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On the mechanics of a growing tumor

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Abstract

In this paper we study tumor growth within the framework of Continuum Mechanics, considering a tumor as a specific case of a growing soft tissue. Using the notion of multiple natural configurations we introduce a mechanical description that splits volumetric growth and mechanical response into two separate contributions. Growth is described as an increase of the mass of the particles of the body and not as an increase of their number. As tumor growth strongly depends upon the availability of nutrients and on the presence of chemical signals, such as growth factors, their diffusion through the growing material is introduced in the description. The model is then applied to describe the homogeneous growth inside a rigid cylinder, a model mimicking the growth of a ductal carcinoma, and to the growth of a multicell spheroid fed by a non-homogeneous diffusion of nutrients. In the latter case residual stresses are generated because the non-uniform distribution of nutrients leads to inhomogeneous growth.

Keywords: Biomechanics; Growth; Tumor

1. Introduction

The description of tumor growth requires taking quite a large number of biological effects into account. This is probably the reason why people have concentrated their effort on modelling the complex response of cell populations to chemical factors and nutrients rather than on the mechanics of the ensemble of tumor cells, i.e., the multicell spheroid. In fact, the approach usually encountered in the literature is to write down a balance equation for the cell population and a set

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of reaction-diffusion equations for those nutrients and chemical factors which are thought to influence growth and motion. The main challenges involved in developing such models are then in describing how cells migrate, reproduce and die and how various chemicals diffuse, are produced and taken up by the cells. On the other hand, these mathematical models do not involve the concept of stress and do not allow the investigation of the relevance that mechanical aspects may have for tumor growth and development (for instance shown in [8]) as well as the impact that tumor growth may have on the surrounding tissues.

In order to overcome this difficulty, very recently a mathematical description of a vascular tumor as a multiphasic system, namely a saturated porous material, has been proposed [1,4,12]. This approach starts from the observation that multicell spheroids are basically made of two constituents: a solid skeleton constituted by an ensemble of sticky cells and an organic liquid filling the extracellular space, which is used by the cells to grow. The introduction of such a mechanical framework allows one to deal with stresses and with their influence on the evolution of the system. However, these models are based on the constitutive assumption that an ensemble of cells behaves as a "viscous growing fluid", so that one does not need to describe the deformations of the material with respect to some reference configuration, but only to deal with their rates. In this respect, it is possible to use an Eulerian framework and the mathematical description of the "growing fluid" just involves an additional source of mass.

Things are more complicated when the material exhibits mechanical properties typical of solids (at least to some extent), as a solid continuum requires the knowledge of its deformation to define a mechanical response. The question in this case is: "Deformation with respect to what?".

In classical Continuum Mechanics a body is seen as a collection of particles [26]. Each particle can be labelled by its location in a certain reference configuration of the body. One way of describing the growth of a body is to imagine that new particles, that were not present in the original configuration, appear. Such an approach has the shortcoming that it is impossible to define a motion that maps the original configuration onto the current one, since the new particles would have no counterpart in the original configuration. A possible way to overcome this difficulty is to solve the problem using an Eulerian frame of reference. On the other hand, the Eulerian approach is not suitable when one tries to solve boundary value problems for solid bodies undergoing large deformations, since boundary conditions can only be formulated in the current configuration, which is an unknown of the problem, often the ultimate goal.

Another important point is the choice between the framework of "single constituent" mechanics and mixture theory. In mixture theory [13] growth reads as a *mass exchange* between phases. As an example, in a tumor spheroid the growth of cells actually occurs at the expense of the extracellular fluid. However, the theory of mixtures, while clarifying the real nature of the mass source, yields two well-known difficulties: the definition in the form of the partial stresses, that is the stress that acts on the components in the mixture, and the imposition of boundary conditions, that typically involve continuity of physical quantities (mass flow, stress) that have a different meaning on the two sides of the boundary [2].

Here we model the growing material as a single phase continuum, in which growth is not seen as an increase of the number of particles, but as an *increase of the mass of the already existing particles*. In the specific case of biological tissues, a particle can be thought of as a small region of space, for example the visual field of a microscope containing a sufficiently large number of cells. In such a case, at any configuration of the body there can be exactly the same particles that were

there in the original configuration, so that it is possible to define a motion that connects all of these configurations. The total mass of the body in going from the original to the current configuration may change because the mass of the particles may have changed. In this single-constituent framework the use of an Eulerian frame of reference is not mandatory.

The modelling of growth of soft tissues within a Continuum Mechanics framework for a single constituent has been discussed in the past by Skalak et al. [23], Rodriguez et al. [22] and an excellent review article on the subject is due to Taber [25]. In these papers the basics of growth kinematics are laid down and also the influence of stress on growth is taken into account.

Recently, Rajagopal and coworkers [15,16] have introduced the notion of multiple natural configurations and used it to study many different phenomena, such as metal plasticity [17], twinning [14], shape memory alloys [18], viscoelastic fluids [19] and crystallization in polymers [21]. The theory for materials with multiple natural configurations is an ideal setting to investigate the process of growth. In fact, the essential difficulty in formalizing the dynamics of growth is to model simultaneously the change in mass and the stresses that accompany it, possibly caused by growth itself or by the application of external loads. The theory for materials with multiple natural configurations enables to separate such contributions in an elegant way and to model each of them individually.

In this paper we will use the notion of multiple natural configurations and the concept of growth mentioned above to study the volumetric growth of a continuous medium in a general way, having in mind tumor growth as a specific application. In particular, we discuss a description of the mechanical properties of a growing medium that splits growth and mechanical response into two separate contributions. The biological mechanism that growth takes place depending upon the availability of nutrients, particularly relevant for tumor growth, is also taken into account.

This paper is organized as follows. Section 2 deals with the kinematics of growth, in Section 3 the concept of multiple natural configurations is applied to growing tissues. Balance laws are introduced in Section 4 while Section 5 is dedicated to clarify relationship between the growth tensor, appearing in the multiple natural configuration framework, and the growth rate appearing in the mass balance equation, which is the quantity usually described by biologists. In Section 6 we discuss the equations for the diffusion of nutrient and in Section 7 we formulate the constitutive equations of this model, which are further specialized to our particular biological case in Section 8. The last section is devoted to some examples of applications in simple geometries, namely isotropic and homogeneous growth inside a rigid cylinder, which mimics the growth of a ductal carcinoma, and isotropic inhomogeneous growth of a sphere regulated by the availability of nutrients, which refers to the growth of a multicell spheroid. In this case, the non-uniform distribution of nutrients leads to inhomogeneous growth: the outer layers grow faster than the inner ones and this in turn generates residual stresses.

2. Kinematics of growth

Let a body be in the configuration κ_0 at time $t = 0$. Suppose that the body has undergone growth or resorption together with the possible application of loads, so that at current time t the configuration is κ_t (see Fig. 1).

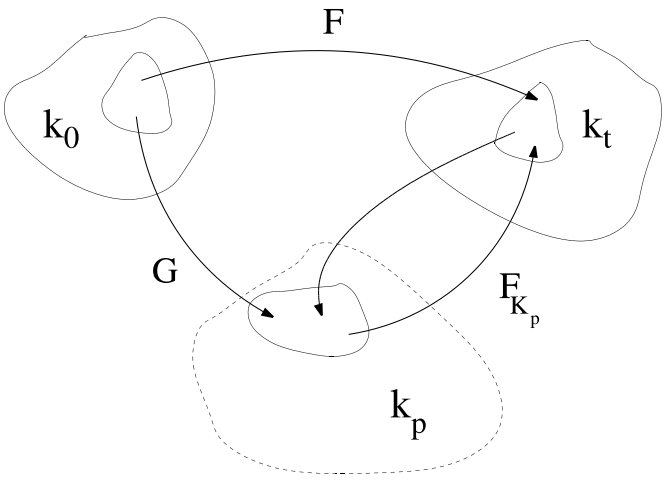

Fig. 1. Diagram of the motion from the original unstressed configuration κ_0 to the current configuration κ_t. If we cut a generic particle out of the body at time t and relieve its state of stress while keeping its mass constant, it will reach its *natural state* at time t. The "*natural configuration* of the body at time t" is the collection of all the particles in their natural states at time t.

Let $\mathbf{X}$ be the position of a given particle at time $t = 0$ and let $\mathbf{x}$ be the position of the same particle in the current configuration κ_t. Since the same particles are present in both the original and current configuration we can define the motion of the body [26]:

$$\mathbf{x} = \boldsymbol{\chi}(\mathbf{X}, t) \tag{2.1}$$

and the corresponding deformation gradient, supposed to be invertible:

$$\mathbf{F} = \frac{\partial \boldsymbol{\chi}}{\partial \mathbf{X}}. \tag{2.2}$$

The velocity is given by

$$\mathbf{v} = \frac{\partial \boldsymbol{\chi}}{\partial t}, \tag{2.3}$$

while

$$\varrho = \varrho(\mathbf{x}, t) \tag{2.4}$$

is the density field at time t so that $\varrho_0(\mathbf{X}) = \varrho(\mathbf{x}(\mathbf{X}, 0), 0)$ is the density field at time $t = 0$. Then, if we denote by $\mathrm{d}V$ the volume occupied by a generic particle at time $t = 0$, the initial mass of the particle will be given by

$$\mathrm{d}M_0 = \varrho_0(\mathbf{X})\,\mathrm{d}V. \tag{2.5}$$

Analogously, the current mass of the same particle at current time is

$$\mathrm{d}M = \varrho(\mathbf{x}, t)\,\mathrm{d}v, \tag{2.6}$$

where dv is the volume of the same particle at time t. We will say that growth takes place at $\mathbf{x}$ if

$$dM > dM_0 \tag{2.7}$$

and, conversely, that resorption takes place if

$$dM < dM_0. \tag{2.8}$$

3. Multiple natural configurations in the modelling of growth

Consider the motion from the original unstressed configuration κ_0 to the current configuration κ_t as depicted in Fig. 1. Each particle of the body may have grown or been resorbed and the state of stress may be different from zero. If we now cut a generic particle out of the body and relieve its state of stress while keeping its mass constant, it will reach a state that is in general different from the one it had in κ_0 and also from the one achieved in κ_t. This is the *natural state* of that particle at time t, while the "*natural configuration* of the body at time t" is the collection of all the particles in their natural states at time t. As indicated in Fig. 1, we can measure the deformation from the natural configuration κ_p through the tensor $\mathbf{F}_{\kappa_p}$, while the path from κ_0 to the natural configuration κ_p, which can be seen as a path of unconstrained growth, will be described by the tensor $\mathbf{G}$, so that the following decomposition holds:

$$\mathbf{F} = \mathbf{F}_{\kappa_p}\mathbf{G}. \tag{3.1}$$

Notice that, since mass is preserved along the path from κ_p to κ_t, the tensor $\mathbf{F}_{\kappa_p}$ is not directly related to growth. Hence we will assume that $\mathbf{F}_{\kappa_p}$ is connected to the stress response of the material while the tensor $\mathbf{G}$ is the one that is directly connected to growth and will be therefore named *growth tensor*. In this way we have separated the contribution of pure growth from the stress-inducing deformation. The tensors $\mathbf{F}_{\kappa_p}$ and $\mathbf{G}$ behave in the same way as the deformation gradient $\mathbf{F}$: the deformation gradient $\mathbf{F}$ is a mapping from a tangent space onto another tangent space, and therefore indicates how the body is deforming locally in going from κ_0 to κ_t. In a completely analogous way $\mathbf{F}_{\kappa_p}$ tells how the body is deforming locally in going from the natural configuration κ_p to κ_t, while $\mathbf{G}$ tells how the body is growing locally. As the deformation gradient $\mathbf{F}$ is invertible, from Eq. (3.1) follows that $\mathbf{F}_{\kappa_p}$ and $\mathbf{G}$ are invertible too.

In what we have done up to now we have tacitly assumed that the natural state reached upon unloading from the current configuration is unique. This is a necessary assumption of the theory for materials with multiple natural configurations. However, notice that many materials obey to this assumption, e.g. elastic materials and also some viscoelastic materials such as the Kelvin–Voigt material. One of the consequences of this assumption is that the density field in the natural configuration is identical to the density field in the original reference configuration.

Let dV_p be the volume of the generic particle in the natural configuration. Then, since mass is preserved between κ_p and κ_t,

$$dM = \varrho_0(\mathbf{X})\, dV_p \tag{3.2}$$

and also from Eqs. (3.2) and (2.5)

$$J_G =: \det \mathbf{G} = \frac{\mathrm{d}V_p}{\mathrm{d}V} = \frac{\mathrm{d}M}{\mathrm{d}M_0}. \tag{3.3}$$

The tensor $\mathbf{G}$ is thus sufficient to tell whether a certain particle is growing or being resorbed. In fact, from Eqs. (2.7), (2.8) and (3.3) we have

$$\begin{aligned} &J_G < 1 \;\Rightarrow\; \text{resorption},\\ &J_G > 1 \;\Rightarrow\; \text{growth}. \end{aligned} \tag{3.4}$$

The polar decomposition theorem can be applied to the growth tensor $\mathbf{G}$: there exist a unique rotation $\mathbf{R}_G$ and a unique symmetric tensor $\mathbf{U}_G$ such that

$$\mathbf{G} = \mathbf{R}_G\mathbf{U}_G. \tag{3.5}$$

If the material is isotropic, without loss of generality one can choose the natural configuration such that

$$\mathbf{G} = \mathbf{U}_G \tag{3.6}$$

and the growth tensor becomes symmetric.

Even if the material is not isotropic, in principle one could include a rotation in the definition of κ_p so that $\mathbf{G}$ is symmetric. However, in general this procedure has the drawback that it does not allow to define the constitutive equation for the stress-induced deformation independently of growth.

4. Balance laws

In this section we write the equations for the balance of mass and linear momentum for a growing continuous medium on the basis of the theory introduced above.

4.1. Mass balance

The motion from κ_0 to κ_t obeys to the usual equation of balance of mass with a source term [13]; in Eulerian form it reads

$$\frac{\partial \varrho}{\partial t} + \operatorname{div}(\varrho\mathbf{v}) \equiv \dot{\varrho} + \varrho \operatorname{div}\mathbf{v} = \Gamma\rho, \tag{4.1}$$

where Γ is the growth rate (possibly dependent on the state variables of the problem). The divergence operator applies to quantities calculated in a fixed position of the space and a superscript dot $(\dot{})$ denotes the material time derivative.

In a Lagrangian frame of reference Eq. (4.1) rewrites

$$(\varrho\dot{J}) = \Gamma\rho J, \tag{4.2}$$

where $J := \det \mathbf{F}$. Since mass conservation is satisfied along the path from the natural configuration to the current one we have:

$$\mathrm{d}M = \varrho_0 \,\mathrm{d}V_p = \varrho \,\mathrm{d}v. \tag{4.3}$$

Using (3.3) we have

$$\varrho_0 J_G \,\mathrm{d}V = \varrho J \,\mathrm{d}V, \tag{4.4}$$

which can be further simplified using (3.1):

$$\varrho_0 = \varrho J_{\kappa_p}, \tag{4.5}$$

where $J_{\kappa_p} := \det \mathbf{F}_{\kappa_p}$.

Eq. (4.5) resembles the usual Lagrangian version of conservation of mass in the absence of mass sources. The simplicity of this last equation is a consequence of our assumption that mass is conserved from κ_p to κ_t.

4.2. Balance of linear momentum

The balance of linear momentum reads:

$$\frac{\partial}{\partial t}(\varrho \mathbf{v}) + \operatorname{div}(\varrho \mathbf{v} \otimes \mathbf{v}) - \operatorname{div} \mathbf{T} = \varrho \mathbf{b} + \Gamma \varrho \mathbf{v}, \tag{4.6}$$

where **T** is the Cauchy stress tensor, **b** is the body force and the last term at the right-hand side represents the contribution to the momentum due to the mass source. Using the mass balance equation (4.1) the momentum equation rewrites

$$\varrho \dot{\mathbf{v}} = \operatorname{div} \mathbf{T} + \varrho \mathbf{b}. \tag{4.7}$$

In the case of biological tissues, the characteristic velocities are so small that we can neglect the inertial terms in Eq. (4.7) and the system can be conveniently described as quasi-static. Moreover, as it is usual in Solid Mechanics, we will neglect the body forces, so that the local form reduces to:

$$\operatorname{div} \mathbf{T} = 0. \tag{4.8}$$

Sometimes a Lagrangian approach is more convenient, in particular when the final configuration of the body is unknown and there are traction boundary conditions. For these cases it is useful to introduce a Lagrangian measure of the stress defined in the original reference configuration κ_0, such as the first Piola–Kirchoff stress tensor defined as

$$\mathbf{P} = J \mathbf{T} \mathbf{F}^{-\mathrm{T}}. \tag{4.9}$$

The equation for the balance of linear momentum in terms of the first Piola–Kirchoff stress tensor simply reads:

$$\operatorname{Div}\mathbf{P} = 0, \tag{4.10}$$

where the operator Div stands for the divergence with respect to the reference configuration.

5. Growth tensor and growth rate

In the biological literature it is usual to measure and possibly model the growth rate Γ rather than the growth tensor $\mathbf{G}$. Indeed, the growth rate and the growth tensor are connected as we will show next. Differentiating (4.5) with respect to time we have

$$\dot{\varrho} = -\varrho\frac{\dot{J}_{\kappa_p}}{J_{\kappa_p}} \tag{5.1}$$

and substituting it into (4.2) we obtain:

$$\frac{\dot{J}}{J} - \frac{\dot{J}_{\kappa_p}}{J_{\kappa_p}} = \Gamma. \tag{5.2}$$

Recalling from Eq. (3.1) that $J = J_G J_{\kappa_p}$ we obtain:

$$\frac{\dot{J}_G}{J_G} = \Gamma. \tag{5.3}$$

From standard tensor calculus

$$\operatorname{tr}\mathbf{D}_g = \frac{\dot{J}_G}{J_G}, \tag{5.4}$$

where

$$\mathbf{D}_G := \operatorname{sym}(\dot{\mathbf{G}}\mathbf{G}^{-1}), \tag{5.5}$$

so we can rewrite (5.14) as

$$\operatorname{tr}\mathbf{D}_g = \Gamma. \tag{5.6}$$

The latter relationship reveals that one of the principal invariants of $\mathbf{D}_g$ is the growth rate Γ appearing in the mass balance Eq. (4.1). Thus, given the constitutive equation for $\mathbf{G}$, Γ is immediately recovered from (5.3) or (5.6). Vice versa, a measurement of Γ characterizes partially the growth tensor $\mathbf{G}$. It might be noticed, though, that for isotropic growth, i.e. $\mathbf{G} = g\mathbf{I}$ where g is a scalar, Eq. (5.3) rewrites

$$\frac{3\dot{g}}{g} = \Gamma \tag{5.7}$$

so that in this case the knowledge of Γ determines $\mathbf{G}$ completely.

Notice that the equations obtained substituting Eq. (5.6) into the mass balance equations of the present paper differ from the analogous ones in Rodriguez et al. [22], who restrict themselves to the case of incompressible materials. Of course, their balance equation can be recovered in the present context assuming that the density is constant.

6. Nutrient factors

As a specific character, the growth of biological tissues is strongly dictated by the availability of nutrient and by the influence of several chemical signals, e.g. growth factors. In particular, a tumor mass in its early stages is fed by the environment thanks to the nutrient diffusing in the interstitial liquid. When a tumor mass has become so big that this mechanism does not provide sufficient nutrient anymore, the internal region becomes hypoxic. [1] At this time the tumor stimulates the creation of a vascular structure, a stage called *angiogenesis*. In this paper we just focus on the first part of tumor growth, when the availability of nutrients is essentially dictated by diffusion.

Nutrient factors are dissolved in the interstitial liquid, which in our one-component model is indistinguishable from the tumor body. Therefore we assume that the concentration of nutrient $n(\mathbf{x}, t)$ obeys the following reaction–diffusion equation [11]

$$\frac{\partial n}{\partial t} + \operatorname{div}(n\mathbf{v}) - \operatorname{div}(D(n)\operatorname{grad} n) = -\gamma n\rho. \tag{6.1}$$

Eq. (6.1) is a mass balance law for the nutrient: its concentration at a fixed point changes in time because of the transport due to the velocity field $\mathbf{v}$, because of the diffusion due to Brownian motion and because of the uptake by the tumor appearing at the right-hand side, where γ is the absorption rate. Of course, a more complex uptake function could be considered: we retain a linear one for the sake of simplicity. In addition a hyperbolic model for *diffusion* of nutrient could be more proper. Sticking with parabolic equations, the non-linear diffusivity ensures that if the concentration of nutrient has compact support initially, the support will remain compact at any subsequent finite time, its boundary propagating at finite speed. A thorough discussion of the diffusion phenomena in living tissues and related problems can be found in [6].

We assume that the concentration of n is constant at the boundary of the tumor, so that the boundary condition reads:

$$n|_{\text{boundary}} = n_0. \tag{6.2}$$

The equations that describe the motion of the nutrient are coupled to the mass and momentum balance equations by the RHS of (6.1) and are conveniently rewritten in Lagrangian coordinates

[1] Roughly speaking, this phenomenon is related to the fact that, if R is the radius of a tumor spheroid, the influx of nutrient is proportional to its surface ($\sim R^2$) and, instead, the consumption is proportional to the tumor mass (of order R^3).

using Reynolds' transport theorem (see for instance [7]). For a reference system fixed on the body by standard calculations we obtain:

$$\frac{\partial}{\partial t}(n) - \mathrm{Div}[D(n)J\mathbf{F}^{-1}\mathrm{Div}(J\mathbf{F}^{-\mathrm{T}}n)] = -\gamma n\rho J. \tag{6.3}$$

The equation can be further simplified observing that the time needed to get a steady state for chemical quantities is usually much smaller than the typical time needed for growth. In this respect, we can assume that diffusion and production always balance in Eq. (6.3):

$$\mathrm{Div}\left[D\mathbf{F}^{-1}\mathrm{Div}(J\mathbf{F}^{-1}n)\right] = \gamma n\rho J. \tag{6.4}$$

The same steady equation would be obtained starting from a hyperbolic model.

7. Constitutive equations

To close the equation of motion (4.8) or (4.10), together with the balance of mass (4.5), we need to prescribe the constitutive equations that account for the behavior of the material as a function of the applied loads and of the available nutrient diffusing through the interior. In particular, we need to prescribe a constitutive equation for the response of the material from the natural configuration, i.e., for the path κ_p to κ_t, and independently, an evolution equation for the natural configuration itself, i.e., for the path κ_0 to κ_p.

In analogy with [16] we assume that the mechanical response is hyperelastic from the natural configuration, so that the tumor will be modelled as a hyperelastic material that is capable of growing. Of course, this is a simplification of the behavior of the material, which, in principle, would be better approximated using a viscoelastic constitutive equation. Nevertheless, since in the case of tumor spheroids the characteristic times of the rate dependent response of the material are much less than the characteristic times of growth and of mechanical loading, the material can be thought of as a hyperelastic material without introducing a significant error. We can then introduce an energy function W_{κ_p} such as [26]

$$W = W_{\kappa_p}(\mathbf{F}_{\kappa_p}) \tag{7.1}$$

from which we can derive the Cauchy stress tensor:

$$\mathbf{T} = \varrho\mathbf{F}_{\kappa_p}\left(\frac{\partial W_{\kappa_p}}{\partial \mathbf{F}_{\kappa_p}}\right)^{\mathrm{T}}, \tag{7.2}$$

where the subscript κ_p at W denotes the dependence of the functional on the natural configuration. In this way the material is always elastic from the natural configuration, but it might not exhibit *the same* elastic properties. To be more precise, we are modelling the mechanical response of the material from the natural configurations as a family of elastic materials, each member being

identified by the particular natural configuration. This feature allows one to model the mechanical effects of cell differentiation, which may accompany growth. The particular case in which the energy function W does not depend on κ_p is common in plasticity and has been discussed in [10,17].

In order to satisfy the principle of material frame indifference, Eq. (7.1) must be recast in the following form:

$$W = W_{\kappa_p}(\mathbf{C}_{\kappa_p}), \tag{7.3}$$

where

$$\mathbf{C}_{\kappa_p} := \mathbf{F}_{\kappa_p}^{\mathrm{T}}\mathbf{F}_{\kappa_p}. \tag{7.4}$$

If the material is isotropic, then Eq. (7.3) can be written in terms of the principal invariants of $\mathbf{C}_{\kappa_p}$ only:

$$W = W_{\kappa_p}(\mathrm{I}_{\kappa_p}, \mathrm{II}_{\kappa_p}, \mathrm{III}_{\kappa_p}). \tag{7.5}$$

Once it is known how the material behaves from each natural configuration, we need to describe how the natural configurations evolve [16]. In general, this can be simply done by prescribing a suitable evolution equation for the growth tensor $\mathbf{G}$, which may depend on a variety of quantities,

$$\dot{\mathbf{G}} = \mathscr{G}(\mathbf{X}, t, \mathbf{G}, \mathbf{S}, n), \tag{7.6}$$

where

$$\mathbf{S} = J\mathbf{F}^{-1}\mathbf{T}\mathbf{F}^{-\mathrm{T}} \tag{7.7}$$

is the second Piola–Kirchoff stress tensor. The evolution equation can depend on the applied stress, as is well known in the case of bones, in which growth is regulated by Wolff's law, but also other cases of stress-dependent growth have been observed [5]. In particular for the case of tumors it is worth to mention the experimental work of Helmlinger et al. [8].

The growth tensor $\mathbf{G}$ is an invariant tensor, i.e., its form does not change upon frame changes and therefore it can be differentiated directly with respect to time. Analogously, the second Piola–Kirchoff stress tensor $\mathbf{S}$ is an invariant measure of stress and this is the reason why it has been adopted in the RHS of (7.6).

Notice that the evolution equation for G involves the nutrient and the stress, thus coupling the growth tensor $\mathbf{G}$ with other relevant quantities of the behavior of the material. Therefore, in general, one cannot look at growth as being separated from the overall mechanical response, and actually Eq. (7.6) has to be solved simultaneously with the other equations of motion. In this sense, the diagram in Fig. 1 means that at each time the two paths leading to κ_t are to be considered jointly.

8. Specific constitutive assumptions

The second part of the paper will be devoted to the application of the general theory illustrated above via specific constitutive assumptions. Generally speaking, we are conscious that anisotropy is a crucial characteristic of biological tissues. However, in the case of tumor spheroids, the assumption of isotropy is definitely very reasonable. On the other hand, there is experimental evidence [8] that tumor spheroids are compressible, thus we model the response from the natural configurations as an isotropic compressible non-linearly elastic material. For simplicity we assume that the type of material response is the same for each natural configuration. The specific model we refer to is a material of the Blatz–Ko type [3], one of the most widely used compressible hyperelastic materials. The strain energy function of a general Blatz–Ko material is

$$W = \frac{vf}{2}\left[(\mathrm{I}_{\kappa_p} - 3) - \frac{2}{q}(\mathrm{III}_{\kappa_p}^{q/2} - 1)\right] + \frac{v(1-f)}{2}\left[\left(\frac{\mathrm{II}_{\kappa_p}}{\mathrm{III}_{\kappa_p}} - 3\right) - \frac{2}{q}(\mathrm{III}_{\kappa_p}^{-(q/2)} - 1)\right], \tag{8.1}$$

where v, q and f are material constants satisfying the following restrictions:

$$v > 0, \qquad 0 < f \leqslant 1, \qquad q < 0. \tag{8.2}$$

For the sake of simplicity we restrict ourselves to the case $f = 1$. From (7.2) it immediately follows that the Cauchy stress tensor takes the form

$$\mathbf{T} = \frac{\mu}{J_{\kappa_p}}[-(J_{\kappa_p})^q\mathbf{I} + \mathbf{B}_{\kappa_p}], \tag{8.3}$$

where $\mathbf{B}_{\kappa_p} = \mathbf{F}_{\kappa_p}\mathbf{F}_{\kappa_p}^{\mathrm{T}}$ and we have used the balance of mass in the form (4.5) defining $\mu = \varrho_0 v$. Substituting (8.3) into (4.9) we obtain the first Piola–Kirchoff stress tensor:

$$\mathbf{P} = \mu J_G[-(J_{\kappa_p})^q\mathbf{F}_{\kappa_p}^{-\mathrm{T}} + \mathbf{F}_{\kappa_p}]\mathbf{G}^{-\mathrm{T}}. \tag{8.4}$$

The simplest form of the growth tensor is

$$\mathbf{G}(\mathbf{X}, t, n) = g(\mathbf{X}, t, n)\mathbf{I}, \tag{8.5}$$

where the scalar function g is the growth function. Eq. (8.5) implies that growth develops in the same way in all directions, therefore it is isotropic. Growth can be then prescribed through an evolution equation of the form

$$\dot{g} = \mathscr{G}(\mathbf{X}, t, g, n). \tag{8.6}$$

If $g = g(t)$, then growth is said to be homogeneous.

Summarizing, we specialize the growth model to the following governing equations:

$$\varrho_0 = \varrho J_{\kappa_p}, \tag{8.7}$$

$$\mathrm{div}(D\,\mathrm{grad}\,n) = \gamma n\rho, \tag{8.8}$$

$$\operatorname{div}\mathbf{T} = 0 \tag{8.9}$$

supplemented by the specific constitutive equations:

$$\dot{g} = \frac{g}{3}\Gamma(\mathbf{X}, t, n, g), \tag{8.10}$$

$$\mathbf{T} = \frac{\mu}{J_{\kappa_p}}[-(J_{\kappa_p})^q\mathbf{I} + \mathbf{B}_{\kappa_p}]. \tag{8.11}$$

Here the unknowns are the density ϱ, the growth function g, the nutrient n, and the three components of the motion $\boldsymbol{\chi}$, which appear in (8.9) indirectly through (2.1), (2.2) and (3.1).

9. Simple applications

In order to show how the general theory illustrated above can actually be applied, in this section we solve some simple problems, namely the homogeneous growth inside a rigid cylinder and the inhomogeneous growth of a sphere under no applied external loads. The following procedure is adopted: the motion is assumed to have some symmetry and the function g is assumed to have a certain simple form; then we seek a deformation of the material that satisfies the equilibrium equation and appropriate boundary conditions. In the first problem, the deformation is homogeneous, so that the equilibrium equation is automatically satisfied. In the second problem the assumed form of the growth function gives rise to inhomogeneous deformations. In such a case growth is accompanied by residual stresses, as described in [23]: the stress in the material is different from zero even though there are no external forces applied.

9.1. Isotropic and homogeneous growth inside a rigid cylinder

Suppose that the body occupies the space inside a rigid cylinder, a configuration resembling the growth of a tumor in a vessel. This representation recalls a type of breast cancer named ductal carcinoma, in which tumor cells grow inside a breast duct for nearly 10 cm, receiving nutrients through the walls.

Since the cylinder walls are supposed to be rigid, the motion is

$$x = X, \quad y = Y, \quad z = \lambda Z, \tag{9.1}$$

so that the deformation gradient is

$$\mathbf{F} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & \lambda \end{bmatrix} = \operatorname{Diag}\{1, \quad 1, \quad \lambda\}. \tag{9.2}$$

As an example we assume that growth is homogeneous

$$g = g(t). \tag{9.3}$$

This can occur when growth is triggered only if the level of nutrients is above a threshold value $\hat{n}$; for instance, suppose that the growth rate is piecewise constant

$$\Gamma = \hat{\Gamma} H(n - \hat{n}), \tag{9.4}$$

where H is the Heaviside function, which is unity when the concentration of nutrient is above $\hat{n}$ and zero otherwise. In this case Eq. (8.10) can be integrated to give

$$g = \exp(\hat{\Gamma} t/3). \tag{9.5}$$

From (9.3), (9.2) and (3.1), it immediately follows that

$$\mathbf{F}_{\kappa_p} = \mathrm{Diag}\left\{ \frac{1}{g}, \quad \frac{1}{g}, \quad \frac{\lambda}{g} \right\}. \tag{9.6}$$

Substituting it into (8.3) we can write the Cauchy stress tensor:

$$\mathbf{T} = \mu \frac{g^3}{\lambda} \mathrm{Diag}\left\{ \frac{1}{g^2} - \left(\frac{\lambda}{g^3} \right)^q, \quad \frac{1}{g^2} - \left(\frac{\lambda}{g^3} \right)^q, \quad \frac{\lambda^2}{g^2} - \left(\frac{\lambda}{g^3} \right)^q \right\}. \tag{9.7}$$

The relationship between g and λ can be obtained by enforcing the boundary conditions on the top and bottom surface of the cylinder. For simplicity we will assume that these surfaces are stress free, so that $T_{zz} = 0$, and this in turn implies that

$$\lambda = g^{(2-3q)/(2-q)}. \tag{9.8}$$

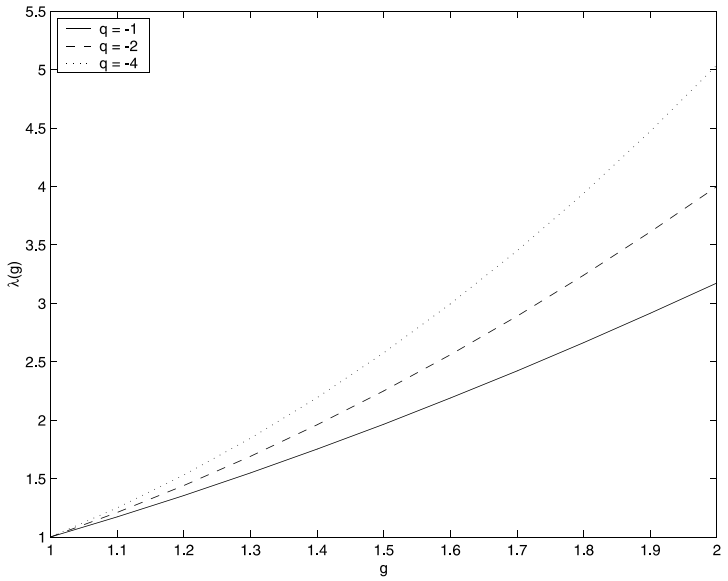

Fig. 2. Growth inside a rigid cylinder: axial displacement of the material as a function of g for different values of q.

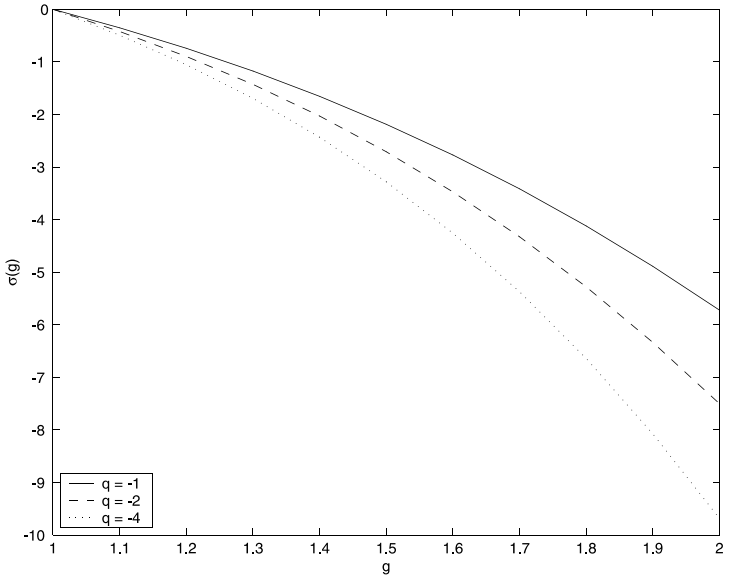

Fig. 3. Growth inside a rigid cylinder: wall stress versus g.

Eq. (9.8) gives the axial displacement of the material as a function of growth. The plot is given in Fig. 2 for different values of q. Of course the displacement is an increasing function of g, and through (9.5) is an exponentially increasing function of time. Another important quantity that can be calculated is the stress exerted by the growing tumor on the wall. By substituting (9.8) into the first components of the RHS of Eq. (9.7) we obtain

$$\sigma_w = \mu\left(g^{2q/(2-q)} - g^{(4-4q)/(2-q)}\right). \tag{9.9}$$

The wall stress as a function of the growth function g is shown in Fig. 3. As we can see, the pressure of the tumor on the duct walls increases in absolute value with growth and with the axial expansion.

9.2. Isotropic and inhomogeneous growth of a sphere: residual stresses

In this problem we look for the deformation of a sphere of initial radius $\bar{R}$ growing freely. Any steady radially symmetric distribution of nutrient will give rise to a growth tensor of the following form:

$$\mathbf{G} = g(R)\mathbf{I}. \tag{9.10}$$

This form of growth is incompatible in the sense of Skalak et al. [24] and residual stresses will arise as a consequence. The determination of these residual stresses is the goal of this problem.

The total deformation will be assumed to be an isotropic volume expansion. In spherical polar coordinates the deformation will be

$$r = \lambda(R), \quad \theta = \Theta, \quad \phi = \Phi. \tag{9.11}$$

The deformation gradient will be

$$\mathbf{F} = \mathrm{Diag}\left\{\lambda', \quad \frac{\lambda}{R}, \quad \frac{\lambda}{R}\right\}, \tag{9.12}$$

where a superscript $(\cdot)'$ denotes differentiation with respect to R. Analogously as before we can calculate $\mathbf{F}_{\kappa_p}$ from the expressions of $\mathbf{F}$ and $\mathbf{G}$:

$$\mathbf{F}_{\kappa_p} = \mathrm{Diag}\left\{\frac{\lambda'}{g}, \quad \frac{\lambda}{gR}, \quad \frac{\lambda}{gR}\right\} \tag{9.13}$$

and plug it into the constitutive equation (8.3). For this problem it is more convenient to use the first Piola–Kirchoff stress tensor (4.9) instead of the Cauchy stress tensor:

$$\mathbf{P} = \mathrm{Diag}\{P_{RR}, \quad P_{\Theta\Theta}, \quad P_{\Phi\Phi}\}, \tag{9.14}$$

where

$$\begin{aligned} P_{RR} &= \mu g\left[\lambda' - \Delta^q \frac{g^2}{\lambda'}\right], \\ P_{\Theta\Theta} &= P_{\Phi\Phi} = \mu g\left[\frac{\lambda}{R} - \Delta^q \frac{g^2 R}{\lambda}\right], \\ \Delta &= J_{\kappa_p} = \frac{\lambda'\lambda^2}{g^3 R^2}. \end{aligned} \tag{9.15}$$

In order to find the relationship between the growth function g and the volume expansion λ we need to satisfy the conservation of linear momentum and the boundary conditions. The only non-trivial equation is

$$\frac{\mathrm{d}}{\mathrm{d}R} P_{RR} + \frac{2}{R}(P_{RR} - P_{\Theta\Theta}) = 0. \tag{9.16}$$

Plugging the components (9.15) into Eq. (9.16) we obtain an ordinary differential equation of the second order in λ:

$$\lambda'' = \left\{\frac{2}{R}\left[\frac{1}{R} + \frac{g^2\Delta^q(1-q)}{\lambda\lambda'}\right](\lambda - \lambda' R) - \left[\lambda' - \frac{3g^2\Delta^q(1-q)}{\lambda'}\right]\frac{g'}{g}\right\} \Big/ \left\{1 + \frac{g^2\Delta^q(1-q)}{(\lambda')^2}\right\}. \tag{9.17}$$

Eq. (9.17) has to be supplemented by a specific form of the growth function $g(R)$. Typically in tumor growth g is an increasing function of R: the outer shell of the tumor spheroid receives more nutrient than the inner one and is thus able to grow more. A particularly simple form is

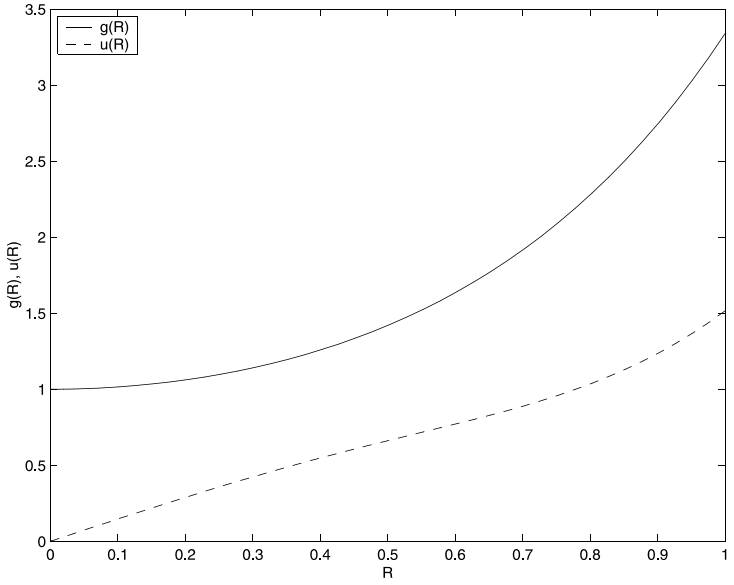

Fig. 4. Isotropic and inhomogeneous growth of a sphere: growth function g and radial displacement $u = r - R$ versus radius.

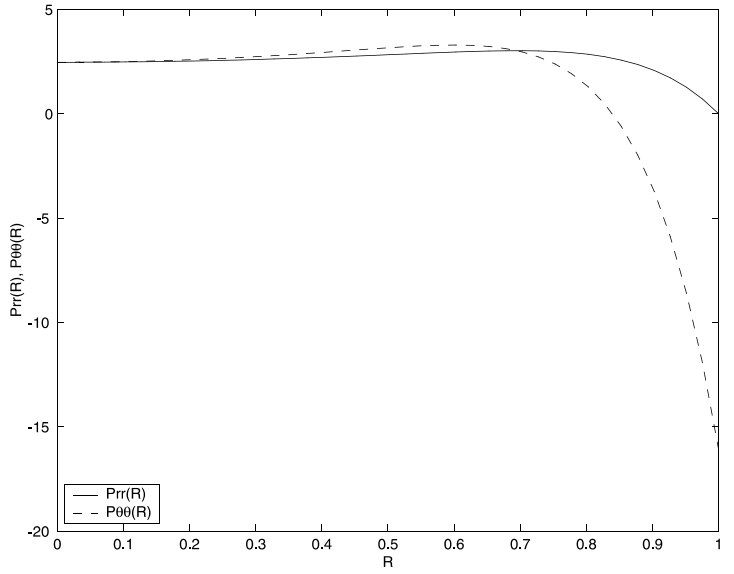

Fig. 5. Isotropic and inhomogeneous growth of a sphere: radial stress and hoop stress.

$$g(R) = \alpha \frac{\sinh(kR)}{R}, \tag{9.18}$$

where α and k are constants.

Eq. (9.17) has to be integrated with the following boundary conditions:

$$P_{RR}|_{R=\bar{R}} = 0, \tag{9.19}$$

$$\lambda|_{R=0} = 0. \tag{9.20}$$

The differential equation (9.18) has been numerically integrated by the fourth order Runge–Kutta scheme, the boundary conditions being satisfied by a shooting method.

The results in terms of radial displacement, radial stress, hoop stress are depicted in Figs. 4 and 5. The stress $P_{\Theta\Theta}$ of the outer layers, which grow more, is in compression, while the inner layers, which grow less, are kept in tension. The radial stress P_{RR} is in tension. The radial displacement and the density are increasing functions of the undeformed radius.

10. Conclusions and open problems

In this paper we have illustrated a possible way to model growth using the theory of materials with multiple natural configurations. Growth is seen as a mass increase determined by an increase in volume at constant density and no new particles are introduced: the same particles constituting the body at the initial time change their mass according to whether there is growth or resorption.

The approach of the present paper enables to properly write a motion that connects the configurations of the body at all possible times with each other and with the original reference configuration. This makes it possible to use the Lagrangian approach to study problems of growth. Such an advantage is not to be underestimated, since in this way it is easy to write boundary conditions in the known undeformed reference configuration, the way it is done in nonlinear elasticity.

The introduction of such a mechanical framework is helpful for describing several phenomena whose description requires the study of the stress evolution inside and outside the growing body. For instance, for the problem at hand, the model allows to describe how the uncontrolled growth of a tumor interacts with the surrounding environment, possibly originating the compression and necrosis of hosting tissues, the collapse of immature blood vessels formed during the angiogenic phase, the inflation and rupture of capsules, membranes and ducts the tumor grows into.

The model presented here is a first investigative step and several extensions and open problems can be mentioned. First of all, the model does not take explicitly into account that the body is growing due to the absorption of some other materials, e.g. organic compounds and water. In absence of some of the vital constituents, no growth is possible. Conversely, when part of the material dies, some of the "bricks" contained in the cellular membrane can be re-used by other cells. In this respect, an approach using mixture theory might be useful [9].

Focusing on the study of the mechanical properties of the growing organic tissue, besides mentioning the necessity of experiments for the characterization of soft tissues like multicell spheroids, it can be observed that an ensemble of cells is held together by membrane receptors that break when daughter cells are generated. Comparing these dislocations with the phenomenological description of plastic deformations suggests that a good model of a growing biological tissue should take plasticity into account.

Another important issue is memory. In fact, it is not yet clear whether the newborn material inherits the same stress state of the generating material, as in this paper, or it is formed in a stress-free state, as in the multinetwork theory [20,27]. Experiments in this directions are needed.

Another open problem concerns aging and stress-dependent growth. These phenomena are well known in biomechanics. However, remaining in the same field, it is known that in bone remodeling insufficient levels of exercise cause muscle wastage, while moderate levels lead to growth of muscle tissue and bones whereas excessive levels cause damage. Recent experiments have shown that also the growth of a tumor spheroid depends in a non-trivial way on the stress field [8].

Finally, some attention should be devoted to the fact that organic tissues are usually made up not only of several types of cells, behaving differently to mechanical and chemical cues, but also of the components that constitute the extracellular matrix.

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