

Stress-modulated growth

D. Ambrosi¹, F. Guana²

¹ Dipartimento di Matematica, Politecnico di Torino,
corso Duca degli Abruzzi 24, 10129 Torino, Italy

² Dipartimento di Matematica, Università di Torino,
via Carlo Alberto 10, 10123 Torino, Italy

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Abstract

The growth and remodeling of soft tissues depend on a number of biological, chemical and mechanical factors, including the state of tension. In many cases the stress field plays such a relevant role that “stress-modulated growth” has become a very topical subject. Recent theoretical achievements suggest that, irrespective of the specific biological material at hand, a component of the stress-growth coupling is tissue-independent and reads as an Eshelby-like tensor. In this paper we investigate the mathematical properties and the qualitative behavior predicted by equations that specialize that model under few simple assumptions. Constitutive equations that satisfy a suitable dissipation principle are compared with heuristic ones that fit well the experimental data. Numerical simulations of the growth of a symmetric annulus are discussed and compared with the predicted qualitative behavior.

Introduction

Biological tissues are conventionally classified in two categories: hard tissues (bones, teeth) and soft tissues (muscles, arteries, ligaments, tendons, skin). The terminology clearly refers to different mechanical properties of the materials, but also the mass addition (resorption) process is very different (see, for example [21]). Hard tissues are characterized by surface (apositional) growth (see Skalak *et al.* [20]), which is deposition or resorption of matter on the external surface of the body. In the bones even internal growth is due to deposition on surfaces, such as the surface of trabeculae or the walls of canals excavated by osteoclast. On the other hand, soft tissues typically undergo volumetric (interstitial) growth, i.e. smooth volumetric resorption of bulk material; the basic mechanisms of this process are much less understood than the former one.

The terminology commonly used in the context of developmental biology, is resumed by Taber in his review paper [21]. The generation of biological forms involves three different processes: *growth*, which is defined as mass change and, if we consider the process of adding mass, can occur through cell division (hyperplasia), cell enlargement (hypertrophy), secretion of extracellular matrix or accretion at external or internal surfaces, otherwise atrophy occurs through cell death, cell shrinkage or resorption; *remodeling*, which involves changes in material

properties and then, changes in microstructure; *morphogenesis*, which consist in a change in shape, involving both growth and remodeling, and usually refers to embryonic development, wound healing or organ regeneration.

In this paper we will deal exclusively with growth. Many studies show a strong interaction between the stress state of the body and finite growth. Yamamoto *et al.* [25] studied the effects of static stress on the mechanical properties of cultured collagen fascicles from the rabbit patellar tendon. The role of stress in the growth of a multicellular spheroid embedded in a poroelastic medium is considered by Helmlinger *et al.* [12]: the evolution in time of the size of the spheroid depends on the external mechanical action in a rather complex way. The most extensively studied biological system consists probably in the arterial walls [14, 21]. Like all tissues whose physiological function is associated with exposure to mechanical forces, arteries are sensitive to changes in their mechanical environment, i.e. to alteration in arterial pressure and blood flow. They are known to thicken while preserving a constant lumen radius when the blood pressure increases; this suggests that they grow depending on the normal stress at the internal wall. Conversely, the more the blood flow rate becomes large, the more the lumen radius increases while keeping a constant ratio between internal and external diameter, thus suggesting that remodeling responds to a variation in the shear stress [24]. The scenario is rather complex and few general conclusions can be drawn, mainly about the existence of bounded states: *in vivo* some systems grow up to a stationary state (homeostasis) that seems to be determined by a preferred state of tension, but *in vitro* unbounded growth is observed too.

Whereas few heuristic growth laws based on these experimental observations have been devised, equations deduced on the guidelines traced by *a priori* stated principles are almost lacking. The reason of this failure is probably twofold. On one hand, the kinematics of growth is a rather recent achievement: it has been clarified by Rodriguez *et al.* [19] in a paper published in 1994 and just in the last decade people started to focus on the *dynamics* of growth. On the other hand, biological systems exhibit such a complex behavior to discourage attempts to devise universal principles as a starting point to deduce constitutive equations.

Among the few examples in the direction of exploiting energy inequalities as a tool to discriminate among possible constitutive laws, it is to be mentioned the constitutive theory for volumetric growth of bodies developed by Epstein and Maugin [5], and then the paper by Garikipati *et al.* [11]. Both studies focus on the mass flux driven by strain and chemical potential gradients, whereas mass production is a *datum* and no constitutive equation is looked for it.

On the basis of the seminal work by Rodriguez *et al.*, in a recent paper Di Carlo and Quiligotti [4] state a dissipative principle to be satisfied for any *growth* process, involving standard forces and *accretive* forces. The exploitation of such an inequality yields constitutive relationships that, in addition to the classical results, provide a direct coupling between stress and growth in terms of an Eshelby-like tensor. The aim of this paper is to investigate the nature of the equations arising from such an approach for a simple material: an elastic solid that can only store mechanical energy. The solution of those equations is explicitly found in simple homogeneous one-dimensional cases, qualitative behavior is discussed and numerical simulations are carried out in more complex geometries.

1 General theory

1.1 Kinematics and balance equations

In this section the main results about kinematics and dynamics of growing one-component solids are reviewed according to [19] and [4].

Let us consider a continuous medium in its initial configuration \mathcal{B}_0 that, after motion and growth, results in the configuration \mathcal{B}_t at time t . We call \mathbf{F} the gradient of deformation tensor, defined as the gradient of the motion function, and $J := \det \mathbf{F}$. The coordinate \mathbf{X} identifies the position of a given particle in the body at $t = 0$. If the system undergoes a quasi-static motion, mass and momentum balance equations written in a reference frame fixed on the solid in its initial configuration read

$$(\rho \dot{J}) = \Gamma \rho J, \quad (1.1)$$

$$\text{Div} (J \mathbf{T} \mathbf{F}^{-T}) = 0, \quad (1.2)$$

where $\rho(\mathbf{X}, t)$ is the mass density, Γ (the inverse of a characteristic time) is the mass production rate, \mathbf{T} is the Cauchy stress tensor and inertial terms and body forces are supposed to be negligible. The fields Γ and \mathbf{T} are to be constitutively assigned. The superposed dot indicates time differentiation.

Soft tissues are often non-homogeneous at a macroscopic level and are never homogeneous at a cellular level. For this reason, some authors state a continuum mechanics theory for soft tissues in the framework of mixture theory [10], [11], [13], [17]. In such a context mass creation (here represented by the r.h.s. of Equation (1.1)) more physically reads as “mass exchange” among the constituents of the mixture. However, as discussed in [10], the crucial issues of stress-modulated growth can be already addressed in the simpler one-component framework and we restrict our attention to these systems in the present work.

In general, inhomogeneous growth generates residual stresses in a body, namely tensions that do not vanish even though the body is unloaded. A typical example is given by arterial walls: if we cut an aorta by two consecutive sections perpendicular to the longitudinal axis of the vessel we obtain a ring, which, if cut radially, will open up into a sector that represents the zero stress state of the vessel. Let us imagine to release this state of residual stress while keeping the mass constant, so that the grown body reaches a state \mathcal{B}_r that is in general different from the one it had in \mathcal{B}_0 , but also from the one achieved in \mathcal{B}_t . This kind of approach agrees with [19], where the set of the descriptors of the mechanical system is defined by introducing a multiplicative decomposition of the gradient of the deformation tensor:

$$\mathbf{F} = \mathbf{F}_r \mathbf{G}. \quad (1.3)$$

A decomposition of this kind has its very roots in plasticity theory and has been proved to be successful to model a number of different phenomena [18]. In this framework \mathbf{G} is the growth tensor and \mathbf{F}_r accounts for mechanical behavior of the grown body.

Out of very special cases, growth is incompatible, the configuration \mathcal{B}_r cannot be a physical state, the tensors \mathbf{F}_r and \mathbf{G} are not integrable and this is why we prefer to call \mathcal{B}_r the *relaxed state* (see Figure 1).

[Figure 1 about here.]

The above characterization of the relaxed state corresponds to require that [1]

$$\dot{J}_g = \Gamma J_g, \quad (1.4)$$

where $J_g := \det \mathbf{G}$. It follows that

$$\Gamma = \text{trace}(\dot{\mathbf{G}}\mathbf{G}^{-1}), \quad (1.5)$$

and the continuity equation (1.1) rewrites in the simple form:

$$(\rho \dot{J}_r) = 0, \quad (1.6)$$

where $J_r := \det \mathbf{F}_r$.

Remark 1 Consider an elastic body. As is well known, the mechanical behavior of the material must be independent on any rotation of the observer and therefore the stress field cannot depend on the rotational part of the polar decomposition of \mathbf{F}_r . Thus, we can always adopt a multiplicative decomposition of the deformation gradient \mathbf{F} in which the rotational part of the polar decomposition of \mathbf{G} is included into \mathbf{F}_r . In this way we can assume that \mathbf{G} is a symmetric positive definite tensor.

1.2 Constitutive theory via a dissipation principle

As usual in biomechanics, in the present context we ignore thermal energy. We assume that energy is supplied to the system in two forms: work of standard external forces that balance the internal ones and energy provided specifically for growth. The energy supplied to the system these ways will be at most all stored as available mechanical energy. Therefore we formally write the following dissipation principle:

$$(J\rho\dot{\psi}) \leq J\mathbf{T} \cdot \mathbf{L} + J\xi, \quad (1.7)$$

where ψ is the free energy per unit mass of the body in the initial configuration \mathcal{B}_0 , ξ is the energy per unit time externally supplied for growth and \mathbf{L} is the tensor velocity of deformation defined as $\mathbf{L} := \dot{\mathbf{F}}\mathbf{F}^{-1}$.

The inequality (1.7) is useless to obtain restrictions on the constitutive equations, without further assumptions that allow its exploitation. A possible approach is due to Fusi *et al.* [10], who postulated a principle of maximum entropy production rate, according to the methodology proposed by Rajagopal and Srinivasa [18].

Here we will adopt the procedure proposed by Di Carlo and Quiligotti [4]: the inequality (1.7) can be successfully exploited when admitting that the energy for growth is externally supplied as the work of some kind of forces that govern the growth process and that we call *accretive* forces:

$$\xi = \rho \mathbb{C} \cdot \dot{\mathbf{G}}\mathbf{G}^{-1}, \quad (1.8)$$

where \mathbb{C} is the tensor referred to the internal accretive forces that are balanced by the external ones \mathbb{B} :

$$\mathbb{C} = \mathbb{B}. \quad (1.9)$$

The quantity $\dot{\mathbf{G}}\mathbf{G}^{-1}$ plays the role of test velocity for the accretive forces. Equation (1.9) is to be understood as a modelization of all the biomechanical stimuli that induce growth, represented under the unifying formalism of *balance of forces*. The introduction of a completely

new balance law in the theory is a strong assumption and its validity will be evaluated in terms of the consequent physical and biological predictions.

Using the continuity equation (1.6) one rewrites the inequality (1.7) as follows

$$\rho J_r(\dot{J}_g \psi) \leq J \mathbf{T} \cdot \mathbf{L} + \rho J \mathbb{C} \cdot \dot{\mathbf{G}} \mathbf{G}^{-1}. \quad (1.10)$$

If we suppose, according to Equation (1.6), that $(\rho J_r)|_{t=0} = 1$ for all \mathbf{X} , we obtain

$$(\dot{J}_g \psi) \leq J \mathbf{T} \cdot \mathbf{L} + \rho J \mathbb{C} \cdot \dot{\mathbf{G}} \mathbf{G}^{-1}. \quad (1.11)$$

Note that the free energy per unit of relaxed volume ($J_g \psi$) is defined unless a constant, while the energy per unit mass in the initial configuration ψ does not. Furthermore, we can observe that the amount of free energy stored by the body naturally depends on the growth in a specific way: it is proportional to the determinant of \mathbf{G} [5].

At this stage we make the constitutive assumption that energy can only be stored in mechanical form and ψ is a function of \mathbf{F}_r : $\psi = \psi(\mathbf{F}_r)$. Then derivatives at the l.h.s. of (1.10) can be carried out in a standard way, obtaining

$$\rho J \psi \mathbf{G}^{-T} \cdot \dot{\mathbf{G}} + \rho J \psi' \cdot \dot{\mathbf{F}}_r \leq J \mathbf{T} \cdot \dot{\mathbf{F}}_r \mathbf{F}_r^{-1} + J \mathbf{T} \cdot \mathbf{F}_r \dot{\mathbf{G}} \mathbf{G}^{-1} \mathbf{F}_r^{-1} + \rho J \mathbb{C} \cdot \dot{\mathbf{G}} \mathbf{G}^{-1}, \quad (1.12)$$

where ψ' denotes the Frechet derivative of ψ . Rearranging the terms one gets

$$\psi \mathbf{I} \cdot \dot{\mathbf{G}} \mathbf{G}^{-1} + \psi' \cdot \dot{\mathbf{F}}_r \leq J_r \mathbf{T} \mathbf{F}_r^{-T} \cdot \dot{\mathbf{F}}_r + \mathbf{F}_r^T J_r \mathbf{T} \mathbf{F}_r^{-T} \cdot \dot{\mathbf{G}} \mathbf{G}^{-1} + \mathbb{C} \cdot \dot{\mathbf{G}} \mathbf{G}^{-1}, \quad (1.13)$$

that is

$$(J_r \mathbf{T} \mathbf{F}_r^{-T} - \psi') \cdot \dot{\mathbf{F}}_r + (\mathbf{F}_r^T J_r \mathbf{T} \mathbf{F}_r^{-T} + \mathbb{C} - \psi \mathbf{I}) \cdot \dot{\mathbf{G}} \mathbf{G}^{-1} \geq 0. \quad (1.14)$$

The requirement (1.14) must hold for arbitrary values of $\dot{\mathbf{F}}_r$ and $\dot{\mathbf{G}} \mathbf{G}^{-1}$. This is possible if and only if

$$\mathbb{C} = \mathbb{C}^+ - \mathbf{F}_r^T J_r \mathbf{T} \mathbf{F}_r^{-T} + \psi \mathbf{I}, \quad (1.15)$$

$$J_r \mathbf{T} \mathbf{F}_r^{-T} = \psi', \quad (1.16)$$

with the restriction

$$\mathbb{C}^+ \cdot \dot{\mathbf{G}} \mathbf{G}^{-1} \geq 0. \quad (1.17)$$

Let us assume that

$$\mathbb{C}^+ = \mathbf{K} \dot{\mathbf{G}} \mathbf{G}^{-1}, \quad (1.18)$$

where \mathbf{K} is a constant symmetric positive-definite matrix. Then we obtain the constitutive relations

$$\mathbf{T} = \frac{1}{J_r} \psi' \mathbf{F}_r^T, \quad (1.19)$$

$$\mathbb{C} = \psi \mathbf{I} - \mathbf{F}_r^T J_r \mathbf{T} \mathbf{F}_r^{-T} + \mathbf{K} \dot{\mathbf{G}} \mathbf{G}^{-1}. \quad (1.20)$$

Finally, the equations to solve are

$$\text{Div}(J \mathbf{T} \mathbf{F}^{-T}) = 0, \quad (1.21)$$

$$\mathbf{K} \dot{\mathbf{G}} = [-(\psi \mathbf{I} - \mathbf{F}_r^T \psi') + \mathbb{C}] \mathbf{G}, \quad (1.22)$$

or, thanks to the balance (1.9) and the continuity equation in the form (1.6)

$$\text{Div}(J_g \psi' \mathbf{G}^{-T}) = 0, \quad (1.23)$$

$$\mathbf{K} \dot{\mathbf{G}} = [-(\psi \mathbf{I} - \mathbf{F}_r^T \psi') + \mathbb{B}] \mathbf{G}. \quad (1.24)$$

After specifying the constitutive form for ψ , the balance equation for standard forces (1.23) reads as three partial differential equations of the second order in space. This system provides the (instantaneous) displacement field for given traction (or displacement) at the boundary and known growth tensor \mathbf{G} . The latter evolves according to the ordinary differential equation in time (1.24) which, in other terms, determines the evolution in time of the relaxed state \mathcal{B}_r . Notably the term in square brackets in Equation (1.24) does not depend on \mathbf{G} and deserves the name of *growth rate* well.

Remark 2 Most biological tissues usually demonstrate rate-dependent response and it is common to adopt viscoelastic constitutive models for them. However the present assumption of hyperelastic material, corresponding to $\psi = \psi(\mathbf{F}_r)$, is not unduly restrictive: a dependence of the free energy on the rate of deformation can be easily included without substantial modifications. Even more important, soft tissues are characterized by relaxation times of the order of 10^3 s. [16], a very small time scale if compared with the typical time of growth (in terms of weeks).

Remark 3 The exploitation of the inequality (1.7) does not strictly dictate any specific form of the constitutive quantities: any choice of the tensor \mathbb{C}^+ satisfying the restriction (1.17) is equally admissible and we choose the form (1.18) just for the sake of simplicity. However, the decoupling of \mathbb{C} into the two additive terms with the special form (1.15) is mandatory to satisfy the dissipation inequality for any process: they represent the irreversible and reversible part of the work of the accretive forces.

2 Growth rate

The external accretive forces \mathbb{B} in (1.24) account for those characteristics of the growth process that pertain to the specific biological system at hand. In the following we restrict to consider the case of \mathbb{B} constant in time and space and, for reasons that will become clear later, we remark this restriction by denoting $\mathbb{B} = \mathbb{E}_o$.

Equations (1.23) and (1.24) form a system of equations for the motion (through its gradient \mathbf{F}) and for the growth tensor. They take a particular mechanical meaning when considering the tensor

$$\mathbf{S} := \psi', \quad (2.1)$$

that can be interpreted as the Piola tensor in the coordinate system of the relaxed state \mathcal{B}_r (in agreement with the definition of DiCarlo and Quiligotti [4]). According to equation (1.24), the growth rate of \mathbf{G} depends on the Eshelby-like tensor

$$\mathbb{E} := \psi \mathbf{I} - \mathbf{F}_r^T \psi'. \quad (2.2)$$

If it exists a one to one relationship between the state of deformation and the stress, then the relation (2.1) can be inverted providing $\mathbf{F}_r = \mathbf{F}_r(\mathbf{S})$. In general, this condition is a very

strong one and many nonlinear relationships cannot be inverted. Fortunately, in the case of many biological soft tissues this inversion is possible, as shown by Fung in [7], [8]. Consider the Eshelby tensor \mathbb{E} as an operator from Lin into Lin :

$$\mathbb{E}(\mathbf{S}) = \psi(\mathbf{F}_r(\mathbf{S}))\mathbf{I} - \mathbf{F}_r^T(\mathbf{S})\mathbf{S}. \quad (2.3)$$

Note that in one spatial dimension the Eshelby tensor is the opposite of the Legendre transform of the strain energy; in the next it will be assumed to be an invertible operator. The equilibrium points of the system (1.24) are the solutions \mathbf{S}_0 of the algebraic equation

$$\mathbb{E}(\mathbf{S}) = \mathbb{E}_o. \quad (2.4)$$

When $\mathbf{S} = \mathbf{S}_0$ every component of the growth tensor is constant in time. However, for the one to one relation discussed above, \mathbf{S}_0 is just a point in the stress space.

A weaker equilibrium condition is formulated when using equations (1.24) and (1.5); by the definition (2.2) one finds

$$\Gamma = -\text{tr}(\mathbf{K}^{-1}(\mathbb{E} - \mathbb{E}_o)), \quad (2.5)$$

and therefore the growth rate Γ is proportional to the trace of the Eshelby tensor. According to equation (2.5), in principle the macroscopic growth of a body can be null even though non-null production and resorption occurs along single directions. Before trying to describe how stress and growth couple in time, let us consider a few examples for equations (2.4) and (2.5) where, for the sake of simplicity, we set $\mathbf{K} = \mathbf{I}$.

2.1 Example: small strain assumption

One-dimensional case We recall that a one dimensional continuum is a very special one because the momentum equation (1.23) reads as an ordinary differential equation, it holds $J_g \mathbf{G}^{-T} = 1$ and, for given traction s at a border, it can be immediately integrated giving $\psi' = s$ at any point of the body for any functional form of $\psi(\mathbf{F}_r)$. Moreover, in one dimension growth is always compatible, residual stress cannot be generated and the growth is driven by the constant (in time and space) stress s .

Consider the infinitesimal strain of an elastic one-dimensional medium: if we indicate by x the stretch ratio, the strain energy reads $\psi = \mu(x-1)^2/2$. This equation holds for $|x-1| \ll 1$ and note that in this context the “small strain” assumption refers to the deformation of \mathcal{B}_t with respect to the relaxed state \mathcal{B}_r . For a given stress s , the Legendre transform of the strain energy reads $\tilde{\psi}(s) = s^2/(2\mu) + s$. This relation holds for $|s| \ll \mu$. Given e_0 and the corresponding s_0 so that $e_0 = -\tilde{\psi}(s_0)$, it follows that growth quadratically depends on the stress field and, according to Figure 2, one can understand that the body always grows for $s > s_0$ (the faster the bigger is the load); if the stress field is smaller than s_0 , the body resorbs.

[Figure 2 about here.]

Three-dimensional case Consider the infinitesimal deformation of an elastic body in the three dimensional space: the strain energy reads

$$\psi = \mu \text{tr}(\mathbf{E}^2) + \frac{\lambda}{2}(\text{tr}(\mathbf{E}))^2, \quad (2.6)$$

where infinitesimal strain and stress tensors are related as follows:

$$\mathbf{E} = \frac{1}{2\mu} \left(\mathbf{S} - \frac{\lambda}{2\mu + 3\lambda} \text{tr}(\mathbf{S}) \mathbf{I} \right). \quad (2.7)$$

We look for the solutions of the equation

$$\Gamma = -\text{tr}(\mathbb{E}(\mathbf{S}) - \mathbb{E}_o) = \text{tr}\mathbb{E}_o + \text{tr}(\mathbf{F}_r^T \mathbf{S}) - 3\psi(\mathbf{S}) = 0. \quad (2.8)$$

By some calculations one gets:

$$\text{tr} \mathbf{E} = \frac{1}{2\mu + 3\lambda} \text{tr} \mathbf{S}, \quad (2.9)$$

$$\text{tr}(\mathbf{E}^2) = \frac{1}{4\mu^2} \left[\text{tr}(\mathbf{S}^2) - \frac{\lambda(3\lambda + 4\mu)}{(2\mu + 3\lambda)^2} (\text{tr} \mathbf{S})^2 \right], \quad (2.10)$$

and the strain energy can be rewritten in terms of the Piola tensor

$$\psi(\mathbf{S}) = \frac{1}{4\mu} \text{tr}(\mathbf{S}^2) - \frac{\lambda}{4\mu(2\mu + 3\lambda)} (\text{tr} \mathbf{S})^2. \quad (2.11)$$

In order to have an expression for the growth rate depending on \mathbf{S} we also need to evaluate

$$\begin{aligned} \text{tr}(\mathbf{F}_r^T \mathbf{S}) &= \mathbf{F}_r \cdot \mathbf{S} = \text{Sym} \mathbf{F}_r \cdot \mathbf{S} = (\mathbf{E} + \mathbf{I}) \cdot \mathbf{S} = \text{tr}(\mathbf{E} \mathbf{S}) + \text{tr} \mathbf{S} \\ &= \frac{1}{2\mu} \left[\text{tr}(\mathbf{S}^2) - \frac{\lambda}{(2\mu + 3\lambda)} (\text{tr} \mathbf{S})^2 \right] + \text{tr} \mathbf{S}, \end{aligned} \quad (2.12)$$

and therefore

$$\Gamma = \text{tr}\mathbb{E}_o - \frac{1}{4\mu} \text{tr}(\mathbf{S}^2) + \frac{\lambda}{4\mu(2\mu + 3\lambda)} (\text{tr} \mathbf{S})^2 + \text{tr} \mathbf{S}. \quad (2.13)$$

The equation $\Gamma = 0$ defines, in the stress space, an ellipsoid of revolution, centered in the origin, with the symmetry axis pointing into the direction $(1, 1, 1)$ (see Appendix A).

3 Stress-modulated growth

Equation (1.24) provides the growth ratio of the body for a given stress field. However, just in the very special one-dimensional case discussed in the example 2.1, the stress is not affected by growth. In general they are coupled and the evolution in time of the body growth can be determined only by solving equations (1.23) and (1.24) together: the growth tensor reads in the momentum equation as a time-dependent parameter that evolves according to an ordinary differential equation.

In the previous section it has been outlined how growth depends on stress, but how does stress evolve in time depending on the growth tensor \mathbf{G} ? A geometrical viewpoint can be useful to illustrate the interplay between tension and growth.

For a given point \mathbf{X} , we call trajectory the curve $\mathbf{S} = \mathbf{S}(\mathbf{G}(t); \mathbf{X})$ in Lin. Let us consider \mathbf{S} as a function of \mathbf{G} for a given deformation \mathbf{F} :

$$\mathbf{S} = \psi'(\mathbf{F}\mathbf{G}^{-1}). \quad (3.1)$$

In the one-dimensional case, if ψ is locally convex, then ψ' is a monotone increasing function of its argument. Considering the expression for \mathbf{S} in (3.1) as a function of \mathbf{G} , we infer that stress always diminishes as growth increases and, *vice versa*, stress diminishes as growth increases. Therefore, going back to the one-dimensional sketch of Figure 2, the system tends to $s = s_0$ (corresponding to no deformation with respect to the relaxed state) according to the direction of the arrows.

In more than one dimension, the situation is more complicated and substantially differs if boundary conditions apply to strain or stress. Consider first the case of pure Dirichlet boundary conditions, i.e. given displacement assigned on the all boundary. In this case the growth process is free to accommodate the stress field according to equation (3.1) in any point of the body. The volume of the body remains unmodified, although its mass locally and globally changes up to reaching the homeostatic stress state in every point of the whole body. Growth and resorption are component by component related to the stress field in a way analogous to the one-dimensional case.

The state \mathbf{S}_0 is a stable equilibrium state. In principle the system could stop growing macroscopically when the stress state lies on any point of the surface $\Gamma = 0$, i.e. when the components of \mathbf{G} balance in such a way that J_g is constant. However, there are no points on such surface where orbits converge and, therefore, there are no stable equilibrium points except $\mathbf{S} = \mathbf{S}_0$, that is $\mathbf{F}_r = \mathbf{I}$ (see Figure 3).

[Figure 3 about here.]

In the case of traction boundary conditions a load is imposed at least on a portion of the boundary. Since the evolution law (1.24) is strictly local, in the whole body the growth remodeling attempts to accomplish stress relaxation up to \mathbf{S}_0 . However, no possibility exists to reach any steady state because the condition (2.4) can never be satisfied in the whole domain. Thus, the only two possible scenarios predicted by the model for a loaded homogeneous material are that the body indefinitely grows or shrinks to a point.

4 Theory and experimentally-based models

The theoretical results and the qualitative predictions illustrated above are based on a few assumptions that can be summarized as follows: the energy in the system can only be stored as strain energy, the growth energy is externally supplied as the work of accretive forces with an Eshelbian reversible component whereas internal standard forces are conservative. At this stage one wonders if the qualitative behavior predicted by the system of equations (1.23)-(1.24) resembles, at least to some extent, the experimental ones.

According to Taber, “experiments show that the growth rate increases with the magnitude of the applied stress” [21] and this is in agreement with the present model. This theory also provides a theoretical growth rate depending on the mechanical characteristics of the tissue, that would be interesting to check by experiments.

A delicate issue regards the existence of equilibrium states. According to the analysis carried out in the previous section, they can only be determined by the *accretive* forces and are therefore expected to be tissue-dependent. In this framework the equilibrium stress \mathbf{S}_0 takes

an appealing biomechanical interpretation as *homeostatic stress*, which indicates the level of tension (compression) that the cells of a specific tissue wish to obtain by remodeling. According to Cannon (1932) the term *homeostasis* indicates “dynamic self-regulation, the property of complex open systems to maintain the structure, functions, internal balances in order to survive”.

Stress-growth relationships fitting very well the data are known for arterial walls. Arteries possess residual stresses even in their healthy state and, in particular, hoop stress has been extensively measured on the basis of opening angles. Modification of the standard (healthy) external loads generates a remodeling process until a new stationary configuration is reached. It is not our aim to illustrate in details the mechanical and physiological characteristics of arterial remodeling (the interested reader may refer to [22]); in the following we just want to check if and how heuristically deduced models that well fit the experimental data compare with the one deduced from an *a priori* dissipation principle.

An artery is often ideally represented as a symmetric annulus of elastic material so that the displacement field is only radial. Given these assumptions, the stress and the growth tensors are diagonal: introducing the radial, angular and axial coordinates (r, θ, z) , the components of the Cauchy stress and growth tensor take the form

$$\mathbf{T} = \text{diag}(T_{rr}, T_{\theta\theta}, T_{zz}), \quad \mathbf{G} = \text{diag}(G_{rr}, G_{\theta\theta}, G_{zz}), \quad (4.2)$$

respectively. The momentum equation reads as an ordinary differential equation in the radial coordinate and usually traction (T_{rr}) is prescribed at the boundaries. Taber proposes the following stress-growth relationship [23], corroborated by extensive comparison with experimental data:

$$\begin{aligned} \dot{G}_{rr} &= k_r(T_{\theta\theta} - T_{\theta\theta}^0), \\ \dot{G}_{\theta\theta} &= k_\theta(T_{\theta\theta} - T_{\theta\theta}^0), \\ \dot{G}_{zz} &= 0, \end{aligned} \quad (4.3)$$

where $T_{\theta\theta}^0$ is the homeostatic stress and shear contributions have been omitted. According to (4.3), the hoop stress plays a dominant role in the model, as the other components of the tension are not invoked. This is probably related to the fact that radial stress in the annulus is fixed by the boundary conditions and therefore no steady state can be obtained by a stress tuning in the body driven by the remodeling process.

In order to compare the growth law (4.3) with the form (1.24), we observe first that every component of the Eshelby tensor nonlinearly depends on all the components of the stress and therefore a linear relationship like the one in (4.3) cannot be obtained by any constitutive assumption. However, we note that

$$-\mathbb{E}(\mathbf{F}_r) = \mathbf{F}_r^T \mathbf{S} - (\psi(\mathbf{I})\mathbf{I} + (\mathbf{F}_r^T - \mathbf{I})\psi'(\mathbf{I}) + o(\mathbf{F}_r)) \quad (4.4)$$

and hence for small deformations the opposite of Eshelby and Piola (and Cauchy) tensors coincide. Taking

$$\mathbb{E}_o = -\text{diag}(T_{\theta\theta}^0, T_{\theta\theta}^0, 0), \quad \mathbf{K} = \text{diag}(1/k_r, 1/k_\theta, 0), \quad (4.5)$$

after linearization in time one gets

$$\dot{\mathbf{G}} = \text{diag}(k_r(T_{\theta\theta} - T_{\theta\theta}^0), k_\theta(T_{\theta\theta} - T_{\theta\theta}^0), 0). \quad (4.6)$$

The relationship (4.6) coincides with (4.3). The growth law (4.6) has a clear biological meaning: there exists a stable equilibrium state corresponding to the homogeneous hoop stress $T_{\theta\theta}^0$. Then the growth law due to Taber is recovered as a linear version of the non-linear one (1.24), provided that the identification holds for infinitesimal strain.

5 Numerical simulations

In this section are shown the results of some numerical simulations of the growth of an homogeneous axisymmetric annulus of non-linear elastic orthotropic material.

Let $\mathbf{u} = (u_r(r), 0, 0) = (u(r), 0, 0) = (\gamma(r) - r, 0, 0)$ be the displacement vector as a function of the radial coordinate r . In one spatial dimension, all the functions are integrable and therefore the delicate issues about the existence of the relaxed state discussed in Section 1.1 do not apply. The reference system can be conveniently set in \mathcal{B}_r and the radial coordinate spans the body in its relaxed configuration.

The strain tensor can be written as

$$\mathbf{F}_r - \mathbf{I} = \mathbf{F}\mathbf{G}^{-1} - \mathbf{I} = \text{diag} \left(\frac{\gamma'}{g_r} - 1, \frac{\gamma}{rg_\theta} - 1, \frac{1}{g_z} - 1 \right). \quad (5.1)$$

In the present section the prime indicates standard derivative with respect to the radial coordinate: $\gamma' := d\gamma/dr$. For the numerical simulations the pseudo-strain energy proposed by Chuong and Fung [3] has been adopted:

$$\psi = \frac{C}{2} \exp \left(b_1 E_{rr}^2 + b_2 E_{\theta\theta}^2 + b_3 E_{zz}^2 + b_4 E_{r\theta}^2 + b_5 E_{rz}^2 + b_6 E_{\theta z}^2 \right), \quad (5.2)$$

where, in the present context, the non-null components of the strain tensor in cylindrical coordinates are

$$E_{rr} = \frac{\gamma'}{g_r} - 1, \quad E_{\theta\theta} = \frac{\gamma}{rg_\theta} - 1, \quad E_{zz} = \frac{1}{g_z} - 1. \quad (5.3)$$

The components of the stress tensor \mathbf{S} are

$$S_{rr} = \frac{\partial \psi}{\partial E_{rr}} = 2b_1 \psi \left(\frac{\gamma'}{g_r} - 1 \right), \quad (5.4)$$

$$S_{\theta\theta} = 2 \frac{\partial \psi}{\partial E_{\theta\theta}} = 2b_2 \psi \left(\frac{\gamma}{rg_\theta} - 1 \right), \quad (5.5)$$

$$S_{zz} = \frac{\partial \psi}{\partial E_{zz}} = 2b_3 \psi \left(\frac{1}{g_z} - 1 \right). \quad (5.6)$$

The momentum equation reads

$$\frac{dS_{rr}}{dr} + \frac{1}{r}(S_{rr} - S_{\theta\theta}) = 0. \quad (5.7)$$

If $\mathbf{G} = \mathbf{G}(r)$ the equation of motion is

$$\left(b_1 \psi \left(\frac{\gamma'}{g_r} - 1 \right) \right)' + \frac{\psi}{r} \left(b_1 \left(\frac{\gamma'}{g_r} - 1 \right) - b_2 \left(\frac{\gamma}{rg_\theta} - 1 \right) \right) = 0. \quad (5.8)$$

In the numerical simulations the following non-dimensional physical and numerical parameters have been used

$$(C, b_1, b_2, b_3) = (1, 0.01, 0.17, 0.09), \quad (5.9)$$

$$(\mathbb{E}_{0,rr}, \mathbb{E}_{0,\theta\theta}, \mathbb{E}_{0,zz}) = (0, -0.001, 0). \quad (5.10)$$

Displacement boundary conditions Two sets of Dirichlet boundary conditions are considered:

$$\left\{ \begin{array}{l} r_1 = 0.8, \\ r_2 = 0.9, \end{array} \right. \quad \left\{ \begin{array}{l} r_1 = 0.8, \\ r_2 = 1.1, \end{array} \right.$$

corresponding to 50% extension or contraction, respectively, when compared with the relaxed configuration $[r_1, r_2] = [0.8, 1]$. In both cases the numerical simulations agree with the qualitative analysis: the radial stress is damped exponentially in time until a homeostatic value \mathbf{S}_0 is uniformly attained in the grown body (Figures 4). The determinant of the growth tensor \mathbf{G} and the trace of the Eshelby tensor exhibit a similar behavior as shown in Figure 5, where J_g (a) and $\text{tr}(\mathbb{E})$ (b) are plotted versus the radial coordinate at different times.

[Figure 4 about here.]

[Figure 5 about here.]

Load boundary conditions Consider an applied load at the internal wall of the cylinder: $S_{rr} = -0.01$. At $t = 0$ the body immediately displaces and the stress field is provided in terms of classical explicit solutions (see [6]). In this case the radial stress is compressive, the hoop and axial ones are tensile, the latter being smaller in magnitude. Corresponding to these states, the components of the Eshelby tensor prime the growth process in terms of production or resorption of mass, depending on their sign. In this case production dominates and both the internal and external radius indefinitely grow (see Figure 6a). The undershoot occurring at $t = 1$ indicates the instantaneous reposition of the boundaries of the grown body after load release ($r_1 = 1.35$ and $r_2 = 1.54$) which is the quantity always measured in practice. The trace of the Eshelby tensor is positive and increasing in time (Figure 6b).

[Figure 6 about here.]

Non-homogeneous body The arguments exposed in Section 3 and the numerical simulations illustrated above show that there is no possibility to obtain a steady state for a loaded homogeneous growing material by the present model. The reason of this is that two simultaneous constraint are to be satisfied at the boundary: the deformation is dictated by the applied load *and* the steady state holds for a specific value of the Eshelby tensor only (the homeostatic value), corresponding in general to a different deformation state.

One possibility to overcome this intrinsic difficulty is to restrict the growth process to an *internal* portion of the body. Assume that the body is non-homogeneous in the sense that growth occurs just for $r_1 + 0.04 \leq r \leq r_2 - 0.04$. This hypothesis goes into the direction suggested by Taber and Humphrey in [24] who, in a more realistic way, include the non-homogeneity of the body as an essential ingredient of arterial wall modeling.

Now the growth process of the loaded annulus reaches a steady state, as illustrated by the

plot of the position of the internal and external radii versus time (Figure 7a). The undershoot occurring at $t = 10$ corresponds to the position of the boundaries of the grown body after unloading ($r_1 = 1.01$ and $r_2 = 1.21$). The growth process accommodates most of the stress of the loaded body in the not-grown region (Figure 8a) by a suitable tuning of the residual stress (Figure 8b). The growth process is radially resorbing and productive for the other components of \mathbf{G} , globally leading to a production process as certified by the value of the determinant of \mathbf{G} (see Figure 7b).

[Figure 7 about here.]

[Figure 8 about here.]

6 Final remarks

In this paper it has been given a qualitative analysis of the stress-modulated growth of a continuum body as predicted by equations that satisfy an *a priori* stated dissipation principle. The *accretive forces* introduced by Di Carlo and Quiligotti are re-interpreted as homeostatic value of the Eshelby stress, coinciding with the classical biomechanical concept of homeostatic stress in the case of infinitesimal strain. In this context, the main result of the present work is that the theory coincides with well established experimental models. Numerical simulations involving a non-linear orthotropic material evolve according to the qualitative predictions. According to the theory, in the finite strain framework no loaded homogeneous body can reach a steady state; it remains an open question whether this is a failure of the model or a prediction. The existence of a bounded "grown" state can be easily obtained by excluding a boundary layer from the growth process, as in the schematical example of Section 5.

In the present paper we have considered bodies that can store energy just in mechanical form; a natural future direction of investigation is to admit more general forms of energy storage (*i.e.* nutrients, like in [2]), corresponding to more general functional forms of the free energy ψ .

A Linear isotropic material

Introducing the notation $S_{xx} = x, S_{yy} = y, S_{zz} = z$, the growth rate corresponding to the infinitesimal strain of an elastic material (2.13) reads:

$$\Gamma = -\frac{1}{4\mu(2\mu + 3\lambda)} [2(\mu + \lambda)(x^2 + y^2 + z^2) - 2\lambda(xy + xz + yz) + x + y + z] + \text{tr } \mathbb{E}_0. \quad (\text{A.1})$$

Null growth rate occurs in the points of the quadric surface

$$\tilde{\Gamma} : 2(\mu + \lambda)(x^2 + y^2 + z^2) - 2\lambda(xy + xz + yz) + x + y + z - 4\mu(2\mu + 3\lambda)\text{tr } \mathbb{E}_0 = 0.$$

Let A be the matrix associated to the surface $\tilde{\Gamma}$ and B the square matrix that represents the corresponding quadratic form:

$$A = \begin{pmatrix} 2(\mu + \lambda) & -\lambda & -\lambda & 1/2 \\ -\lambda & 2(\mu + \lambda) & -\lambda & 1/2 \\ -\lambda & -\lambda & 2(\mu + \lambda) & 1/2 \\ 1/2 & 1/2 & 1/2 & -4\mu(2\mu + 3\lambda)\text{tr } \mathbb{E}_0 \end{pmatrix},$$

$$B = \begin{pmatrix} 2(\mu + \lambda) & -\lambda & -\lambda \\ -\lambda & 2(\mu + \lambda) & -\lambda \\ -\lambda & -\lambda & 2(\mu + \lambda) \end{pmatrix}.$$

The determinants are

$$\det B = 2\mu^3 \left[9 \left(\frac{\lambda}{\mu} \right)^2 + 12 \frac{\lambda}{\mu} + 4 \right] \neq 0 \quad \text{if} \quad \frac{\lambda}{\mu} \neq -\frac{2}{3} \quad (\text{always satisfied}). \quad (\text{A.2})$$

$$\det A = -\frac{3}{4} \left[13 \left(\frac{\lambda}{\mu} \right)^2 + 18 \frac{\lambda}{\mu} + 6 \right] - 4\mu(2\mu + 3\lambda)\text{tr } \mathbb{E}_0 \det B. \quad (\text{A.3})$$

Assuming that $\text{tr } \mathbb{E}_0 \neq 0$, the determinant of A is always non null and therefore $\tilde{\Gamma}$ is not degenerate.

Moreover, the rank of B is equal to 3 and $\tilde{\Gamma}$ is a centered quadric. Its center is the solution of the system $A \cdot X = 0$, where $X = [x y z 1]^T$; it is clear that the solution is the point $O = (0, 0, 0)$.

In order to define the orientation of the surface $\tilde{\Gamma}$ we calculate the eigenvalues and eigenvector of B :

$$\begin{aligned} \det(B - \alpha I) &= 0 \Leftrightarrow \\ \alpha^3 - 6(\mu + \lambda)\alpha^2 + 3(3\lambda^2 + 8\lambda\mu + 4\mu^2)\alpha - 18\lambda^2\mu - 24\lambda\mu^2 - 8\mu^3 &= 0 \Rightarrow \\ \alpha_1 &= 2\mu, \quad \alpha_{2,3} = 2\mu + 3\lambda. \end{aligned} \quad (\text{A.4})$$

The eigenvector corresponding to the eigenvalue α_1 is $\mathbf{v}_1 = (1, 1, 1)$, while any couple of mutual orthogonal vectors in the plane normal to \mathbf{v}_1 can be chosen to complete the set of eigenvectors. The conclusion is that the quadric surface $\tilde{\Gamma}$ is a round ellipsoid oriented in the direction $(1, 1, 1)$ and centered in the origin.

B A special case: constant growth rate

If all the components of \mathbf{G} are constant, the equation of motion takes the form

$$g_\theta^2 g_z (2\mu + \lambda) r^2 \gamma'' + g_\theta^2 g_z (2\mu + \lambda) r \gamma' - g_r^2 g_z (2\mu + \lambda) \gamma + [\lambda - (2\mu + 3\lambda)g_z](g_\theta - g_r)g_\theta g_r r = 0. \quad (\text{B.1})$$

First, consider first the homogeneous equation

$$g^2 r^2 \gamma'' + g^2 r \gamma' - \gamma = 0 \quad (\text{B.2})$$

where $g := g_\theta/g_r$. A function $\gamma = r^n$ is solution of Equation (B.2) if $n = \pm 1/g$. So the general solution of the equation of motion is

$$\gamma(r) = A_1 r^{1/g} + A_2 r^{-1/g} + \tilde{\gamma}, \quad (\text{B.3})$$

where the particular integral has the form $\tilde{\gamma} = a_0 + a_1 r$. Through some calculation we find that $a_0 = 0$, $a_1 = \frac{g_r g_\theta [g_z(2\mu+3\lambda)-\lambda]}{(2\mu+\lambda)(g_\theta+g_r)g_z}$. The constants A_1 and A_2 are determined using the boundary conditions $P_{rr}(r_1) = \tau_1$ and $P_{rr}(r_2) = \tau_2$. This is equivalent to the linear system

$$\begin{aligned} 2(\mu + \lambda)g_z r_i^{(1/g)-1} A_1 - 2\mu g_z r_i^{-(1/g)-1} A_2 &= \tau_i - a_1 \left[(2\mu + \lambda) \frac{g_\theta g_z}{g_r} + \lambda g_z \right] \\ &+ [(2\mu + 3\lambda)g_z - \lambda]g_\theta, \quad i = 1, 2 \end{aligned} \quad (\text{B.4})$$

which has the solution

$$A_1 = \frac{(\tau_1 + c)(r_2^{2/g} - r_1^{2/g}) + r_1^{-(2/g)+2} r_2^{(1/g)+1} [(\tau_2 + c)r_1^{(1/g)-1} - (\tau_1 + c)r_2^{(1/g)-1}]}{2(\mu + \lambda)g_z(r_2^{2/g} - r_1^{2/g})r_1^{(1/g)-1}} \quad (\text{B.5})$$

$$A_2 = \frac{r_1^{(1/g)+1} r_2^{(1/g)+1} [r_1^{(1/g)-1}(\tau_2 + c) - r_2^{(1/g)-1}(\tau_1 + c)]}{2\mu g_z(r_2^{2/g} - r_1^{2/g})} \quad (\text{B.6})$$

where $c = -a_1[(2\mu + \lambda)\frac{g_\theta g_z}{g_r} + \lambda g_z] + [-\lambda + (2\mu + 3\lambda)g_z]g_\theta$.

If $g_r = g_\theta = g_z = 1$, i.e. there is no growth, the solution reduces to $\gamma(r) = (A_1 + a_1)r + A_2(1/r)$, with

$$A_1 + a_1 = \frac{\tau_2 r_2^2 - \tau_1 r_1^2}{2(\mu + \lambda)(r_2^2 - r_1^2)} + 1, \quad A_2 = \frac{r_1^2 r_2^2 (\tau_2 - \tau_1)}{2\mu(r_2^2 - r_1^2)}. \quad (\text{B.7})$$

If we consider now the radial displacement $u_r(r) = \gamma(r) - r = (A_1 + a_1 - 1)r + B_1(1/r)$ we recover the classical solution described by Eringen (see [6], p.212), according to the following relation between the constants $a = r_1$, $b = r_2$, $p_0 = -\tau_1$, $p_1 = -\tau_2$:

$$C_1/2 = A_1 + a_1 - 1 = \frac{-p_1 b^2 + p_0 a^2}{2(\mu + \lambda)(b^2 - a^2)} = \frac{\tau_2 r_2^2 - \tau_1 r_1^2}{2(\mu + \lambda)(r_2^2 - r_1^2)} \quad (\text{B.8})$$

$$C_2 = A_2 = \frac{a^2 b^2 (-p_1 + p_0)}{2\mu(b^2 - a^2)} = \frac{r_1^2 r_2^2 (\tau_2 - \tau_1)}{2\mu(r_2^2 - r_1^2)} \quad (\text{B.9})$$

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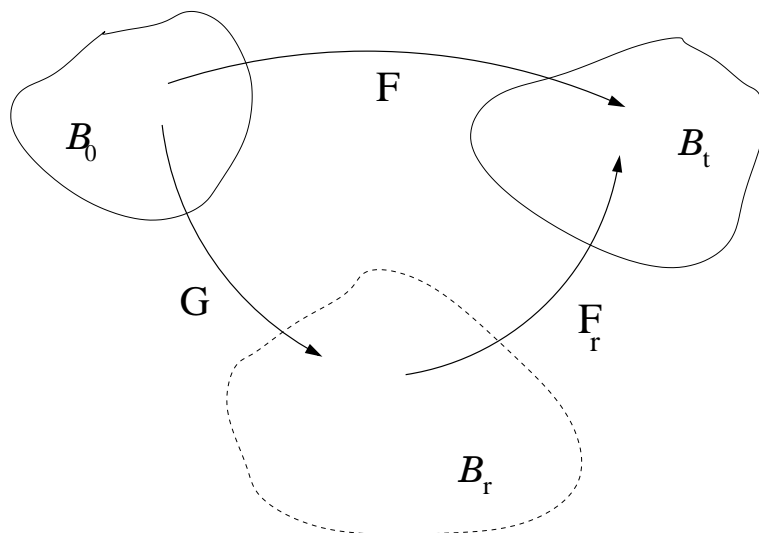


Figure 1: The multiplicative decomposition of the tensor gradient of deformation $\mathbf{F} = \mathbf{F}_r \mathbf{G}$.

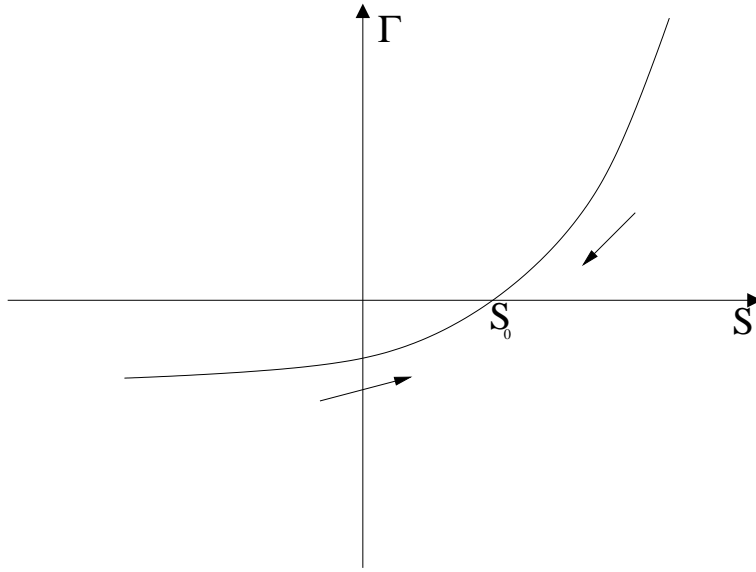


Figure 2: Eshelbian stress-growth relation for an elastic material: the arrows indicate the evolution in time of the total growth rate depending on the stress state.

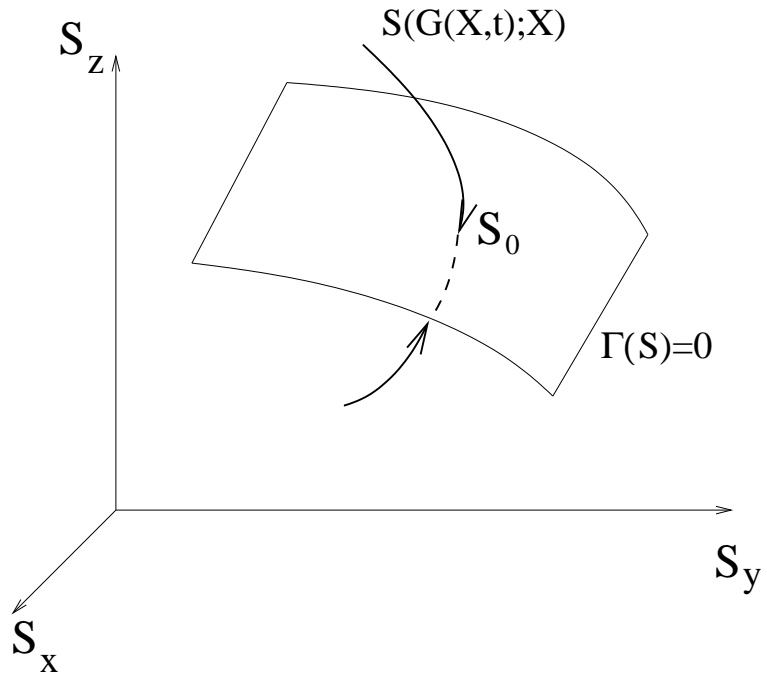


Figure 3: Trajectory of the local stress state of a growing body: the surface $\Gamma = 0$ is of unstable equilibrium.

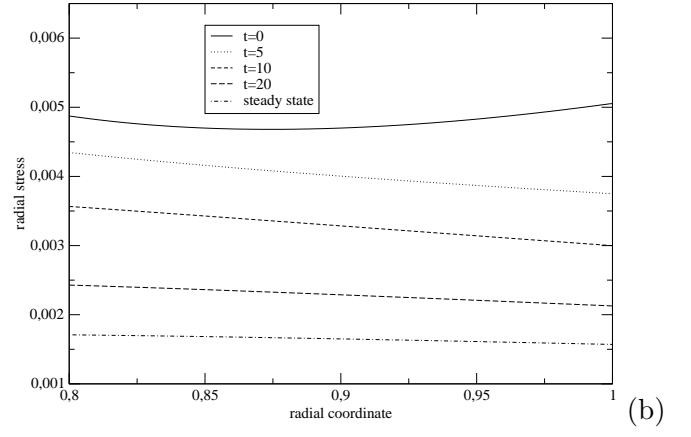
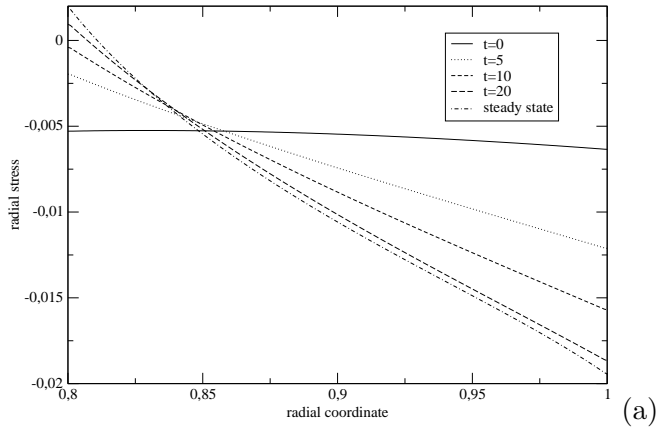


Figure 4: Radial component of the stress versus the radial coordinate for a grown body with displacement boundary conditions: extension (a) and contraction (b) at different times.

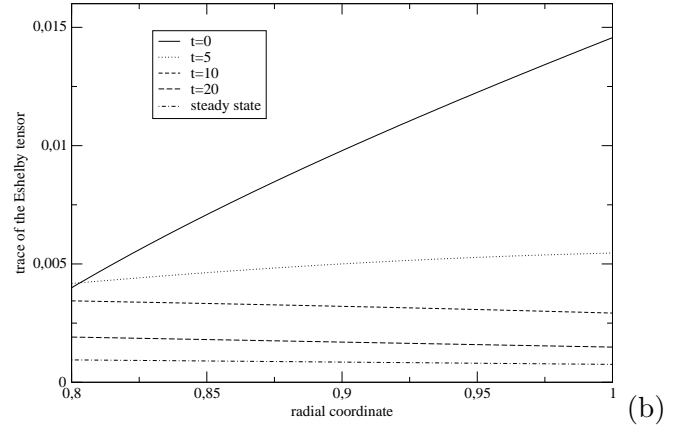
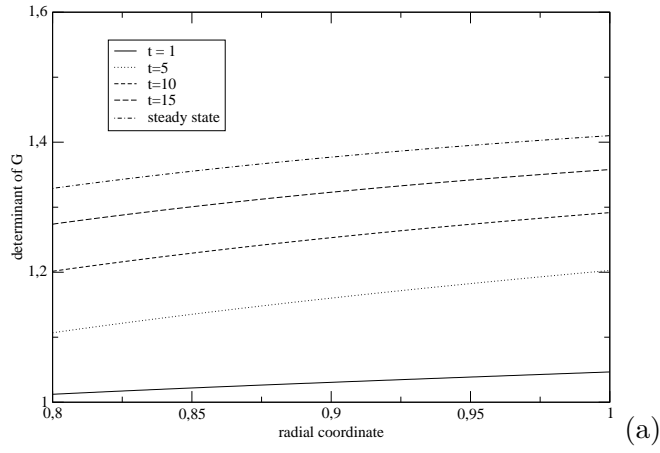


Figure 5: Determinant of the growth tensor \mathbf{G} at different times for a body with applied (extensive) displacement at the boundary (a) and trace of the Eshelby tensor for a body with applied (extensive) displacement at the boundary (b).

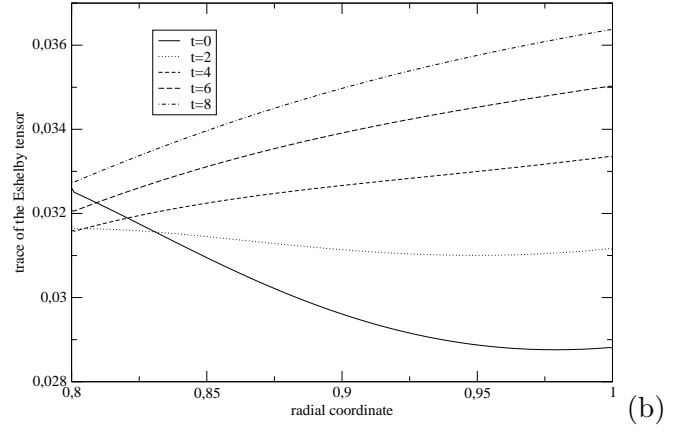
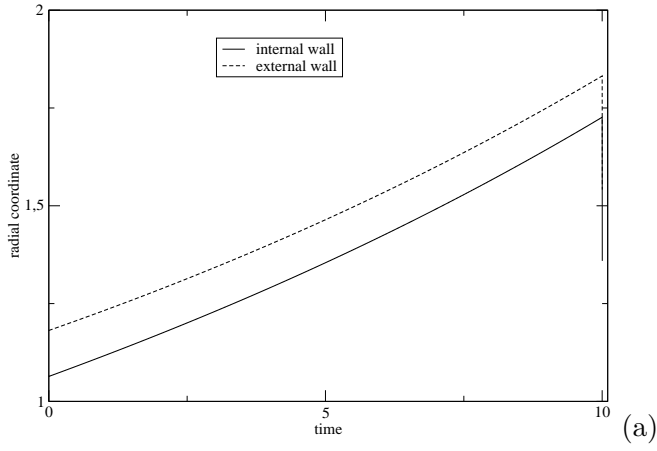


Figure 6: Position of the internal and external boundary versus time for a symmetric annulus undergoing compression at the internal wall (a). The trace of the Eshelby tensor is plotted versus the radial coordinate at different times (b).

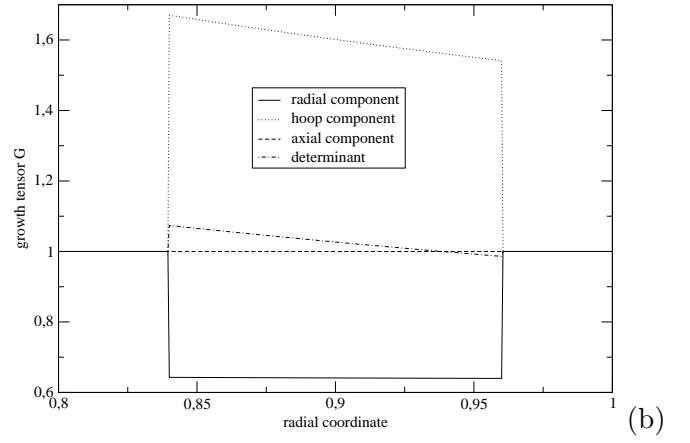
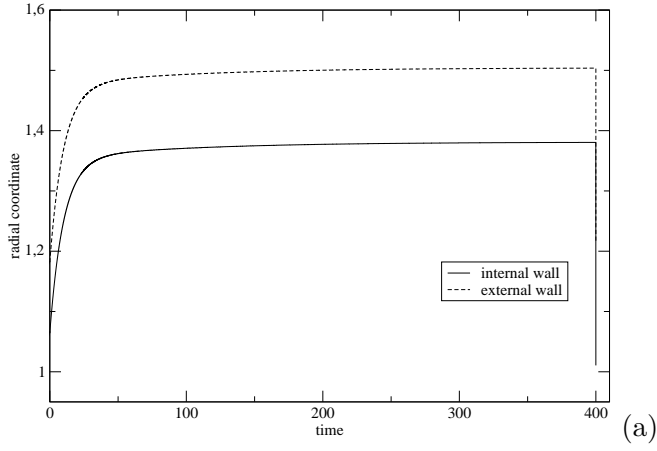


Figure 7: Position of the boundary versus time for non-homogeneous annulus loaded at the internal wall (a). The non-null components and the trace of the growth tensor \mathbf{G} at the steady state are plotted versus the radial coordinate (b)

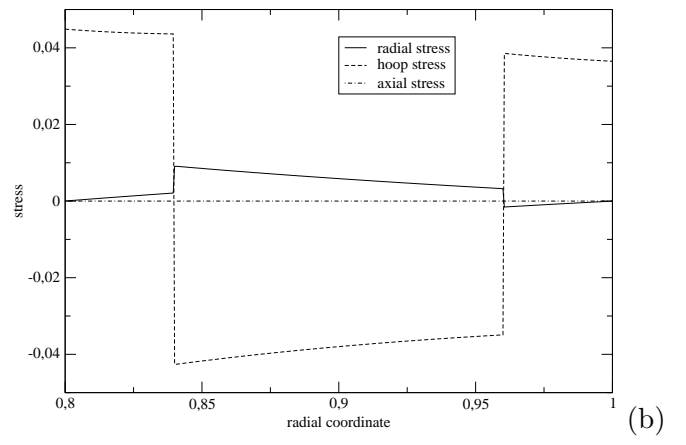
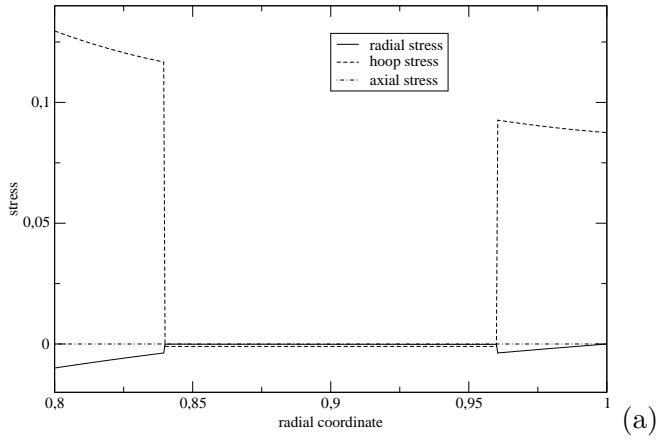


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