1}) + \\ & + \mathbf{T}_s.\mathbf{F}_e \vdots \dot{\mathbf{Q}}_g + [\mathbf{Q}_g : \mathbf{T}_s] : \dot{\mathbf{F}}_e \end{aligned} \tag{52}$$

Substituting the terms in Eqs.(49,50,52) inside the inequality expressed by Eq.(48), we obtain the following simplified form:

$$\begin{aligned}\left(\Psi_i - J\rho_0\frac{\partial\Psi_0}{\partial c_i}\right)\dot{c}_i + \left(\mathbf{Q}_g : \mathbf{T}_s + \mathbf{F}_g.\mathbf{T}_f - J\rho_0\frac{\partial\Psi_0}{\partial\mathbf{F}_e}\right) : \dot{\mathbf{F}}_e + \\ + \left(\left({\mathbf{T}_s}^T : [\mathbf{F}_g^T, \mathbf{F}_g^T]\right)^T - J\rho_0\frac{\partial\Psi_0}{\partial\mathbf{Q}_e}\right) \vdots \dot{\mathbf{Q}}_e + \\ + \left(\mathbf{F}_g.\mathbf{T}_f.\mathbf{F}_e + 2\left({\mathbf{T}_s}^T : [\mathbf{F}_g^T, \mathbf{F}_g^T]\right)^T : \mathbf{Q}_e - J\rho_0\Psi_0\mathbf{I}_{\bar{R}}\right) : (\dot{\mathbf{F}}_g\mathbf{F}_g^{-1})) + \\ + \mathbf{M}.\nabla_R\Psi + \mathbf{J}_{ci}.\nabla_X\Psi_i + \mathbf{T}_s.\mathbf{F}_e \vdots \dot{\mathbf{Q}}_g \geq 0\end{aligned} \tag{53}$$

As the inequality in Eq.(53) must be satisfied by any motion, the following set of constitutive equations for the second gradient material is given:

$$\Psi_i = J\rho_0\frac{\partial\Psi_0}{\partial c_i} \tag{54}$$

$$\left({\mathbf{T}_s}^T : [\mathbf{F}_g^T, \mathbf{F}_g^T]\right)^T = J\rho_0\frac{\partial\Psi_0}{\partial\mathbf{Q}}_e \tag{55}$$

$$\mathbf{Q}_g : \mathbf{T}_s + \mathbf{F}_g.\mathbf{T}_f = J\rho_0\frac{\partial\Psi_0}{\partial\mathbf{F}_e} \tag{56}$$

while Eq.(53) reduces to the following dissipation inequality:

$$\begin{aligned}\left(\mathbf{F}_g.\mathbf{T}_f.\mathbf{F}_e + 2\left({\mathbf{T}_s}^T : [\mathbf{F}_g^T, \mathbf{F}_g^T]\right)^T : \mathbf{Q}_e - J\rho_0\Psi_0\mathbf{I}_{\bar{R}}\right) : (\dot{\mathbf{F}}_g\mathbf{F}_g^{-1}) \\ + \mathbf{M}.\nabla_R\Psi + \mathbf{J}_{ci}.\nabla_X\Psi_i + \mathbf{T}_s.\mathbf{F}_e \vdots \dot{\mathbf{Q}}_g \geq 0\end{aligned} \tag{57}$$

Eq.(57) describes the conditions for the thermodynamical compatibility of the growth and the remodeling processes for a second-gradient continuum.

At this point, it is useful to derive the explicit gradient of the free energy for a second gradient body, which is part of the driving force of true material inhomogeneities in $\mathbf{f}_{inh}$ defined in Eq.(38):

$$\frac{\partial\Psi}{\partial\mathbf{X}}|_{expl} = \frac{\partial\Psi}{\partial\mathbf{F}_g} : \nabla_R\mathbf{F}_g + \frac{\partial\Psi}{\partial\mathbf{Q}_g} \vdots \nabla_R\mathbf{Q}_g \tag{58}$$

Recalling the constitutive equations in Eqs.(54, 55, 56), the following relations hold:

$$\rho_0\frac{\partial\Psi}{\partial\mathbf{F}_g} = -\mathbf{F}_g^{-1}\left[-J\rho_0\Psi_0\mathbf{I}_{\bar{R}} + J\rho_0\frac{\partial\Psi_0}{\partial\mathbf{F}_e}.\mathbf{F}_e + 2J\rho_0\frac{\partial\Psi_0}{\partial\mathbf{Q}_e} : \mathbf{Q}_e - \mathbf{Q}_g : \mathbf{T}_s.\mathbf{F}_e\right] \tag{59}$$

$$\rho_0\frac{\partial\Psi}{\partial\mathbf{Q}_g} = -\mathbf{T}_s.\mathbf{F}_e \tag{60}$$

Using the previous relations to build a geometrical meaningful expression, Eq.(58) can be rewritten in a new simplified form as a function of the material Eshelby tensors, as follows:

$$-\rho_0 \frac{\partial \Psi}{\partial \mathbf{X}}|_{expl} = [\mathbf{b}_f + \mathbf{\Lambda} : \mathbf{b}_s] : \mathbf{\Gamma} + \mathbf{b}_s . \mathbf{F}_g^{-1} \vdots \nabla_R \mathbf{Q}_g = \mathbf{b}_f : \mathbf{\Gamma} + \mathbf{b}_s \vdots \nabla_R \ \mathbf{\Lambda} \tag{61}$$

In Eq.(61) we introduced the symbols of the first-order (generally not symmetric) material connection $\mathbf{\Gamma}$, and of the symmetric second-order linear connection $\mathbf{\Lambda}$, defined as:

$$(\mathbf{\Gamma})^I_{JK} = (\mathbf{F}_g)^\alpha_J . (\mathbf{F}_g^{-1})^I_{\alpha,K}; \qquad (\mathbf{\Lambda})^I_{JK} = (\mathbf{F}_g^{-1})^I_\alpha . (\mathbf{Q}_g)^\alpha_{JK} \tag{62}$$

In this novel form, the expression of the driving force in Eq.(61) reflects the decomposition of the effects due to the torsion and the curvature of the material connections in the evolution of true material inhomogeneities. The difference between the two geometrical connections in Eq.(62) is also known as the second-gradient inhomogeneity tensor, as proposed by deLeon and Epstein (1993), giving a local measure of the material homogeneity.

4.3 Admissible constitutive models for mass transport and chemical diffusion

Let us consider the problem to define a suitable constitutive definition of the mass flux $\mathbf{M}$ in a second gradient continuum. The thermodynamical compatibility would suggest to restrict to dissipative models for mass transport and chemical diffusion that satisfy the following inequality:

$$\mathbf{M} . \nabla_R \Psi + \mathbf{J}_{ci} . \nabla_R \Psi_{ci} \geq 0 \tag{63}$$

where the material gradient $\nabla_R \Psi$ can be expressed in isothermal conditions as follows:

$$\nabla_R \Psi = \frac{\partial \Psi}{\partial \mathbf{X}}|_{expl} + \frac{\partial \Psi}{\partial c_i} . \nabla_R c_i + \rho_0^{-1} \left(\mathbf{T}_f : (\nabla_R \mathbf{F}) + \mathbf{T}_s \vdots \nabla_R \nabla_R \mathbf{F} \right) \tag{64}$$

In Eq.(64) the explicit material gradient must be expressed through the second order connection based on $\mathbf{F}_g$ and $\mathbf{Q}_g$, following the same procedure used in Eq.(61).

A dissipative constitutive equation for $\mathbf{M}$ can be expressed in function of the inverse velocity $\mathbf{V}$ in the following form:

$$\mathbf{M} = K^+(c_i, \Theta)(\mathbf{V} . \nabla_R \Psi)\mathbf{V} \tag{65}$$

where $K^+(c_i, \Theta)$ is a positive definite scalar function, which, in a general chemotactic model, may depend both on the temperature and on the concentration c_i of the chemical species, directly driving the diffusive mass transfer. It is useful to notice that:

$$\mathbf{v} \otimes \mathbf{m} = (-\mathbf{F}.\mathbf{V}) \otimes J^{-1}K^+(c)(\mathbf{V} \cdot \nabla_R \Psi)\mathbf{F}.\mathbf{V} = \mathbf{m} \otimes \mathbf{v} \tag{66}$$

implying the equilibrium of the angular momentum generated by the mass transport defined in Eq.(65) with a symmetric of first order Cauchy stress. In this sense, the proposed dissipative evolution law for $\mathbf{M}$ can be seen as a single phase extension of the continuum treatment of a multiphase growing material proposed by Garikipati et al. (2004).

If we consider a mass transport driven by the diffusion of a specific chemical species c_M, a more suitable formulation can be proposed. Recalling the expression for the chemical potential in Eq.(54), a proper constitutive equation for the mass flux can be defined as:

$$\mathbf{M} = -\left[(\mathbf{V}.\nabla_R \Psi)^{-1} \frac{\partial \Psi_0}{\partial c_M} \mathbf{J}_{cM}.\nabla_R(J\rho_0)\right] \mathbf{V} \tag{67}$$

where the energy dissipation due to the mass transport is modeled only by the internal variable c_M. From the inequality in Eq.(63), a thermodynamically admissible form of the chemical flux is:

$$\mathbf{J}_{cM} = \frac{\partial^2 \Psi_0}{\partial c_M^2} \nabla_R c_M.\mathbb{K}_c^+(\mathbf{F}, \nabla_R \mathbf{F}) \tag{68}$$

where $\mathbb{K}_c^+(\mathbf{F}, \nabla_R \mathbf{F})$ is a positive definite chemical mobility tensor, which may depend on the thermodynamical state of the continuum. Eq.(68) is a well known constitutive model for solvent migration in polymers (Hong et al., 2008), and can include curvature effects in a second order continuum model.

Finally, in the limit of quasi-static elastic deformations ($\mathbf{v} \sim 0$), a static version of Eq.(67) is obtained, imposing the following constitutive equation for the mass transport:

$$\mathbf{M} = -\left[(\mathbf{J}_{cM}.\nabla_R \Psi)^{-1} \frac{\partial \Psi_0}{\partial c_M} \mathbf{J}_{cM}.\nabla_R(J\rho_0)\right] \mathbf{J}_{cM} \tag{69}$$

Recalling the dissipative behavior for the diffusing internal variable c_M in Eq.(68), the static constitutive relation in Eq.(69) represents a purely chemotactic behavior for a given chemical

diffusivity inside the body.

4.4 Remodeling theory: first and second gradient material evolution laws

The remodeling theory for a gradient continuum deals with the definition of the evolution laws for both $\mathbf{F}_g$ and $\mathbf{Q}_g$, describing the first and the second gradient inhomogeneities, respectively. Substituting the constitutive relation for the stress, Eqs.(55, 56), into the dissipation inequality expressed in Eq.(57), we obtain the following simplified expression:

$$\begin{gathered}\left(J\rho_0\frac{\partial\Psi_0}{\partial\mathbf{F}_e}.\mathbf{F}_e+2J\rho_0\frac{\partial\Psi_0}{\partial\mathbf{Q}_e}:\mathbf{Q}_e-J\rho_0\Psi_0\mathbf{I}_{\bar{R}}-\mathbf{Q}_g:\mathbf{T}_s.\mathbf{F}_e\right):\mathbf{L}_g+\\+\dot{\mathbf{Q}}_g\vdots\mathbf{T}_s.\mathbf{F}_e\geq 0\end{gathered}\tag{70}$$

where $\mathbf{L}_g=\dot{\mathbf{F}}_g.\mathbf{F}_g^{-1}$ represents the velocity gradient of the first-order inhomogeneities in the growing continuum, and we omit for notation compactness the transport terms. In analogy with Eq.(40), we can define the following first-order Eshelbian operator:

$$\mathbf{b}_f(\psi)=\psi(\mathbf{F}_e,\nabla_R\mathbf{F}_e)\mathbf{I}_{\bar{R}}-\frac{\partial\psi}{\partial\mathbf{F}_e}.\mathbf{F}_e-\left(2\frac{\partial\psi}{\partial\mathbf{Q}_e}:\mathbf{Q}_e\right)\tag{71}$$

so that the dissipation inequality can be written as:

$$-\mathbf{b}_f(\Psi):\mathbf{L}_g+(\dot{\mathbf{Q}}_g-\mathbf{L}_g.\mathbf{Q}_g)\vdots\mathbf{T}_s.\mathbf{F}_e\geq 0\tag{72}$$

Similarly to Eqs.(41), the frame indifference for the material isomorphism in Eq.(42) imposes that $\boldsymbol{b}_f(\Psi)$ is a symmetric tensor (Svendsen et al., 2009). For a growing isotropic continuum, material frame indifference suggest the following admissible form of first-order evolution law:

$$\mathbf{L}_g=-f^+(c_i,\Theta)\rho_0\mathbf{b}_f(\Psi)\tag{73}$$

where $f^+(c_i,\Theta)$ is a positive definite scalar function, whose expression represents a specific temperature-dependent (e.g. Arrhenius-based relations) chemical kinetics driving first-order mass remodeling. The first-order evolution law in Eq.(73) is a second order generalization of the results obtained for inelastic continua, as the first order Eshelby tensor in the intermediate state

is the symmetric stress conjugate of the growth velocity gradient (Maugin, 1994; Svendsen, 2001). Moreover, the symmetry of the driving force expressed by $\mathbf{b}_f(\Psi)$ is a necessary requirement, as pointed out by Skalak et al. (1982), as the symmetric part of $\mathbf{F}_g$ is the only shape-changing deformation in growth. The proposed first-order evolution equation contains a second-order correction to the remodeling laws proposed in biomechanical literature (Di Carlo and Quiligotti, 2002; Ambrosi and Guana, 2007; Taber, 2009).

Recalling the definition of the second-order material connection $\mathbf{\Lambda}$ in Eq.(62), the following identity holds:

$$\dot{\mathbf{\Lambda}}(\mathbf{F}_g, \mathbf{Q}_g, \dot{\mathbf{F}}_g) = \mathbf{F}_g^{-1}.\dot{\mathbf{Q}}_g - \mathbf{F}_g^{-1}.\mathbf{L}_g.\mathbf{Q}_g \tag{74}$$

From Eq.(72), a suggestive form for the evolution of second-order inhomogeneities can be written as follows:

$$\dot{\mathbf{\Lambda}}(\mathbf{F}_g, \mathbf{Q}_g, \mathbf{b}_f) = g^+(c_i, \Theta)(\mathbf{T}_s.\mathbf{F})^T = g^+(c_i, \Theta)(\mathbf{b}_s)^T \tag{75}$$

where $g^+(c_i, \Theta)$ is a positive definite scalar function, and $\mathbf{b}_s$ is the material second-order Eshelby tensor, which is found to be the thermodynamical driving of second-order mass inhomogeneities. In order to investigate whether such a second-order constitutive law fulfils the principle of material covariance (Elzanowski and Epstein, 1992; Epstein and Elzanowski, 2007), let us consider the tensorial transformation law of the couple $\{\mathbf{F}_g, \mathbf{Q}_g\}$ upon a change of reference configuration defined by the mapping λ:

$$\mathbf{F}_g^* = \mathbf{F}_g \ .(\nabla_R \lambda) \tag{76}$$

$$\mathbf{Q}_g^* = \mathbf{F}_g \ .(\nabla_R \nabla_R \lambda) \ + \mathbf{Q}_g : [(\nabla_R \lambda), (\nabla_R \lambda)] \tag{77}$$

The time derivation of Eq.(77) gives the temporal change of the second gradient, as follows:

$$\dot{\mathbf{Q}}_g^* = \dot{\mathbf{Q}}_g : [(\nabla_R \lambda), (\nabla_R \lambda)] + \dot{\mathbf{F}}_g.(\nabla_R \nabla_R \lambda) \tag{78}$$

From Eq.(78), the most general evolution law for the second gradient inhomogeneities for an isotropic continuum is of the following kind:

$$\dot{\mathbf{Q}}_g^* = \mathcal{Q}(\mathbf{F}_g, \mathbf{Q}_g, \dot{\mathbf{F}}_g) = \mathcal{Q}(\mathbf{F}_g, \mathbf{Q}_g, \mathbf{b}_f, \mathbf{b}_s) \tag{79}$$

where we have considered an evolution of the first gradient inhomogeneities as described by Eq.(73). A suitable evolution law for the second gradient requires that the third order tensor $\mathcal{Q}$ be independent on the choice of the reference configuration. If we make a change in the reference frame so that $\nabla_R \lambda = \mathbf{F}_g^{-1}$ (the reference configuration corresponds to the grown intermediate state), Eq.(78) takes on the following expression:

$$\dot{\mathbf{Q}}_g^* = \mathcal{Q}(\mathbf{I}, \mathbb{O}, \mathbf{b}) = \dot{\mathbf{Q}}_g : [{\mathbf{F}_g}^{-1}, {\mathbf{F}_g}^{-1}] - \dot{\mathbf{F}}_g.{\mathbf{F}_g}^{-1}.\mathbf{Q}_g : [{\mathbf{F}_g}^{-1}, {\mathbf{F}_g}^{-1}] \tag{80}$$

where $\mathbb{O}$ is the zero third order tensor, and we used the tensorial transformation for the inverse of a second order tensor (i.e. $\mathbf{Q}_g^{-1} = -\mathbf{F}_g^{-1}.(\mathbf{Q}_g) : [\mathbf{F}_g^{-1}, \mathbf{F}_g^{-1}]$). The most general law for the time evolution of $\mathbf{Q}_g$, from Eq.(75,80), takes the following form:

$$\dot{\mathbf{Q}}_g - \mathbf{L}_g.\mathbf{Q}_g = \mathcal{Q}(\mathbf{I}, \mathbb{O}, \mathbf{b}) : [\mathbf{F}_g, \mathbf{F}_g] = \mathbf{F}_g.\dot{\mathbf{\Lambda}} = g^+(c_i, \Theta)\mathbf{F}_g.(\mathbf{b}_s)^T \tag{81}$$

which states that the second-order evolution law is invariant with respect to arbitrary changes of the reference configuration.

Summarizing, our findings demonstrate that the first- and second-order Eshelby tensors are the driving stresses for first- and second-order material inhomogeneity, respectively. Material remodeling can evolve according to the two separate evolution laws in Eqs.(73, 75), that can be rewritten as:

$$\dot{\mathbf{F}}_g = -f^+(c_i, \Theta)\rho_0 \cdot \mathbf{b}_f(\Psi).(\mathbf{F}_g)^{-1} \tag{82}$$

$$\dot{\mathbf{Q}}_g = -f^+(c_i, \Theta)\rho_0 \cdot \mathbf{b}_f(\Psi).\mathbf{Q}_g + g^+(c_i, \Theta)\mathbf{F}_g.(\mathbf{b}_s)^T \tag{83}$$

If we choose a non-evolving second-order gradient (i.e. $\mathcal{Q}(\mathbf{I}, \mathbb{O}, \mathbf{b}) = g^+(c_i, \Theta) = 0$), the second-order transplant passively follows the time evolution of the first-order transplant, and we find the classical evolution law for a material with a Toupin type symmetry (Epstein, 1999).

5 Application of the proposed theory to biomechanical problems

In this section we apply the proposed constitutive theory to model the effects of an Eshelbian coupling on volumetric growth and mass transport in two biomechanical examples. First, we consider the avascular development of a ductal carcinoma, illustrating how both mechanotransduction and spatial limitation of nutrient diffusion can inhibit growth. Secondly, we apply the proposed evolution equations for material inhomogeneities to analyze the remodeling laws driving homeostasis in blood vessels, both in healthy and in pathological conditions.

5.1 Early development of ductal carcinoma: an example of stress-inhibited growth in confined geometry

The ductal carcinoma in situ represents the initial growth phase of breast cancer. Originated from a malignant transformation of epithelial cells, the growing tumor at this stage is non-invasive, thanks to the spatial confinement due to the basement membrane of the duct glands. In fact, the carcinoma expands inside the lumen of the breast duct, having a diameter in the range of 0.2-0.5 mm, which is filled with extracellular liquid. On the outer surface, the growing mass is surrounded by the basement membrane of the duct wall, which is permeable to biochemical factors but forms a protective mechanical barrier between the tumor and the outer healthy stroma. Compared to previous modeling efforts (Franks et al., 2003, 2005), here the aim is to model the early development using the proposed Eshelbian coupling between volumetric growth and nutrient diffusion, which is considered the growth source for the avascular tumor. For matters of simplicity, we make the hypothesis that the duct walls are rigid and no adhesion mechanism exists between the tumor cells and the basement membrane, so that the carcinoma can be modeled as a cylindric mass, which can freely expand along the longitudinal axis of the duct. Considering that the nutrients are supplied through the lateral boundaries, by diffusion mechanisms from the surrounding stroma through the basement membrane, we can assume the

following expression for the growth tensor:

$$\mathbf{F}_g = \frac{\partial g(R,t)}{\partial R}\mathbf{e}_{ri} \otimes \mathbf{e}_R + \frac{g(R,t)}{R}\mathbf{e}_{\theta i} \otimes \mathbf{e}_\Theta + \mathbf{e}_{zi} \otimes \mathbf{e}_Z \tag{84}$$

where the subscript i denote vectors in the intermediate grown configuration, which is generally incompatible with the geometrical confinement of the duct wall. By means of Eq.(84), we describe a time-dependent radial growth function $g(R,t)$, leading to a local volume variation expressed by $J(R,t) = det\mathbf{F}_g$. The elastic tensor $\mathbf{F}_e$ represents the isochoric deformation which restores compatibility at the outer radius R_o of the tumor; in particular, it keeps in contact the tumor with the duct wall, and avoids singularity in the deformation along the axis of the cylinder:

$$\mathbf{F}_e = \left(\frac{g(R_o,t)}{R_o}\right)^{-1}\mathbf{e}_r \otimes \mathbf{e}_{ri} + \left(\frac{g(R_o,t)}{R_o}\right)^{-1}\mathbf{e}_\theta \otimes \mathbf{e}_{\theta i} + \left(\frac{g(R_o,t)}{R_o}\right)^{2}\mathbf{e}_z \otimes \mathbf{e}_{zi} \tag{85}$$

where $\frac{g(R_o,t)^2}{2} = \int_0^{Ro} J(R,t)R \cdot dR$ for overall compatibility. Eq.(85) represents a homogeneous tensor, so that $\nabla_R\mathbf{F}_e = \mathbf{F}_e.\nabla_R\mathbf{F}_g$. For matters of simplicity we assume $\mathbf{Q}_g = 0$ and independent on time, and we deal only with first gradient components in the definition of the stress measures. In terms of constitutive behavior, we assume a simple neo-Hookean strain energy function associated with the incompressible elastic deformation. The free energy of the tumor mass can be decomposed into the sum of the elastic contribution and the free chemical energy $\Psi_n(n)$ due to the nutrient absorption:

$$\Psi(\mathbf{F}_g, \mathbf{F}_e, n) = J(R,t) \cdot \Psi_0(\mathbf{F}_e, n) = J(R,t) \cdot \{c_1(\mathbf{F}_e : \mathbf{I} - 3) + p(det\mathbf{F}_e - 1) - \Psi_n(n)\} \tag{86}$$

The quantity p is the Lagrange multiplier which takes into account the local incompressibility of $\mathbf{F}_e$, and it can be evaluated by imposing stress-free condition in the z direction. Using the constitutive relations in Eq.(56), the Cauchy stress is given by:

$$\boldsymbol{\sigma} = 2c_1\rho_0(R,t)\mathbf{F}_e\mathbf{F}_e^T - p\mathbf{I} = 2c_1\rho_0(R,t)\left[\mathbf{F}_e\mathbf{F}_e^T - \left(\frac{g(R_o,t)}{R_o}\right)^4\mathbf{I}\right] \tag{87}$$

where $\sigma_{rr} = \sigma_{\theta\theta} = 2c_1\rho_0(R,t) \cdot \left[\left(\frac{g(R_o,t)}{R_o}\right)^{-2} - \left(\frac{g(R_o,t)}{R_o}\right)^4\right]$. When considering the equilibrium condition $\nabla.(\boldsymbol{\sigma} + \mathbf{v} \otimes \mathbf{m}) = 0$, we obtain that $\left[\left(\frac{g(R_o,t)}{R_o}\right)^{-2} - \left(\frac{g(R_o,t)}{R_o}\right)^4\right]\nabla_R(\rho_0(R,t)) + \nabla.(\mathbf{v} \otimes$

$\mathbf{m}) = 0$. Making the hypothesis that the growth process occurs in a quasi-static manner ($\mathbf{v} \sim 0$), and recalling that $\rho_0(R,t) = \rho_g J(R,t)$, an equilibrated configuration can be achieved if:

$$\nabla_R \rho_0(R,t) = \rho_0(R,t)\mathbf{F}_g : \nabla_R \mathbf{F}_g = 0 \tag{88}$$

In biomechanical terms, a slow growth process is forced to evolve in order to make the strain energy function homogeneous: a condition that we take as a definition of homeostasis. As a matter of fact, the mass diffusivity of tumor cells is about $10^{-10}\mathrm{m}^2\mathrm{s}^{-1}$ (Byrne and Chaplain, 1995), which, for a characteristic lengthscale of order 10^{-1}mm, gives a diffusive time-scale of minutes, much smaller than the characteristic growth time (days-weeks). An inhomogeneous volumetric growth therefore generate a diffusive mass flow inside the material, that rapidly restores a homogeneous distribution of the material density in the growth time-scale.

In order to describe the stress-driven regulations in the growth characteristics of the ductal carcinoma, we propose an Eshelbian coupling between the volumetric growth rate within tumor and the diffusion of the supplying nutrients, as discussed in Eq.(73). In particular, we choose in Eq.(6) the following form for the nutrient consumption:

$$\xi(\mathbf{F}, \nabla_R \mathbf{F}) = -\Sigma_0(\dot{J}/J)\mathbf{I} : \mathbf{L}_g = \begin{cases} -n(R,t)\gamma_n \mathbf{I} : \mathbf{L_g} & \mathbf{I} : \mathbf{L}_g > 0 \\ 0 & \mathbf{I} : \mathbf{L}_g \leq 0 \end{cases} \tag{89}$$

According to Eq.(89), nutrients are continuously supplied at duct wall ($n(R_o,t) = n_{ext}$), and they are absorbed within the tumor, giving rise to volumetric growth ($\xi < 0$ if $\mathbf{I} : \mathbf{L}_g = \dot{J}/J > 0$) with a rate proportional to their local concentration. From Eq.(71), the Eshelbian stress measure which drives local inhomogeneities can be expressed as:

$$\mathbf{b}_f = J(R,t) \cdot \left[\psi \mathbf{I}_{\bar{R}} - 2c_1 \left(\mathbf{F}_e^T \mathbf{F}_e - \left(\frac{g(R_o,t)}{R_o} \right)^4 \mathbf{I}_{\bar{R}} \right) \right] \tag{90}$$

so that $(b_f)_{RR} = (b_f)_{\Theta\Theta} = 3c_1 J(R,t) \cdot \left[\left(\frac{g(R_o,t)}{R_o} \right)^4 - 1 \right]$. Recalling the compatibility of nutrient diffusion in Eq.(7, 68), the remodeling law in Eq.(73), and the constitutive law in Eq.(54), the coupling of growth rate and internal stress within the tumor is given by the following equations:

$$\frac{\dot{J}(R,t)}{J(R,t)} = \rho_0 K_p \cdot \left\{ \Psi_n(R,t) - 3c_1 \cdot \left[\left(\frac{g(R_o,t)}{R_o} \right)^4 - 1 \right] \right\} \tag{91}$$

$$\dot{n}(R,t) = D_n \left(\frac{g(R_o,t)}{R_o}\right)^2 \nabla_R \cdot \left(\frac{g^2(R,t)}{J \cdot R^2} \nabla_R n(R,t)\right) - \Sigma_0(\dot{J}/J, n(R,t)) \tag{92}$$

where K_p,D_n are positive definite material constants, that define the rate of volumetric growth (in general we can assume different rates for tumor cell mitosis and apoptosis, represented by K_p and K_d) and the diffusion coefficient of the nutrients, respectively. Taking glucose as the main nutrient in the avascular phase, a simple expression for the chemical free energy is given by $\Psi_n = \Psi_g \cdot n(R,t)/\rho_g$, where Ψ_g represents the free energy resulting from the glycolysis reaction converting a molecule of glucose to pyruvate and two ATPs (Garrett and Grisham (2005) measured physiological values of Ψ_g/ρ_g=$4 \cdot 10^5$ J Kg^{-1}).

If the characteristic time of nutrient diffusion is much smaller than the characteristic time of growth (approximation of very small tumor, with $\gamma_n << 1$), the level of nutrient is n_{ext} everywhere, and the tumor grows homogeneously, with $g(R,t) = g_0(t) \cdot R$. The growth rate is simply given by the expression in Eq.(91), simplified as:

$$\dot{g}_0(t) = \frac{g_0(t)\rho_g K_p}{2} \cdot \left\{ \frac{\Psi_g n_{ext}}{\rho_g} - 3c_1 \cdot \left[g_0(t)^4 - 1\right] \right\} \tag{93}$$

which, taking the initial condition $g_0(0) = 1$, can be integrated:

$$g_0(t) = \frac{\left(1 + \frac{\Psi_g \cdot n_{ext}}{3c_1\rho_g}\right)^{\frac{1}{4}} \cdot Exp\left[\frac{3}{2}c_1\rho_g K_p \left(1 + \frac{\Psi_g \cdot n_{ext}}{3c_1\rho_g}\right) \cdot t\right]}{\left(\frac{\Psi_g \cdot n_{ext}}{3c_1\rho_g} + Exp\left[6c_1\rho_g K_p \left(1 + \frac{\Psi_g \cdot n_{ext}}{3c_1\rho_g}\right) \cdot t\right]\right)^{\frac{1}{4}}} \tag{94}$$

Eq.(94) points out stress inhibition on growth, through the existence of a limiting value $g_{max} = \sqrt[4]{1 + \frac{\Psi_g \cdot n_{ext}}{3c_1\rho_g}}$. This effect is more evident approximating the Eq.(94) with its Taylor expansion on $\frac{\Psi_g \cdot n_{ext}}{3c_1\rho_g}$, which at first order gives:

$$g_0(t) = 1 + \frac{\Psi_g \cdot n_{ext}}{12c_1\rho_g} \left\{1 - Exp\left[-2c_1\rho_g K_p \cdot t\right]\right\} \tag{95}$$

The evolution law of the stress-inhibited growth function, predicted by Eq.(94), is shown in Figure 2 for different values of the elastic modulus. Compared to the experimental data reported by Helmlinger et al. (1997)(Fig.1 therein), our theoretical predictions give a remarkably faithful description of the stress-inhibition in the growth kinetics of multicellular spheroids. In particular,

we find that an increase of the elasticity modulus implies a decrease both of the maximum volume increase and of the characteristic growth time, all curves having the same initial kinetics.

In the case of bigger tumors, the duct diameter is large enough that the characteristic time-

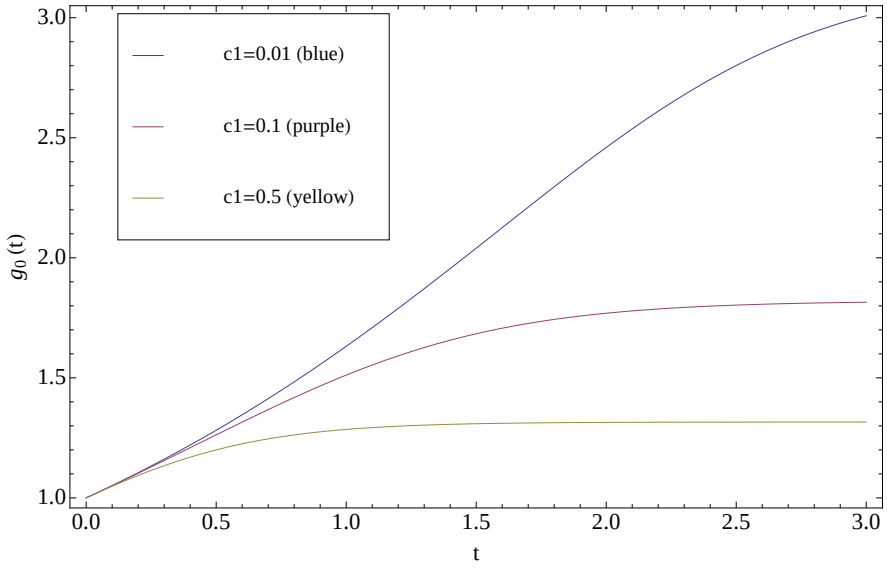

Figure 2: Plot of the homogeneous growth function $g_0(t)$ over time t,from Eq.(94), shown for several values of elastic coefficient c_1 (all the other material coefficients are set equal to one).

scales of growth and diffusion are of the same order. According to Eqs.(91,92), an inhibition effect of growth arises from spatially limited nutrient diffusion inside tumor from the boundary. Let us rewrite the two equations in dimensionless form:

$$\tilde{\dot{J}}/J = \tilde{A}\tilde{n}(\tilde{R},\tilde{t}) - \left[\left(\frac{g(R_o,t)}{R_o}\right)^4 - 1\right] \tag{96}$$

$$\dot{\tilde{n}}(\tilde{R},\tilde{t}) = \left(\frac{g(R_o,t)}{R_o}\right)^2 \tilde{\nabla}_R \cdot \left(\frac{g^2(R,t)}{J\cdot R^2}\tilde{\nabla}_R\tilde{n}(\tilde{R},\tilde{t})\right) - \gamma_n\tilde{n}(\tilde{R},\tilde{t})\cdot\tilde{\dot{J}}/J \tag{97}$$

where $\tilde{t} = t/\tau_c, \tilde{R} = R/R_c, \tilde{n} = n/n_{ext}$ are dimensionless variables, and:

$$\tau_c = \frac{1}{3c_1\rho_0 K_p}; \qquad R_c = \sqrt{D_n\tau_c}; \qquad \tilde{A} = \frac{\Psi_g\cdot n_{ext}}{3c_1\rho_0} \tag{98}$$

From experimental measurements, the elastic modulus for a tumor aggregate is $c_1\rho_g$= 6 KPa (Suresh, 2007), the diffusion coefficient of glucose is D_g= 4.22 10^{-11} m^2 s^{-1}, and the cell doubling

time τ_c ranges between (in vitro) 14-28 hours and (in-situ) 20 days (Narayanan et al., 2010). From the reported data, we derive that a characteristic length is given by $\sqrt{\tau_c \cdot D_n}$= 1.4 mm (in vitro) - 8 mm (in situ), to be compared versus the radius of the carcinoma, which is in the the range of 0.2 (healthy)-5 (pathological) mm. A stationary solution (corresponding to no volumetric growth rate in Eq.(96), i.e. $g_0^4 = 1 + \tilde{A}$) occurs when a steady state where the maximum amount of chemical free energy has been transformed into volumetric growth under thermodynamical consistency. The transient time depends both on the nutrient uptake rate γ_n and on the tumor size; the material parameter γ_n given by the ratio between the uptake rate of the glucose (which in the general case is linked to oxygen concentration, cellular density and the pH of the matter, as measured by Casciari et al. (2005)) and the volumetric growth rate. Finally, as nutrients decay from the border to the core of the carcinoma, from Eq.(96) we expect that in bigger tumors the growth rate localizes at the external annulus, while a mass transport of interstitial fluid from the borders will act to restore a homogeneous mass density inside the necrotic core. Such a consideration is in accordance with the histological observations in clinical studies, where the increase in the size of the growing carcinoma determines the presence of a large necrotic core surrounded by an annulus of very proliferative cells in contact with the duct wall. The different evolution of the solid and liquid components inside the carcinoma is out of reach for the proposed model, and can be treated considering a multiphase body in a mixture theory (Ciarletta et al., 2011).

5.2 Remodeling laws in blood vessels: formation and dissipation of material inhomogeneities

5.2.1 Second gradient solution of the nonlinear hyperelastic problem

In this section we consider the classical problems of the stress-driven growth and the genesis of residual strains in blood vessels. In terms of continuum mechanics this problem concerns the determination of thermodynamically-consistent remodeling laws for an incompatible grown state. We focus on long vessels with negligible axial pre-stretch, so that we can assume a

plane state of deformation. Because of the symmetry of the problem, the growth and elastic deformation tensors can be expressed in the most general form as follows:

$$\mathbf{F}_g = \frac{\partial g(R,t)}{\partial R}\mathbf{e}_{\bar{r}} \otimes \mathbf{e}_R + g_\theta(t)\frac{g(R,t)}{R}\mathbf{e}_{\bar{\theta}} \otimes \mathbf{e}_\Theta \tag{99}$$

$$\mathbf{F}_e = \sqrt{g_\theta(t)}\frac{\sqrt{r^2(R,t) - A(t)}}{r(R,t)}\mathbf{e}_r \otimes \mathbf{e}_{\bar{r}} + \frac{1}{\sqrt{g_\theta(t)}}\frac{r(R,t)}{\sqrt{r^2(R,t) - A(t)}}\mathbf{e}_\theta \otimes \mathbf{e}_{\bar{\theta}} \tag{100}$$

where the upper-barred unit vectors apply in the intermediate state (incompatible when $g_\theta \neq 1$), and $A(t)$ represents the purely elastic part of the deformation which allows to fulfill the boundary conditions with the given growth state. The dependence in time of g_θ and A is characterized by quite different time scales: while growth occurs with long characteristic time t_g, the elastic response related to A is related both on t_g (implicitly, by g_θ) and on the characteristic fast time t_l of the external load (i.e. the blood pulse), and $t_l << t_g$. Considering that the typical viscoelastic relaxation time for soft tissues is about 100 s, the elastic variable A can be considered as made of a fast oscillation on t_l, and of a slow-varying average value $< \mathrm{A} >$, calculated on the characteristic time t_g.

Defining the elastic Cauchy-Green tensor $\mathbf{E}_e = 1/2(\mathbf{F}_e^T\mathbf{F}_e - \mathbf{I})$, arguments of material objectivity suggest the following constitutive assumption for the blood vessel:

$$\Psi(\mathbf{F}, \nabla_R\mathbf{F}) = det\mathbf{F}_g \cdot \Psi_0(\mathbf{E}_e, \nabla_{\bar{R}}\mathbf{E}_e) \tag{101}$$

where:

$$\Psi_0(\mathbf{E}_e, \nabla_{\bar{R}}\mathbf{E}_e) = c_1 \cdot \mathbf{E}_e : \mathbf{I} + (\nabla_{\bar{R}}\mathbf{E}_e)^T \vdots \mathbb{H} \vdots \nabla_{\bar{R}}\mathbf{E}_e - p \cdot (\mathrm{det}\mathbf{F}_\mathrm{e} - 1) \tag{102}$$

where c_1 is the neo-Hookean elastic modulus, p is the incompressibility constraint, and $\mathbb{H}$ is the sixth-order second-gradient elasticity tensor. Defining the second Piola-Kirchhoff hyperstress $\mathbf{S}_s$ as follows:

$$\mathbf{S}_s = \frac{\partial \Psi_0}{\partial \nabla_{\bar{R}}\mathbf{E}_e} = \frac{\partial \Psi_0}{\partial \mathbf{Q}_e}.\mathbf{F}_e^{-T} \tag{103}$$

and recalling that $(\mathbf{S}_s)_{KIj} = (\mathbf{S}_s)_{KJi}$, from Eq.(101) the second gradient constitutive equation can be written as:

$$\begin{pmatrix} (\mathbf{S}_s)_{\bar{r}\bar{r}r} \\ (\mathbf{S}_s)_{\bar{r}\bar{\theta}\theta} \\ (\mathbf{S}_s)_{\bar{\theta}\bar{\theta}r} \end{pmatrix} = \begin{pmatrix} 4k_1 + k_2 + 4k_3 + 2k_4 + 4k_5 & 2k_1 + 4k_3 & 2k_1 + k_2 \\ 2k_1 + 4k_3 & 4(k_3 + k_4 + k_5) & 2k_1 + 4k_5 \\ 2k_1 + k_2 & 2k_1 + 4k_5 & k_2 + 2k_4 \end{pmatrix} \cdot \begin{pmatrix} (\nabla_{\bar{R}}\mathbf{E}_e)_{r\bar{r}\bar{r}} \\ (\nabla_{\bar{R}}\mathbf{E}_e)_{\theta\bar{\theta}\bar{r}} \\ (\nabla_{\bar{R}}\mathbf{E}_e)_{r\bar{\theta}\bar{\theta}} \end{pmatrix} \tag{104}$$

where $k_n (n = 1, .., 5)$ are the five material parameters needed to model the second gradient dependence of the non-linear isotropic mechanical response of the tissue (dell'Isola et al., 2009). Recalling the constitutive relations defined in Eqs.(55, 56), the Cauchy stress tensor $\boldsymbol{\sigma}_f$ and hyperstress tensor $\boldsymbol{\sigma}_s$ can be written as:

$$\boldsymbol{\sigma}_s = J^{-1}(\mathbf{T}_s)^T : [\mathbf{F}^T, \mathbf{F}^T] \tag{105}$$

$$\boldsymbol{\sigma}_f = J^{-1}(\mathbf{F}.\mathbf{T}_f + \nabla_R\mathbf{F} : \mathbf{T}_s) \tag{106}$$

Neglecting the body forces and the inertial terms in Eq.(17), the equilibrium equation is given as follows:

$$\nabla_{\mathrm{r}} \cdot \boldsymbol{\sigma}^* = \nabla_{\mathrm{r}} \cdot (\boldsymbol{\sigma}_f - \nabla_{\mathrm{r}} \cdot \boldsymbol{\sigma}_s) = -\mathbf{v} \cdot \nabla_{\mathrm{r}}\mathbf{m} \simeq 0 \tag{107}$$

where $\boldsymbol{\sigma}_f$ is a symmetric tensor from Eq.(41). The boundary conditions for the stress and hyperstress at the outer $(r = r_o)$ and inner $(r = r_i)$ surface read:

$$(\boldsymbol{\sigma}_f - \nabla_{\mathrm{r}} \cdot \boldsymbol{\sigma}_s) \cdot \mathbf{e}_r + Ł(\boldsymbol{\sigma}_s\mathbf{e}_r) = \begin{cases} 0 & \text{at} \quad r = r_o \\ -p_i & \text{at} \quad r = r_i \end{cases} \tag{108}$$

$$(\mathbf{e}_r \otimes \mathbf{e}_r) : \boldsymbol{\sigma}_s = (\nabla^{\mathrm{t}}_{\mathrm{r}}\mathbf{e}_r : \mathbf{I}_L)^{-1} \cdot \nabla^{\mathrm{t}}_{\mathrm{r}}(\mathbf{e}_r.\boldsymbol{\sigma}_s) : \mathbf{I}_L = 0 \quad \text{at} \quad \mathrm{r} = \mathrm{r_o}, \mathrm{r_i} \tag{109}$$

where $\nabla^t_r(\cdot) = \nabla_r(\cdot)(\mathbf{I}_L - \mathbf{e}_r \otimes \mathbf{e}_r)$ is the spatial tangential gradient, $\mathbf{I}_L$ is the spatial unit dyadic, and we introduced the spatial operator $Ł(\cdot) = (\nabla^{\mathrm{t}}_{\mathrm{r}}\mathbf{e}_r : \mathbf{I}_L)(\mathbf{e}_r \otimes \mathbf{e}_r) : (\cdot) - \nabla^{\mathrm{t}}_{\mathrm{r}}(\mathbf{e}_r.(\cdot)) : \mathbf{I}_L$. The meaning of the boundary condition in Eq.(109) stems by the observation that, using the surface divergence theorem, over a closed surface $\oint Ł(\boldsymbol{\sigma}_s\mathbf{e}_r)rd\theta = 0$. Therefore, a vanishing hyperstress term on the r.h.s. of Eq.(109) means a zero energy release due to variations of the reference

material position for a fixed spatial configuration. Finally, the plane strain assumption allows us to simplify the governing equilibrium equation as follows:

$$\frac{\partial \sigma^*_{rr}}{\partial r} + \frac{\sigma^*_{rr} - \sigma^*_{\theta\theta}}{r} = 0 \tag{110}$$

Considering the boundary conditions in Eqs.(108, 109), the solution is formally given by:

$$\sigma^*_{rr}(r) = -\int_r^{r_o} \frac{\sigma^*_{\theta\theta} - \sigma^*_{rr}}{r} \mathrm{dr} \tag{111}$$

$$p_i = \int_{r_i}^{r_o} \frac{\sigma^*_{\theta\theta} - \sigma^*_{rr}}{r} \mathrm{dr} \tag{112}$$

In general, the boundary condition at the inner surface doesn't involve the Lagrange multiplier p, so it can be used to derive the elastic deformation $A(t)$ as a function of the growth parameters $g_\theta, g(R,t)$ and of the initial dimensions R_i and R_o.

Starting from the solution given by Eqs.(111, 112), we will consider in the following two possible remodeling laws for the formation and the dissipation of residual strains in healthy and pathological conditions, respectively.

5.2.2 Remodeling towards homeostasis: formation laws of residual strains in arteries

The formation of residual strains in arteries is a process occurring at the early stages of their development. In this section, we introduce a simple evolution law of material inhomogeneities that takes into account the coupling between growth and pressure inside the vessel. As emphasized by Humphrey and Wilson (2003), the local production of growth factors inside the vessel is driven by the local response of smooth cells receptors, which are circumferentially oriented within the tissue wall. While it is still physiologically unclear if the feedback mechanism is stress- or strain-driven, the homeostatic state in physiological arteries seems to correspond to a homogeneous deformation inside the tissue (Ogden, 2003). As discussed in the previous example, the equilibrium condition given by Eq.(107) imposes that a generally inhomogeneous volumetric growth process must be regulated by some internal regulatory mechanisms in order to achieve

a homogeneous deformation inside the vessel. In terms of our continuum treatment, on the basis of the relations in Eqs.(34, 58), we can consider that the remodeling processes rearrange the material inhomogeneities in order to create a physical state where $\nabla_R \Psi = 0$ everywhere. From Eqs.(99,100) this situation corresponds to a steady state solution at time-scale t_r given by: $g(R,t) = g_r(t_r) \cdot R$, $< \mathrm{A} > (\mathrm{t_r}) = 0$.

For matters of simplicity, we assume slow and homogeneous remodeling and growth processes ($det\mathbf{F}_g = J = g_\theta(t) \cdot g_r^2(t)$, with $[\dot{g}_\theta(t), \dot{g}_r(t)] << \dot{p}_i$), and we set the initial conditions $g_\theta(0) = g_r(0) = 1$. In this case, the non-zero components of the second gradient tensor of the deformation are the following:

$$(\nabla_R \mathbf{F})_{rRR} = \frac{AJ}{(A + JR^2)^{3/2}} \tag{113}$$

$$(\nabla_R \mathbf{F})_{r\Theta\Theta} = (\nabla_R \mathbf{F})_{\theta R\Theta} = (\nabla_R \mathbf{F})_{\theta\Theta R} = -\frac{A}{R^2(A + JR^2)^{1/2}} \tag{114}$$

In order to evaluate the contribution of the second order terms to the elastic response, let us recall that the material coefficients k_i in Eq.(104) contain an internal length-scale l, that can be expressed as $l = \sqrt{k_i/c_1}$ according to Mindlin (1965). In terms of strain energy contributions, if $l << R_o$ the second gradient terms from Eq.(114) can be neglected compared to the first order elastic deformation. In this case, using the constitutive assumptions in Eq.(101, 102), the boundary condition in Eq.(112) can be rewritten as:

$$\frac{p_i}{2c_1} = \frac{g_\theta J}{2} \cdot \frac{R_o^2 - R_i^2}{(JR_o^2 + A)(JR_i^2 + A)} \cdot A - \frac{g_\theta}{2} \cdot ln\left(\frac{JR_o^2 + A}{JR_i^2 + A}\right) + \frac{1}{g_\theta} ln\left(\frac{R_o}{R_i}\right) + O(\boldsymbol{\sigma}_s) \tag{115}$$

where p_i can be considered as the physiological average value inside the blood vessel, and we neglige the direct dependence of the Cauchy hyperstress in $O(\boldsymbol{\sigma}_s)$. Under these assumptions, a remodeling law for the material growth velocity is therefore independent on the second gradient transplant, whose evolution, in turn, will only drive changes on mass diffusivity properties. Keeping this separation in mind, and knowing that volumetric growth (given by $\dot{J}/J = \dot{\mathbf{F}}_g \mathbf{F}_g^{-1} : \mathbf{I}$) happens at the very early development, we can consider that the remodeling processes have a longer characteristic time, imposing at the time scale t_r that $\dot{J}/J = 2\dot{g}_r/g_r + \dot{g}_\theta/g_\theta \sim 0$. Making

the time derivative of the slow variables in Eq.(115) at this characteristic time-scale t_r, we obtain that:

$$\left[\frac{p_i}{2c_1} - \frac{2}{g_\theta} ln\left(\frac{R_o}{R_i}\right)\right] \cdot \frac{\dot{g}_\theta}{g_\theta} = -\dot{A} \cdot \left(\frac{g_\theta \cdot (R_o^2 - R_i^2) \cdot (2R_o^2 R_i^2 + A(R_o^2 + R_i^2))}{2(JR_o^2 + A)^2 (JR_i^2 + A)^2}\right) \tag{116}$$

The term in square bracket in Eq.(116) is negative at the initial time, and we look for a steady homeostatic solution ($\nabla_R \mathbf{F}) = 0$ in Eqs.(113, 114), so that a system of coupled evolution laws for the remodeling processes can be imposed as follows:

$$\frac{\dot{g}_\theta}{g_\theta} = -K^+ \cdot A = -2\frac{\dot{g}_r}{g_r} \tag{117}$$

which, from Eq.(116), drives the evolution of the deformation inside the blood vessel as:

$$\frac{\dot{A}}{A} = K^+ \frac{2(JR_o^2 + A)^2 (JR_i^2 + A)^2 \left[\frac{p_i}{2c_1} - \frac{2}{g_\theta} ln\left(\frac{R_o}{R_i}\right)\right]}{g_\theta \cdot (R_o^2 - R_i^2) \cdot (2R_o^2 R_i^2 + A(R_o^2 + R_i^2))} \leq 0 \tag{118}$$

The remodeling process described in Eqs.(117) forces the evolution of the material inhomogeneities towards a homeostatic steady state configuration where $A(t_r) = 0$, and $g_\theta(t_r)$ can be determined from Eq.(115) as:

$$\frac{p_i}{2c_1} = \left(\frac{1}{g_\theta(t_r)} - g_\theta(t_r)\right) ln\left(\frac{R_o}{R_i}\right) \tag{119}$$

The remodeling process creates an incompatible grown state ($g_\theta(t_r) < 1$), that originates the formation of residual strain within the blood vessel (residual compression at the inner surface and residual tension at the outer), so that the tissue has a non-zero strain energy function for $\mathbf{F}_e = \mathbf{I}$. Moreover, it has been shown that a bifurcation of the elastic equilibrium can occur for a threshold value of $g_\theta(t_r)$ in thick vessels (Destrade et al., 2010).

During the creation of a residually-stressed configuration, the remodeling processes consume energy inside the tissue, so they must be driven by a local strain energy source Ψ_s in order to evolve. The dissipation inequality in Eq.(72) provides an estimate of the minimum value of local strain energy source Ψ_s compatible with thermodynamical requirements:

$$-\left(\frac{\dot{g}_\theta}{g_\theta} + \frac{\dot{g}_r}{g_r}\right) \cdot (\mathbf{b}_f)_{\bar{\Theta}\bar{\Theta}} - \frac{\dot{g}_r}{g_r} \cdot (\mathbf{b}_f)_{\bar{R}\bar{R}} + \Psi_s \geq 0 \tag{120}$$

Putting together the evolution laws for remodeling in Eq.(117) with the constitutive assumptions in Eqs.(71,101,102), the previous inequality can be transformed into the following:

$$\Psi_s \geq \frac{K^+ A}{2} \cdot [(\mathbf{b}_f)_{\bar{R}\bar{R}} - (\mathbf{b}_f)_{\bar{\Theta}\bar{\Theta}}] = \frac{c_1 K^+ A \cdot ((JR^2 + A)^2 - g_\theta^2 J^2 R^4)}{g_\theta R^2 (JR^2 + A)} \geq 0 \tag{121}$$

The previous dissipation inequality states that the remodeling processes can evolve if and only if the local driving forces of the material inhomogeneities are above a minimum threshold intensity dictated by the local Eshelbian coupling.

5.2.3 Dissipation of residual strains: evolution laws for aneurysms

While in the previous paragraph we studied the thermodynamical evolution of an healthy artery towards an homeostatic condition, in this section we focus on the remodeling laws in pathological conditions, such as the typical case of aneurysm formation in arteries. The loss of the homeostatic state can be linked both to the degradation of elastin or collagen fibers, and to an abnormal regulation of the feedback mechanisms controlling tissue remodeling. In the following we will consider the two hypothesis separately, formulating simple constitutive models for energy dissipation.

As discussed in the previous paragraph, at the beginning of the remodeling processes, which possibly may lead to aneurysm formation, the artery undergoes a homogenous deformation expressed as:

$$\mathbf{F}_e = \sqrt{g_\theta(0)}\mathbf{e}_r \otimes \mathbf{e}_{\bar{r}} + \frac{1}{\sqrt{g_\theta(0)}}\mathbf{e}_\theta \otimes \mathbf{e}_{\bar{\theta}} \tag{122}$$

The only non-zero components of the second gradient of the deformation are:

$$(\nabla_{\bar{r}}\mathbf{F}_e)_{r\bar{\theta}\bar{\theta}} = (\nabla_{\bar{r}}\mathbf{F}_e)_{\theta\bar{r}\bar{\theta}} = \frac{g_\theta(0) - 1}{\sqrt{J(0)}R} \tag{123}$$

from which we recall how second gradient effects in stress become more relevant for small vessels (i.e. capillaries). The Eshelby stress given by Eq.(71) can be rewritten, using the constitutive assumptions in Eqs.(102, 103), as follows:

$$\mathbf{b}_f(\psi) = J \cdot \left(\psi_0(\mathbf{F}_e, \mathbf{Q}_e)\mathbf{I}_{\bar{R}} - 2c_1 \mathbf{F}_e^T.\mathbf{F}_e + p\mathbf{I}_{\bar{R}} - 2\mathbf{S}_s.\mathbf{F}_e^T : \mathbf{Q}_e\right) \tag{124}$$

If we deal with large arteries, e.g. the abdominal ascending aorta (internal diameter about 36 mm), we can neglect second order terms in Eq.(124), so that the dissipation inequality in Eq.(72) can be rewritten as:

$$-\rho_0 J \cdot \left(\psi_0 \mathbf{I}_{\bar{R}} - 2c_1 \mathbf{F}_e^T.\mathbf{F}_e + p\mathbf{I}_{\bar{R}}\right) : \mathbf{L}_g + \mathbf{b}_s \vdots \dot{\mathbf{\Lambda}} \geq 0 \tag{125}$$

In the previous equation, further developments can be written as follows:

$$\left(\psi_0 \mathbf{I}_{\bar{R}} - 2c_1 \mathbf{F}_e^T.\mathbf{F}_e + p\mathbf{I}_{\bar{R}}\right) : \mathbf{L}_g = -\left(\frac{\dot{g}_\theta}{g_\theta} + \frac{\dot{g}_r}{g_r}\right) \cdot (\Psi_0 - (\boldsymbol{\sigma}_f)_{\theta\theta}) - \frac{\dot{g}_r}{g_r} \cdot (\Psi_0 - (\boldsymbol{\sigma}_f)_{rr}) \tag{126}$$

$$\mathbf{b}_s = \rho_0 J(\mathbf{S}_s.\mathbf{F}_e^T : [\mathbf{F}_g^{-T}, \mathbf{F}_g^{-T}]).\mathbf{F} \tag{127}$$

Recalling the elastic solution in Eq.(111), the term $(\boldsymbol{\sigma}_f)_{rr}$ in Eq.(126) is always negative, so a possible remodeling law for arterial aneurysms is given by:

$$\frac{\dot{g}_\theta}{g_\theta} = -\frac{\dot{g}_r}{g_r} = 1/t_c \tag{128}$$

where t_c is a positive definite material constant, representing the characteristic time of volume absorption (note that $\dot{J}/J = -1/t_c$). A numerical solution of the remodeling law expressed by Eq.(128) is depicted in Figure 3, where the initial homogeneous solution evolves with an exponential increase of the outer and inner radii under a constant internal pressure.

If we focus on the possibility that material remodeling is governed by an abnormal regulation of the homeostatic mechanisms (driven, for example, by a long-term persistence of blood hypertension), we can impose that the inhomogeneities evolve at constant volume, so that:

$$\frac{\dot{g}_\theta}{g_\theta} + 2\frac{\dot{g}_r}{g_r} = 0 \tag{129}$$

In this scenario, the first term of the dissipation inequality in Eq.(125) can be written as:

$$\left(\frac{\dot{g}_r}{g_r}\right) \cdot [(\boldsymbol{\sigma}_f)_{rr} - (\boldsymbol{\sigma}_f)_{\theta\theta}] = -\left(\frac{\dot{g}_r}{g_r}\right) \cdot \left[\frac{2c_1 \cdot ((JR^2 + A)^2 - g_\theta^2 J^2 R^4)}{g_\theta R^2 (JR^2 + A)}\right] \geq 0 \tag{130}$$

Considering that the term between square bracket is always positive for $A > 0$ and $g_\theta < 1$, a simple remodeling law in this range of values can be written as $\dot{g}_\theta/g_\theta = -2\dot{g}_r/g_r = 1/t_{rm}$. The numerical solution for this evolution law is depicted in Figure 4; in this case t_{rm} is a characteristic

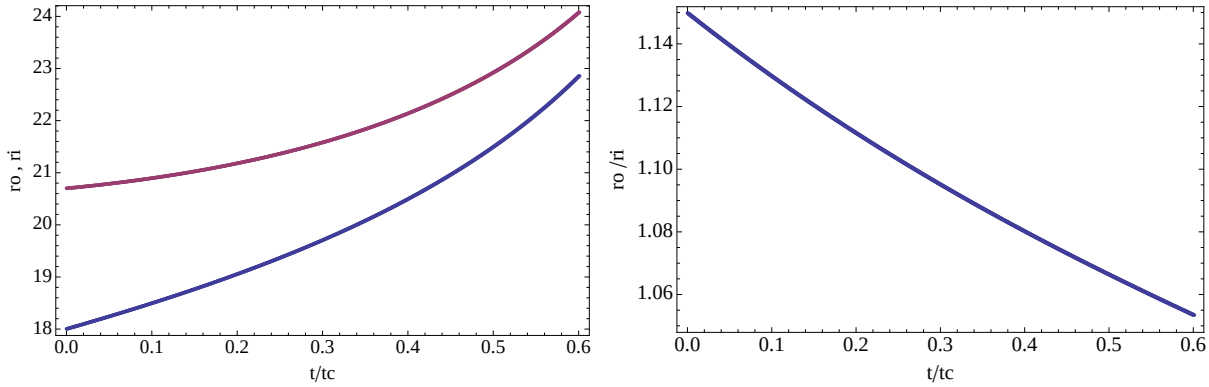

Figure 3: Evolution of the outer an inner radii (left) and thickness ratio (right) according to the evolution equation in Eq.(128) for an ascending aorta (length-scales given in mm). The numerical solution has been calculated setting p_i=160mmHg, c_1=150KPa and J(0)=1, with an initial homogeneous deformation (g_θ=0.777). The depicted curves have been obtained solving Eq.(115) using Newton's method.

time of the remodeling process, which happens this time without volume variations. In energetic terms, such an evolution of material inhomogeneities correspond to a progressive dissipation of the residual strain that had been formed during early arterial development.

Finally, we proposed a simplified analysis, where the material has been considered isotropic and

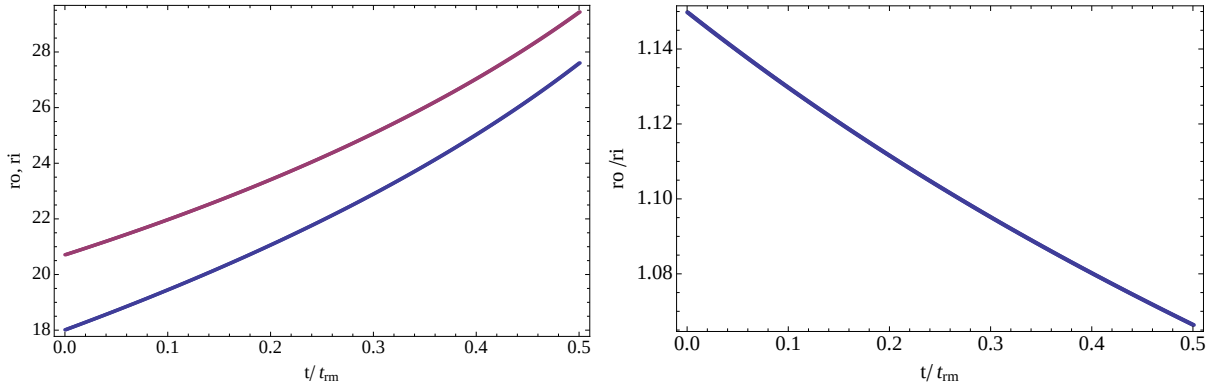

Figure 4: Evolution of the outer an inner radii (left) and thickness ratio (right) according to the evolution equation $\dot{g}_\theta/g_\theta = -2\dot{g}_r/g_r = 1/t_{rm}$ for an ascending aorta (length-scales given in mm). The numerical solution has been calculate setting p_i=160mmHg, c_1=150KPa and J(0)=1, from an initial homogeneous deformation (g_θ=0.777). The depicted curves have been obtained solving Eq.(115) using Newton's method.

the volumetric growth is homogeneous. The proposed evolution laws for aneurysms formation are

compatible with the experimental data on human aorta, reporting an increase of the opening angle (i.e. a decrease of residual stresses) as a function of age (Okamoto et al., 2002). In a more realistic approach, one should take into account that the tissue is strongly directionally reinforced and growth can be inhomogeneous in pathological conditions, including the formation of arterial plaques. Even if adding these characteristics in the hyperelastic model would change the expression of the deformation field over time, the remodeling laws would be still valid, because the sign of $(\boldsymbol{\sigma}_f)_{rr}$ and $(\boldsymbol{\sigma}_f)_{rr} - (\boldsymbol{\sigma}_f)_{\theta\theta}$ wouldn't change, being uniquely driven by the transmural pressure.

6 Discussion and Conclusion

In this manuscript we have derived the kinematic description and the main balance equations of a novel thermomechanical growth theory for a second-gradient continuum. Mass changes are defined by a material isomorphism where growth processes act as local rearrangements of the material inhomogeneities: a first-order uniformity transplant determines the extent of volumetric growth, while a second-order transplant takes into account the curvature effects induced by a local differential deformation. In the framework of a second gradient hyperelastic theory, we have stated the first single-phase continuum theory accounting both for volumetric growth and for mass transport phenomena. The diffusion of biochemical species (e.g. morphogens, nutrients, migration signals) inside a biological matter are considered in the theory of configurations forces with internal variable to describe the constitutive equations of the model. Mass transport phenomena have been found to depend both on the first- and on the second-order material connections, possibly withstanding a chemotactic behavior with respect to diffusing biochemical agents. Interestingly, we have demonstrated that the driving forces of mass diffusion can be written in terms of covariant material derivatives based on the two connections, reflecting in a purely geometrical manner the presence of a (first-order) torsion and a (second-order) curvature. This result of our study has important implications in other fields, e.g. modeling local structural rearrangements of translational and rotational dislocations. Thermodynamical arguments

have also shown that the first- and second-order Eshelby tensors are the stress measures driving the rearrangement of the first and the second-order material inhomogeneities, respectively. In particular, an evolution law for the velocity gradient of the first-order transplant can be built as a function of the symmetric first-order Eshelby stress in the grown state (see Eq.73), extending a well-known result for inelastic materials. Another major result is the definition of the first stress-driven evolution law for the second-order transplant, expressed in Eq.(81) as a function of the completely material Eshelby hyperstress. The expression of remodeling evolution laws for first- and second-order material inhomogeneities is of great importance for a correct thermodynamical description of morphogenetic events. The illustrated theory has been applied to two examples of biomechanical interest. In the first example, we show how a simple Eshelbian coupling in the first-order evolution law can describe the stress-driven inhibition for the growth of a ductal carcinoma, regardless of the spatial availability of growth factors. The depicted behavior represents a well-known experimental result on the growth of multicellular spheroids (Helmlinger et al., 1997), supporting the idea that the distribution of mechanical stresses can be actively implicated in the initiation and the development of morphogenetic movements (Bischofs and Schwarz, 2003). In the second biomechanical example, we apply the second-gradient theory to explain the generation of residual strains in healthy arteries and the material rearrangement during aneurysms formation. In particular, we have formulated a growth evolution law with a stress-driven feedback, based on thermodynamical compatibility, for the regulation of homeostatic conditions of a healthy artery. Our results are consistent with the experimental observations that cell organization in soft media are strongly influenced by mechano-sensing (Nelson et al., 2005), suggesting that homeostasis is the equilibrium thermodynamical state (if any) where the internal energy of the continuum is homogeneously distributed. We conclude that diffusive mass fluxes might play a fundamental role in the active regulations of homeostatic conditions, possibly being involved in the integral feedback mechanisms driving local growth rates (Shraiman, 2005). On the other hand, we have demonstrated how the formation of aneurysms can result from the disruption of these regulation mechanisms, through simple evolution laws

where the Eshelbian coupling drives a spontaneous dissipation of the residual energy.

Although the complexity of the governing equations makes difficult to handle them analytically when mass transport, growth and material remodeling occur on characteristic times of the same order, the proposed continuum theory is suitable for computational applications. Notably, it avoids the typical drawbacks of multiphase models in the definition of boundary conditions and partial stresses. The coupled treatment of mass transport phenomena with the evolution of material inhomogeneities can bring insights into the dynamics of cellular migrations. Cellular movements are, in fact, crucial not only for normal embryonic development or in healing processes (Jacinto et al., 2001), but also in some pathological conditions, abnormal mobility and adhesiveness in adult cells being involved in the initiation of tumor metastasis (Aman and Piotrowski, 2010). Accounting for simultaneous growth and remodeling processes which may depend on local concentration of diffusing morphogens, the proposed constitutive theory can help deciphering the control mechanisms regulating the orchestration of cellular dynamics during embryogenesis (Lecuit and Lenne, 2007; Ciarletta et al., 2009). In particular, a second-gradient model is necessary when dealing with geometrical feedbacks in growth control depending on local curvature. The determination of the local geometrical control on cell growth is one of the main challenges in developmental biology, as it has been observed that cell shape alone may govern whether individual cells grow or die (Chen et al., 1997). Finally, the biomechanical quantification of curvature-dependent effects on growth can help not only in understanding the growth patterns of cellular aggregates, but also has important applications for optimizing scaffolds in regenerative medicine and tissue engineering (Rumpler et al., 2008).

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