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Mechanical Aspects of Growth in Soft Tissues.

D. Ambrosi - F. Guana

Sunto. – *Negli ultimi anni grande attenzione è stata dedicata alla comprensione dei processi di crescita dei tessuti molli regolati dallo stato di sforzo. Recenti sviluppi teorici suggeriscono che esista un accoppiamento sforzo-crescita attraverso il tensore Eshelby, indipendente dal tessuto biologico in esame. In questo articolo si studiano le proprietà meccaniche e il comportamento qualitativo dettati dalle equazioni che caratterizzano il modello sotto alcune semplici ipotesi. Le equazioni dedotte da un principio di dissipazione sono confrontate con le equazioni fenomenologiche che descrivono in modo accurato i dati sperimentali. Vengono inoltre discussi i risultati di simulazioni numeriche sulla crescita di un anello simmetrico elastico in relazione al processo di rimodellamento osservato nelle arterie.*

Summary. – *In the last years many efforts have been devoted to understand the stress-modulated growth of soft tissues. Recent theoretical achievements suggest that 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. Equations strictly deduced from a dissipation principle are compared with heuristic ones that fit well the experimental data. Numerical simulations of the growth of a symmetric annulus are discussed.*

Introduction.

The stress-modulated growth of soft tissues has been the subject of several of experimental papers concerning a variety of specific biological systems. The most extensively studied biological systems are probably arterial walls [5, 7], with their complex behavior in response to changes in blood pressure or blood flow rate [9]. While few heuristic growth laws based on these experimental observations have been devised, equations strictly deduced from *a priori* principles are almost lacking. In a recent paper DiCarlo and Quiligotti [3], on the basis of the theory of Rodriguez *et al.* [6], state a dissipative principle 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. Aim of this paper is to investigate the nature of the equations that arise from such an approach for a simple material: an elastic solid that can only store mechanical energy.

For a more extended analysis as well as for further results we refer to [2].

1. – Kinematics and balance equations.

In this section are reviewed the main results about kinematics and dynamics of growing one-component solids according to [6] and [3]. 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 $\boldsymbol{F}$ the deformation gradient, i.e. the gradient of the motion function, and $J := \det \boldsymbol{F}$. The coordinate $\boldsymbol{X}$ spans the body $\mathcal{B}_0$. 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

$$(1.1) \qquad \dot{(\varrho J)} = \Gamma \varrho J, \qquad \operatorname{Div}(J\boldsymbol{T}\boldsymbol{F}^{-T}) = 0\,,$$

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

According to [6], the space of the descriptors of the system is enlarged by introducing a multiplicative decomposition of the deformation gradient, similar to the one used in plasticity theory: $\boldsymbol{F} = \boldsymbol{F}_r \boldsymbol{G}$. In this framework $\boldsymbol{G}$ is the growth tensor and $\boldsymbol{F}_r$ accounts for mechanical behavior of the grown body. In general, inhomogeneous growth originates residual stresses in a body. Then $\mathcal{B}_r$ has to be understood as the *configuration* that a body would take when the integrity condition is relaxed and internal stresses vanish, even if, out of very special cases, it cannot be a physical state; this is why we prefer to call $\mathcal{B}_r$ the *relaxed state*. This characterization of the state $\mathcal{B}_r$ corresponds to require that

$$(1.2) \qquad \Gamma = \frac{\dot{J}_g}{J_g} = \operatorname{trace}(\dot{\boldsymbol{G}}\boldsymbol{G}^{-1}),$$

where $J_g := \det \boldsymbol{G}$ [1]. The continuity equation $(1.1)_1$, with $J_r := \det \boldsymbol{F}_r$, rewrites in the form:

$$(1.3) \qquad \dot{(\varrho J_r)} = 0\,.$$

REMARK. – Consider an elastic body. As 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 rotation part of the polar decomposition of $\boldsymbol{F}_r$. It follows that after operating the multiplicative decomposition of the deformation gradient described above, we can always take the polar decomposition of the tensor $\boldsymbol{F}_r$, incorporate the rotation part into $\boldsymbol{G}$ and then keep such a decomposition to replace the original one. Therefore we can always suppose that $\boldsymbol{F}_r$ is a symmetric positive definite tensor.

2. – Constitutive theory via a dissipation principle.

In the present context thermal energy is neglected, as usual in biomechanics. Energy is supplied to the system in terms of work of standard external forces that balance the internal ones and it will be at most all stored as available mechanical energy, while the energy required for the growth process is externally supplied as the work of *accretive* forces [3]. We therefore write the following dissipation principle:

$$(J\dot{\varrho\psi}) \leqslant J\boldsymbol{T}\cdot\boldsymbol{L} + J\varrho\boldsymbol{C}\cdot\dot{\boldsymbol{G}}\boldsymbol{G}^{-1}, \tag{2.1}$$

where ψ is the free energy per unit mass of the body in the initial configuration $\mathcal{B}_0$, supposed to be a convex function $\psi = \psi(\boldsymbol{F}_r)$ and $\boldsymbol{C}$ is the tensor of internal accretive forces that are balanced by the external ones $\boldsymbol{B}$ ($\boldsymbol{C} = \boldsymbol{B}$). After some calculations, from (2.1) we obtain

$$(J_r\boldsymbol{T}\boldsymbol{F}_r^{-T} - \psi')\cdot\dot{\boldsymbol{F}}_r + (\boldsymbol{F}_r^T J_r\boldsymbol{T}\boldsymbol{F}_r^{-T} + \boldsymbol{C} - \psi\boldsymbol{I})\cdot\dot{\boldsymbol{G}}\boldsymbol{G}^{-1} \geqslant 0 \tag{2.2}$$

where ψ' denotes the Frechet derivative of ψ and we have supposed $(\varrho J_r)\,|_{t=0} = 1$ for all $\boldsymbol{X}$.

We assume that $\boldsymbol{C}$ can be additively decomposed into two terms corresponding to reversible and irreversible contribution: $\boldsymbol{C} = \boldsymbol{C}^+ - \boldsymbol{F}_r^T J_r\boldsymbol{T}\boldsymbol{F}_r^{-T} + \psi\boldsymbol{I}$. The inequality (2.2) is always satisfied if $J_r\boldsymbol{T}\boldsymbol{F}_r^{-T} = \psi'$, $\boldsymbol{C}^+ = \mathrm{K}\dot{\boldsymbol{G}}\boldsymbol{G}^{-1}$, where K is a constant symmetric positive-definite matrix. These assumptions yield the constitutive relationships

$$\boldsymbol{T} = \frac{1}{J_r}\psi'\boldsymbol{F}_r^T, \qquad \boldsymbol{C} = \psi\boldsymbol{I} - \boldsymbol{F}_r^T J_r\boldsymbol{T}\boldsymbol{F}_r^{-T} + \mathrm{K}\dot{\boldsymbol{G}}\boldsymbol{G}^{-1}. \tag{2.3}$$

Finally, thanks the continuity equation in the form (1.3), the equations to solve are

$$\mathrm{Div}\,(J_g\psi'\boldsymbol{G}^{-T}) = 0\,, \tag{2.4}$$

$$\mathrm{K}\dot{\boldsymbol{G}} = [-(\psi\boldsymbol{I} - \boldsymbol{F}_r^T\psi') + \boldsymbol{B}]\boldsymbol{G}\,. \tag{2.5}$$

After specifying the constitutive form for ψ, the balance equation for standard forces (2.4) provides the (instantaneous) displacement field for given traction (or displacement) at the boundary and known growth tensor $\boldsymbol{G}$. The latter evolves according to the ordinary differential equation in time (2.5) which, in other terms, determines the evolution in time of the relaxed state $\mathcal{B}_r$.

3. – Growth rate.

The accretive forces $\boldsymbol{B}$ in (2.5) 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 $\boldsymbol{B} = \mathbb{E}_0$ constant in time and space. According to equation (2.5), the growth rate of $\boldsymbol{G}$ depends on the Eshelby-like tensor

$$\mathbb{E} := \psi \boldsymbol{I} - \boldsymbol{F}_r^T \psi' , \tag{3.1}$$

that in one spatial dimension is the opposite of the Legendre transform of the strain energy. Consider the tensor $\boldsymbol{S} := \psi'$, that can be interpreted as the Piola tensor in the coordinate system of the relaxed state. It can be shown that it exists a one to one relationship between stress $\boldsymbol{S}$ and $\mathbb{E}$. The equilibrium points of the system (2.5) are the solutions $\boldsymbol{S}_0$ of the algebraic equation $\mathbb{E}(\boldsymbol{S}) = \mathbb{E}_0$. When $\boldsymbol{S} = \boldsymbol{S}_0$ every component of the growth tensor is constant in time.

A weaker equilibrium condition is formulated when using equations (2.5) and (1.2); by the definition (3.1) one finds that the growth rate Γ is proportional to the trace of the Eshelby tensor

$$\Gamma = -\operatorname{tr}(\mathrm{K}^{-1}(\mathbb{E} - \mathbb{E}_0)) , \tag{3.2}$$

In principle the macroscopic growth of a body can be null even though growth occurs along single directions. As an example, consider the infinitesimal deformation of an elastic body in the three dimensional space: the strain energy and the infinitesimal strain read

$$\psi = \mu \operatorname{tr}(\boldsymbol{E}^2) + \frac{\lambda}{2}(\operatorname{tr}(\boldsymbol{E}))^2, \qquad \boldsymbol{E} = \frac{1}{2\mu}\left(\boldsymbol{S} - \frac{\lambda}{2\mu + 3\lambda}\operatorname{tr}(\boldsymbol{S})\,\boldsymbol{I}\right). \tag{3.3}$$

By some calculations one gets the following expression for the growth rate:

$$\Gamma = \operatorname{tr}\mathbb{E}_o - \frac{1}{4\mu}\operatorname{tr}(\boldsymbol{S}^2) + \frac{\lambda}{4\mu(2\mu + 3\lambda)}(\operatorname{tr}\boldsymbol{S})^2 + \operatorname{tr}\boldsymbol{S} . \tag{3.4}$$

The equation $\Gamma = 0$ defines, in the stress space, a round ellipsoid, centered in the origin, with the symmetry axis pointing into the direction $(1, 1, 1)$. When the stress state lies on this surface the system stops growing macroscopically.

At this stage one wonders if the qualitative behavior predicted by the system of equations (2.4)-(2.5) resembles, at least at some extent, the experimental one. According to Taber «experiments show that the growth rate increases with the magnitude of the applied stress» [7] and this is in agreement with the present model. Moreover, if we consider the case of arterial walls, we can show that the well known stress-growth relationships [8], that fit well the experimental data, are included in the theoretical framework provided by the present theory, where growth rate is deduced from *a priori* principle. In fact, under suitable assumptions and through a process of linearization in time, the growth laws proposed by Taber (omitting shear contributions) in the form

$$\dot{G}_{rr} = k_r (T_{\theta\theta} - T^0_{\theta\theta}), \quad \dot{G}_{\theta\theta} = k_\theta (T_{\theta\theta} - T^0_{\theta\theta}), \quad \dot{G}_{zz} = 0 \tag{3.5}$$

where $T^0_{\theta\theta}$ is the homeostatic stress, can be deduced from (2.5).

4. – Stress-modulated growth.

In the section above it has been outlined how growth depends on stress, but how does stress evolve in time depending on the growth tensor $\boldsymbol{G}$? Let us consider $\boldsymbol{S}$ as a function of $\boldsymbol{G}$ for a given deformation $\boldsymbol{F}$:

$$\boldsymbol{S} = \psi'(\boldsymbol{F}\boldsymbol{G}^{-1}). \tag{4.1}$$

The situation differs substantially if boundary conditions apply to strain or stress. In the case of pure Dirichlet boundary conditions the growth process is free to accommodate the stress field according to equation (4.1) in any point of the body. The volume of the body remains unmodified, although its mass locally and globally changes up to reaching in the whole body the stable homeostatic stress state $\boldsymbol{S} = \boldsymbol{S}_0$, that is $\boldsymbol{F}_r = \boldsymbol{I}$. In case of traction boundary conditions a load is imposed at least on a portion of the boundary. As the evolution law (2.5) is strictly local, in the whole body the growth attempts to accomplish stress relaxation. However, no possibility exists to reach any steady state because the condition $\mathbb{E}(\boldsymbol{S}) = \mathbb{E}_0$ can never be satisfied in all the domain. The only two possible scenarios are therefore that the body indefinitely grows (under tension) or shrinks to a point (under compression). When both tensile and compressive stress are generated by the boundary conditions, the system will however evolve case by case toward these two final states and no other equilibrium states are expected to exist.

5. – Numerical simulations.

Let us represent the artery as a symmetric annulus of elastic material. Then the displacement vector $\boldsymbol{u} = (u_r(r), 0, 0) = (\gamma(r) - r, 0, 0)$ is a function only of the radial coordinate r fixed on the body in its initial configuration ($r_1 \leqslant r \leqslant r_2$). We assume that deformation is small when compared with the relaxed state and therefore we adopt the form of the stress tensor $\boldsymbol{S}$ and strain energy for linear isotropic elastic material (3.3) where $\boldsymbol{E} = \mathrm{Sym}(\boldsymbol{F}_r - \boldsymbol{I}) =$

diag $(\gamma'/g_r - 1,\ \gamma/rg_\theta - 1,\ 1/g_z - 1)$. Strain is usually not small in mechanics of soft tissues and exponential strain energies are usually adopted; however nonlinearity does not affect the qualitative behavior predicted by the mathematical model, which is the subject of this early investigation.

If $\boldsymbol{G} = \boldsymbol{G}(r)$ the equation of motion in cylindrical coordinates is

$$(2\mu+\lambda)\frac{g_\theta g_z}{g_r}\gamma'' + \tag{5.1}$$

$$+(2\mu+\lambda)\left[\left(\frac{g_\theta g_z}{g_r}\right)' + \frac{1}{r}\frac{g_\theta g_z}{g_r}\right]\gamma' + \left[\lambda g_z' - (2\mu+\lambda)\frac{g_r g_z}{r g_\theta}\right]\frac{\gamma}{r} +$$

$$+\lambda g_\theta' - (2\mu+3\lambda)(g_\theta g_z)' + \frac{\lambda}{r}(g_\theta - g_r) - (2\mu+3\lambda)\frac{g_z}{r}(g_\theta - g_r) = 0\,.$$

Displacement boundary conditions. Two sets of Dirichlet boundary conditions are considered, corresponding to 50% extension or contraction. In both cases the numerical simulations agree with the qualitative analysis: the radial stress is damped exponentially in time thus newly leading to a homeostatic stress $\boldsymbol{S}_0$ of the grown body.

Load boundary conditions. Consider an applied load at the internal wall of the cylinder. At $t = 0$ the body immediately displaces and the stress field is provided in terms of classical explicit solutions (see [4]). 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 of mass and both the internal and external radius grow indefinitely. The process reaches a steady state if we assume that the body is not homogeneous but composed by two layers and that there is no growth in the internal one (for the sake of simplicity, take $\mathbb{E}_0 = 0$). The growth process accommodates all the stress in the ungrown region by a suitable tuning of residual stress.

Note that if there is no growth, i.e. $g_r = g_\theta = g_z = 1$, the solution of (5.1) reduces to the classical one described by Eringen [4] for a cylindrical tube subject to internal and external pressures.

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