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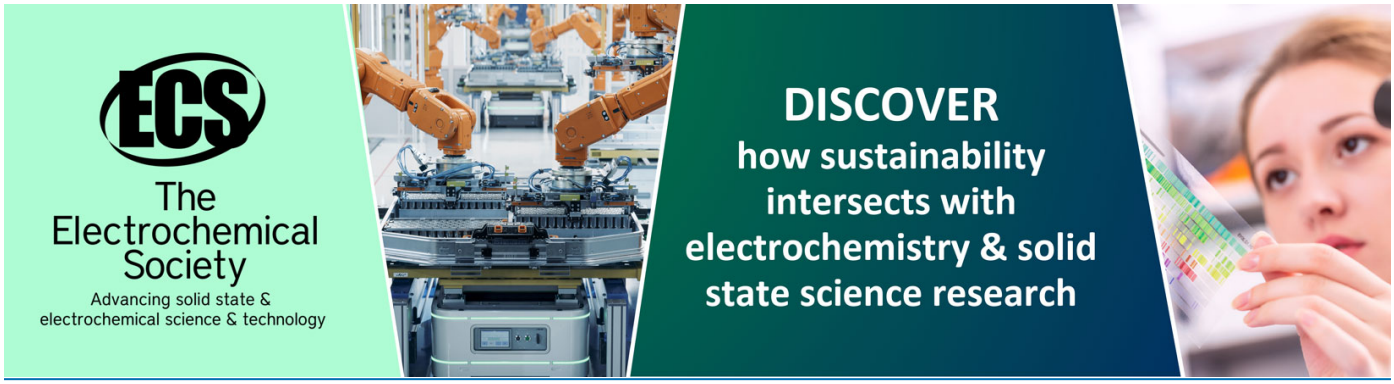

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A Stress Driven Growth Model for Soft Tissue Considering Biological Availability

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Abstract. Some of the key factors that regulate growth and remodeling of tissues are fundamentally mechanical. However, it is important to take into account the role of bioavailability together with the stresses and strains in the processes of normal or pathological growth. In this sense, the model presented in this work is oriented to describe the growth of soft biological tissue under "stress driven growth" and depending on the biological availability of the organism. The general theoretical framework is given by a kinematic formulation in large strain combined with the thermodynamic basis of open systems. The formulation uses a multiplicative decomposition of deformation gradient, splitting it in a growth part and visco-elastic part. The strains due to growth are incompatible and are controlled by an unbalanced stresses related to a homeostatic state. Growth implies a volume change with an increase of mass maintaining constant the density. One of the most interesting features of the proposed model is the generation of new tissue taking into account the contribution of mass to the system controlled through biological availability. Because soft biological tissues in general have a hierarchical structure with several components (usually a soft matrix reinforced with collagen fibers), the developed growth model is suitable for the characterization of the growth of each component. This allows considering a different behavior for each of them in the context of a generalized theory of mixtures. Finally, we illustrate the response of the model in case of growth and atrophy with an application example.

1. Introduction

Since the formulation of the first continuum growth model, called “Adaptive Elasticity Theory", submitted more than a quarter century by Cowin and Hegedus (1976), the modeling and simulation of biomechanical processes has been a growing interest. In contrast to traditional materials (passive) the biomaterials (active), both hard and soft tissues show the ability to adapt not only its external shape but also the internal microstructure to the environment changes.

The theory of adaptive elasticity (Cowin and Hegedus 1976) considers the biological structure as an open system which allows a constant exchange of mass, momentum, energy and entropy with the surrounding environment. There are other models, such as Epstein and Maugin (2000) that allows exchanges in terms of mass flows. These flows are typically attributed to the migration of cells resulting from a source of mass due to growth, contraction, death, division or cell enlargement.

Soft tissue modeling requires a geometric description based on a nonlinear kinematics to address the problems of large strains (Rodriguez et al. 1994, Cowin 1996, Holzapfel et al. 2003, Gasser and Holzapfel 2002). Laboratory tests show that many biological soft tissues are incompressible or nearly incompressible when subjected to large strains and the material exhibits a strong viscous behavior (Fung 1996).

The analysis of stress-driven growth of soft tissues has been an important research topic in biomechanics. An important contribution to the general study of finite volumetric growth in these tissues was made by Rodriguez et al. (1994). They introduced the multiplicative decomposition of the total deformation gradient in an elastic part and a growth part. This multiplicative decomposition is employed here to characterize the changes in volume associated with growth.

The mechanical stimulus is not the only necessary factor to produce a mass change; the biological field is also involved. Metabolism must be able to generate the new tissue in response to stimulus. The main contribution of this work is the consideration of biological availability for growth by means of a proposed internal variable.

2. Constitutive model

2.1. Generalities

The growth of soft tissues is an important mechanical process for their normal development, but there are situations that it also occurs under certain pathological conditions. An example of this is vascular and cardiac hypertrophy, manifested by increased stress in the walls of the tissues (Humphrey 2002).

It is now well established through previous works (Skalak et al. 1996, Rodriguez et al. 1994), that growth and remodeling produce incompatible strains. For example, if the growth of some cells compress others, elastic stresses are developed which tend to eliminate gaps and avoid overlap between them. For this reason, Fung (1981) proposed that both cardiac hypertrophy and normal growth are developed in response to increased hemodynamic load, altering both systolic and diastolic heart walls. The same situation occurs in bone tissue where the osteocytes motivate the cell development due to its sensitivity to applied stresses (Baiotto and Zidi, 2004).

There are several proposed laws to the growth of bones, but was Fung (1996) who proposed that the tissue growth is a function of the stresses acting on them. In this formulation, growth / atrophy of parts of the tissue occur so that the stresses reach a steady state:

- If stress grows beyond equilibrium states growth occurs to reduce this stress.
- If the stress is below the current equilibrium state, resorption or atrophy occurs to achieve equilibrium.

2.2. Governing equations

The formulation proposed in this article derives from the works by Rodriguez et al (1994), Lubarda and Hoger (2002) and Himpel et al (2005). Growth is considered by means of a multiplicative decomposition of the deformation gradient $\boldsymbol{F}$. The kinematics in finite strains is expressed in its simplest form (Lubarda and Hoger; 2002), as:

$$\boldsymbol{F} = \boldsymbol{F}^{ev} \cdot \boldsymbol{F}^{g} \tag{1}$$

where $\boldsymbol{F}^{ev}$ is the elastic-viscous part and $\boldsymbol{F}^{g}$ is the incompatible part, which includes "growth / atrophy" phenomena. The total volume change can be written as $d\mathrm{v} = J\, dV = (J^{ev} J^{g})\, dV$, where $J = \det \boldsymbol{F}$, $J^{ev} = \det \boldsymbol{F}^{ev}$ and $J^{g} = \det \boldsymbol{F}^{g}$.

The previously described kinematics is also accompanied by the following change of mass,

$$dm = \rho_0^{\mathrm{ini}}\, dV + \left[\int_t R_0\, dt\right] dV \;\Rightarrow\; \rho\, d\mathrm{v} = \rho_0^{\mathrm{ini}}\, dV + \left[\int_t R_0\, dt\right] dV \Rightarrow \rho_0 = \rho_0^{\mathrm{ini}} + \int_t R_0\, dt \tag{2}$$

where ρ_0^{ini} and ρ_0 represent the density in the reference configuration at the beginning of the process and at any moment of it, ρ is the density in the current configuration, dm and dv are the mass and volume differentials in the current configuration and R_0 the source of mass in the reference configuration.

In the case of the phenomenon known as growth (increase in volume with constant density) or atrophy (decrease in volume with constant density) there is a mass change at constant density, which forces to change the volume. This concept leads to a new mass balance and hence the following definition of the source of mass,

$$R_0 = \rho_0 \,\text{tr}\hat{\boldsymbol{L}}^g = J^g \,\rho_0^{\text{ini}} \,\text{tr}\hat{\boldsymbol{L}}^g = J^g \,\rho_0^{\text{ini}} \,\text{tr}\left(\dot{\boldsymbol{F}}^g \cdot \boldsymbol{F}^{g-1}\right) \tag{3}$$

where $\hat{\boldsymbol{L}}^g$ is the velocity growth gradient. Thus, if the strain growth gradient $\boldsymbol{F}^g$ and its temporal evolution are known, the source of mass results immediately known.

For the mechanical treatment of the tissue an elastic-viscous potential $W(\rho_0, \hat{\boldsymbol{C}}, \boldsymbol{\Gamma}^{\text{v}})$ is defined, where $\hat{\boldsymbol{C}} = \boldsymbol{F}^{ev^T} \cdot \boldsymbol{F}^{ev}$ is the right elastic-viscous Cauchy tensor, $\boldsymbol{\Gamma}^{\text{v}}$ is viscous variable, that in this short work will not be considered. Based on this potential the following stresses are obtained

$$\hat{\boldsymbol{S}} = 2\,\rho_0 \frac{\partial W(\rho_0, \hat{\boldsymbol{C}}, \boldsymbol{\Gamma}^{\text{v}})}{\partial \hat{\boldsymbol{C}}} \;\text{; with}\; \boldsymbol{S} = \boldsymbol{F}^{g^{-1}} \cdot \hat{\boldsymbol{S}} \cdot \boldsymbol{F}^{g^{-T}}; \;\text{and}\; \boldsymbol{\sigma} = \boldsymbol{F} \cdot \boldsymbol{S} \cdot \boldsymbol{F}^T \tag{4}$$

where $\boldsymbol{S}$ and $\hat{\boldsymbol{S}}$ are the second Piola-Kirchhoff stress tensor in the referential and intermedia configuration.

2.3. Isotropic growth/atrophy

The isotropic deformation gradient is defined as (Lubarda and Hoger 2002)

$$\boldsymbol{F}^g = \vartheta \cdot \boldsymbol{I} \tag{5}$$

where ϑ is the isotropic growth stretch. From eq. (5) the growth Jacobean is $J^g = \vartheta^3$ and the density is

$$\rho_0 = J^g \,\hat{\rho} = \vartheta^3 \,\hat{\rho} \tag{6}$$

where $\hat{\rho}$ is the density in the intermediate configuration.

The rate of growth can be expressed as:

$$\hat{\boldsymbol{L}}^g = \dot{\boldsymbol{F}}^g \cdot \boldsymbol{F}^{g-1} = \frac{\dot{\vartheta}}{\vartheta}\boldsymbol{I} \tag{7}$$

During the growth process the density is conserved. The mass source from eq. (3) results :

$$R_0 = \vartheta^3 \,\rho_0^{\text{ini}} \,\text{tr}\left(\dot{\boldsymbol{F}}^g \cdot \boldsymbol{F}^{g-1}\right) \tag{8}$$

For a certain range of stresses there is a homeostatic equilibrium without mass change. In this state new cells are produced only to replace those that die, so mass and volume remain constant. This equilibrium state is defined by an upper limit σ_{eq}^{*+} and a lower one σ_{eq}^{*-}. For stresses higher than the upper limit a mechanical stimulus growth zone is defined. The lower limit corresponds to the start of the atrophy zone. The trace of the Cauchy stress tensor is proposed to define the evolution rule of ϑ. This choice is made to allow a more straightforward definition of the limits of growth and atrophy zones.

A simple mechanical stimulus generation is no enough to produce a mass increase, but it is necessary that the metabolism is able to allow tissue growth. For this purpose the necessary nutrients, enzymes etc. must be available. Besides the growth stimulus a biological availability is needed.
Following these considerations the evolution rule proposed is expressed as:

$$\dot{\vartheta} = K(\dot{\vartheta}_{MAX})\, g(tr\sigma, \sigma^*_{eq})\; f(\theta) \tag{9}$$

where $K(\dot{\vartheta}_{MAX})$ is a function that controls the maximum growth rate $\dot{\vartheta}_{MAX}$, $g(tr\sigma, \sigma^*_{eq})$ determinates the growth/atrophy rate as a function of the Cauchy stress, $f(\theta)$ is a function that regulates the metabolic part of the growth phenomena and allows, or not, growth according with biological availability to generate new tissue.

The growth rate is also limited by the maximum rate of mass production $R_{\max}$. The maximum growth rate is:

$$\dot{\vartheta}_{MAX} \cong \vartheta \sqrt[3]{R_{\max}} \tag{10}$$

The function K is defined as follows:

$$\begin{cases} K(\dot{\vartheta}_{MAX}) = 1 & If\ \ g(tr\sigma, \sigma^*_{eq}) < \dot{\vartheta}_{MAX} \\ K(\dot{\vartheta}_{MAX}) = \dfrac{1}{g(tr\sigma, \sigma^*_{eq})}\dot{\vartheta}_{MAX} & If\ \ g(tr\sigma, \sigma^*_{eq}) > \dot{\vartheta}_{MAX} \end{cases}, \tag{11}$$

The maximum growth rate is bounded in this way. In the case of atrophy the rate at which the tissue can be reabsorbed defines the rate of mass decrease. The limit functions for growth and atrophy are named $K(\dot{\vartheta}^+_{MAX})$ and $K(\dot{\vartheta}^-_{MAX})$ respectively.

Three zones are defined for the growth stimulus function $g(tr\sigma, \sigma^*_{eq})$:

1) Atrophy zone: if $tr\sigma < \sigma^{*-}_{eq}$,

2) Homeostatic equilibrium zone: if $\sigma^{*+}_{eq} > tr\sigma > \sigma^{*-}_{eq}$,

3) Growing zone: if $tr\sigma > \sigma^{*+}_{eq}$.

In the zone of homeostatic equilibrium the growing rate is zero. In the atrophy and growing zones a linear relationship with k^+ and k^- slopes is adopted.

The expression of the function of mechanical stimulus for each zone is:

$$\begin{cases} g(tr\sigma, \sigma^*_{eq}) = k^+\,(tr\sigma - \sigma^{*+}_{eq}) & If\ (tr\sigma - \sigma^{*+}_{eq}) > 0 \\ g(tr\sigma, \sigma^*_{eq}) = 0 & If\ \sigma^{*+}_{eq} > tr\sigma > \sigma^{*-}_{eq} \\ g(tr\sigma, \sigma^*_{eq}) = k^-\,(tr\sigma - \sigma^{*-}_{eq}) & If\ (tr\sigma - \sigma^{*-}_{eq}) < 0 \end{cases}, \tag{12}$$

The effect of the biological availability is developed in the next section.

2.4. Biological availability for growth

Stress driven growth/atrophy is based on the concept of adding or removing mass motivated by a mechanical stimulus. During this process, incompatible strains are developed. These strains are related with the growth part of the stress gradient $\boldsymbol{F}^{\mathrm{g}}$.

The biological availability concept works as an activation law. Growth will only take place if the metabolism of the cells is capable of generating new tissue and a growth mechanical stimulus is present. When we refer to biological availability it must be understood that all the elements necessary for growth (proteins, enzymes, growth factors, etc.) are present. We will refer to these elements as "nutrients" from now on.

A variable of biological availability for growth θ is introduced. This variable is responsible of the activation of the mass change and represents the mass production that the metabolism can sustain with the available nutrients.

The availability of nutrients in a given time is obtained by a balance between nutrients incorporated and those used for growing tissue. In this work the amount of nutrients entering the system is taken into account by the function $\boldsymbol{N}^{\mathrm{i}}(t)$. It considers an initial reserve of nutrients R_i and a discrete

contribution of nutrients A_t at regular time intervals. The values of $\boldsymbol{N}^{\mathrm{i}}(t)$ are dimensionless and represents the mass increasement of nutrients referred to the initial mass of the system. For instance a value of $\boldsymbol{N}^{\mathrm{i}} = 1.02$ represents the entry to the system of nutrients enough to generate an increase of mass of the tissue of 2% of the original mass. Fig. 1 shows the function of nutrients contribution.

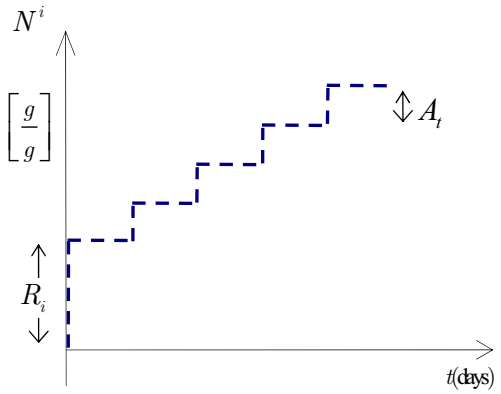

Figure 1. Nutrients entering the system.

The biological availability function proposed results from the balance between the nutrients contributed to the system and those used in growing the tissue:

$$\theta(t) = N^i(t) - \det[\boldsymbol{F}^g(t)]\frac{\rho_0}{\rho_t}, \tag{13}$$

During growth phenomena density remains constant $\rho_0 = \rho_t$.

Biological availability will increase whenever the rate of nutrients contribution is greater than the growing rate. However, there is a physical limit to the amount of nutrients the system can keep in reserve. Consequently, an upper boundary for the biological availability $\theta^{\max}$ is incorporated in the formulation.

3. Numerical implementation of growth

The proposed formulation has been implemented in a finite element code. The isotropic growth stretch ϑ given by eq. (9), is treated as an internal variable written in an incremental way:

$$\Delta\vartheta = \dot{\vartheta}\Delta t \;\Rightarrow\; \Re_\vartheta = -\Delta\vartheta + \left[K(\dot{\vartheta}_{MAX})\, g(tr\sigma, \sigma^*_{eq})\; f(\theta)\right]\Delta t = 0 \tag{14}$$

The solution is achieved minimizing the residue using a Newton-Raphson scheme.

$$\Re_\vartheta^{k+1} = \Re_\vartheta^k - \Delta\vartheta + \frac{\partial\dot{\vartheta}}{\partial\vartheta}\Delta\vartheta\,\Delta t = 0 \tag{15}$$

$$\Delta\vartheta = \left(1 - \frac{\partial\dot{\vartheta}}{\partial\vartheta}\Delta t\right)^{-1}\Re_\vartheta^k \;\Rightarrow\; \vartheta^{k+1} = \vartheta^k + \Delta\vartheta \tag{16}$$

A mixed FEM formulation, pressure- displacement (Crisfield 1997) has been used in this work to avoid locking and instability issues.

The proposed algorithm for growth/atrophy is resumed as follows:

1. Initialize variables with previous step values.

$$\boldsymbol{F}^{ev} = \boldsymbol{F} \cdot \boldsymbol{F}^{g^{-1}}\Big|_n \quad \Rightarrow \quad \hat{\boldsymbol{C}} = \boldsymbol{F}^{evT} \cdot \boldsymbol{F}^{ev} \quad ; \quad \rho_0 = \rho_{0\boldsymbol{n}} \quad ; \quad \vartheta = \vartheta_{\boldsymbol{n}}$$

$$\boldsymbol{\sigma} = \boldsymbol{F} \cdot \boldsymbol{S} \cdot \boldsymbol{F}^T$$

2. Control of growth/atrophy condition.

if $\mathrm{tr}\sigma \geq \sigma_{eq}^{*+}$ then (Growth)

$$g(\mathrm{tr}\sigma, \sigma_{eq}^{*}) = k^{+}\,(\mathrm{tr}\sigma - \sigma_{eq}^{*+})\ ; \ \Rightarrow K(\dot{\vartheta}_{MAX}^{+})$$

if $\Rightarrow \left(K(\dot{\vartheta}_{MAX}^{+})\,k^{+}\,(\mathrm{tr}\sigma - \sigma_{eq}^{*+})\,\Delta t\right)^3 < \theta(t) \quad \Rightarrow \quad \Delta\vartheta = K(\dot{\vartheta}_{MAX}^{+})\,k^{+}\,(\mathrm{tr}\sigma - \sigma_{eq}^{*+})\Delta t$

else $\Delta\vartheta = \sqrt[3]{\theta(t)}$

elseif $\mathrm{tr}\sigma < \sigma_{eq}^{*-}$ then (Atrophy)

$$g(\mathrm{tr}\sigma, \sigma_{eq}^{*}) = k^{-}\,(\mathrm{tr}\sigma - \sigma_{eq}^{*-})\ ; \ \Rightarrow K(\dot{\vartheta}_{MAX}^{-});$$

$$\Delta\vartheta = K(\dot{\vartheta}_{MAX}^{-})\,k^{+}\,(\mathrm{tr}\sigma - \sigma_{eq}^{*+})\Delta t$$

Else

$\Delta\dot{\vartheta} = 0$ (Homeostatic equilibrium) $\rightarrow$ **GoTo 4**

3. Newton-Raphson solution of growth/atrophy problem.

3.1 Growth/atrophy residue.

$$\Re_{\vartheta} = -\Delta\vartheta + \left[K(\dot{\vartheta}_{MAX})\,g(\mathrm{tr}\sigma, \sigma_{eq}^{*})\ f(\theta)\right]\Delta t$$

3.2 Tolerance control.

if $\|\Re_{\vartheta}\| \leq$ Tol **Go To 4**

3.3 Density and growth/atrophy stretch update:

$$\Delta\vartheta = \left(1 - \frac{\partial\dot{\vartheta}}{\partial\vartheta}\Delta t\right)^{-1} \Re_{\vartheta}^{k} \ \Rightarrow\ \vartheta^{k+1} = \vartheta^{k} + \Delta\vartheta \ \Rightarrow\ \rho_0 = \vartheta^3\rho^{\mathrm{ini}}$$

3.4 Checks biological availability for growth.

if $J^g\Big|_{n+1}^{k+1} - J^g\Big|_n < \theta(t) \ \Rightarrow\ \vartheta^{k+1} = \vartheta^{k+1}$

else $\Rightarrow\ \vartheta^{k+1} = \sqrt[3]{\theta(t)}$

3.5 Update of growth stretch and Cauchy stresses.

$$\boldsymbol{F}^{g} = \vartheta \cdot \boldsymbol{I} \quad \Rightarrow \quad \boldsymbol{F}^{ev} = \boldsymbol{F} \cdot \boldsymbol{F}^{g^{-1}}\Big|_n \Rightarrow \hat{\boldsymbol{C}} = \boldsymbol{F}^{evT} \cdot \boldsymbol{F}^{ev}$$

$$\vartheta = \vartheta_{\boldsymbol{n}} \quad \boldsymbol{\sigma} = \boldsymbol{F} \cdot \boldsymbol{S} \cdot \boldsymbol{F}^T$$

GoTo 3.1.

4 EXIT

4. Application example

In this section a conceptual example is presented. The hexahedral element subjected to uniaxial stretching is shown in figure 2.

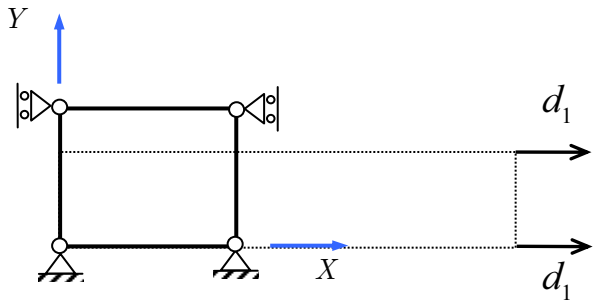

Figure 2. Boundary conditions and prescribed displacements.

The material corresponds to arterial tissue, which has been characterized by the Yeoh constitutive model $W = \sum_n C_n (I_1 - 3)^a$; $n = 3$, whose material constants corresponding to coronary artery tests are depicted in Table 1.

Table 1. Yeoh constants for coronary artery, VCor6 – Long (Claes 2007).

C_{10} [MPa]	C_{20} [MPa]	C_{30}[MPa]
0.058400	0.026500	0.000200

The metabolic parameters have been extrapolated form animal models. The maximum mass production rate is $R_{\max} = 1.13\%$ day , corresponding to studies of stress-induced changes of the arterial wall thickness in response to hypertension in rats (Fridez et al. 2003). Growth upper limit σ_{eq}^{*+} is adopted as 0.40 KPa. Three cases are considered regarding the biological availability:

1) Unlimited availability of nutrients.
2) An initial reserve of $R_i = 2\%$ and $A_{0.5} = 0.20\%$ each half day.
3) An initial reserve of $R_i = 1\%$ and $A_{0.5} = 0.15\%$ each half day.

The element is stretched in three equal steps as shown in Fig. 3a. For the initial stretch step the trace of the Kirchhoff stress tensor is 0.818 KPa. This value is higher than the growth stimulus boundary and the growth stretch value increases as can be seen in Fig. 3c. When the tissue grows the growth part of the deformation gradient increases while the elastic part decreases and stress relaxes (Fig. 3b). The growth stimulus is a function of the stress and it also decreases. For the case of unlimited biological availability the growth rate is controlled exclusively by the stresses. The tissue growth rate is then given by k^+ and by the stress imbalance ($tr\hat{\sigma} - \sigma_{eq}^{*+}$), eq. (12).

For the second case biological availability is limited by an initial reserve of $R_i = 2\%$ and a discrete contribution $A_{0.5} = 0.20\%$ each half day. For the first stretch step the growth rate is similar to the unlimited availability case because it is sustained mainly by the initial reserve. At day fourteen the nutrients reserve is depleted and growth rate is now limited by the biological availability. It can be seen in Fig. 3b and 3c that, even if the evolution of the growth stretch is different, the model converges to the same stress states corresponding to the limit of the homeostatic equilibrium.

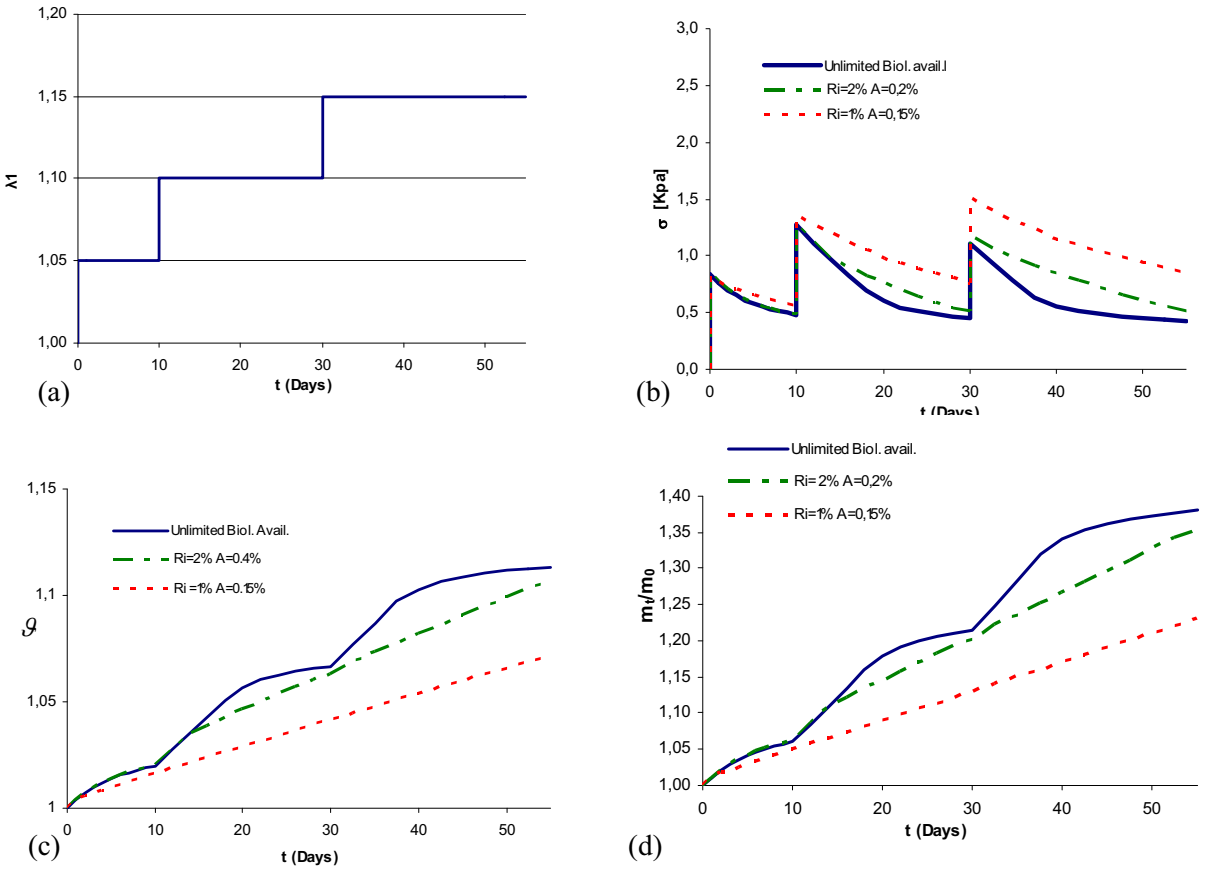

Figure 3. a) Stretch λ_1, b) Kirchhoff stress, c) Growing stretch, d) Mass increase.

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In the third case a more restricted nutrients income is considered and the growth rate is now limited by biological availability from the second day. The stress relaxation is smaller as can be seen in Fig. 3b. Fig. 3d shows mass ratio evolution (current mass/initial mass), in this case the mass increase is more noticeable.

To analyze in more detail the evolution of the biological availability a single stretch $\lambda_1 = 1.075$ is applied using the same mesh already described and considering for the nutrients an initial reserve of $R_i = 2\%$ and a discrete contribution $A_{0.5} = 0.15\%$ each half day (Fig. 4).

During the first four days the growth rate is limited by the maximum rate of mass production $R_{\max}$ and consequently the growth slope is constant (Fig. 4c). From day four to eight the growth rate is smaller than the limit imposed by maximum rate of mass production and it is proportional to the stress imbalance.

The biological availability decreases steeply during the first eight days, given the high grow rate. In this lapse the nutrients that entered the system and the initial reserve are depleted. Between days eight and twenty four all the nutrients that enter the system are used for growth as can be seen in Fig. 4d. The growth rate is limited then by the biological availability. After day twenty four the mechanical stimulus diminished to a level at which the growth rate is smaller than the rate of nutrients income and consequently the biological availability increases until its limit is reached.

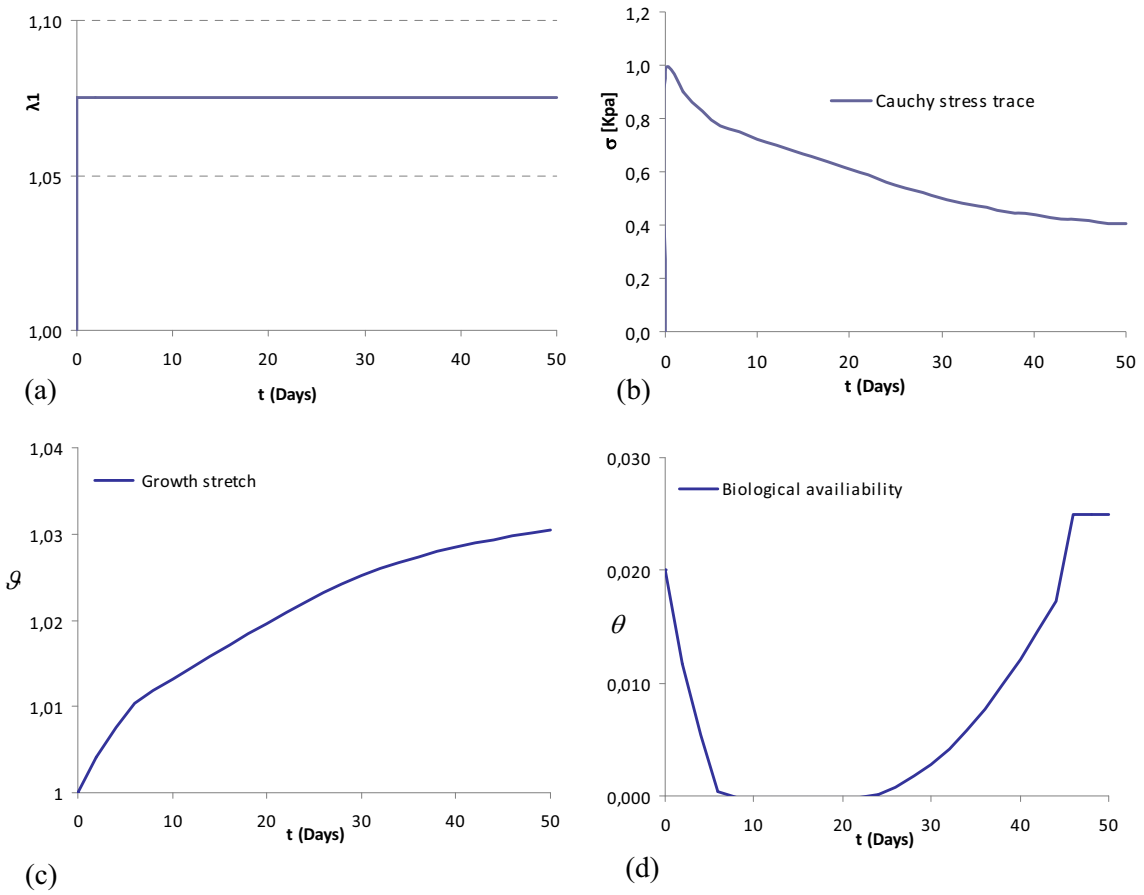

Figure 4. a) Stretch λ_1, b) Cauchy stress, x direction, c) Growth stretch d) Biological availability for growth θ.

5. Conclusions

A model for growth of soft tissues accounting for biological availability is proposed in this work. Growth stimulus is defined as a function of the stress field using the trace of Cauchy stress. However this stimulus generation is not enough to produce growth in the tissue, it is necessary that the metabolism allows the tissue to grow. For this reason the concept of biological availability is introduced as a limit in the mass source. This limit takes into account that metabolism requires a series of elements to sustain the growth process. All these elements are considered in a simplified way as nutrients. An internal scalar variable θ is proposed to account for the mentioned biological availability.

In the numerical implementation the nutrients entering the system are simulated in a simplified way by a temporal function parameterized at each integration point level. In future works an implementation based on the solution of a coupled mass transport field will be developed.

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