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# Rate-independent growth and remodelling of soft biological tissues: a constrained mixture approach for finite element analysis

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## Abstract

Constrained mixture models of soft tissue growth and remodelling enable one to simulate many evolving conditions in health, disease, and its treatment, but they tend to be computationally expensive. Here, we present results from a new rate-independent 3D computational formulation for soft tissue growth and remodelling based on a mechanobiologically equilibrated solution, which allows computation of fully resolved long-term responses as well as quasi-equilibrated evolutions for which imposed perturbations are slow relative to the adaptive process. The formulation retains mechanobiologically important properties, like different material properties and rates of turnover of the individual constituents that define the tissue. The associated implicit numerical algorithm at stress integration points is compact and easily implemented within existing finite element solvers. Its consistent linearization yields quadratic convergence during global finite element iterations, with computational efficiency comparable to that for finite strain elasticity. Numerical simulations of complex situations for arterial mechanics, including the enlargement of aneurysms, demonstrate its computational efficiency and robustness. We submit, therefore, that constrained mixture models of growth and remodelling can now be used more widely.

**Keywords:** growth, remodelling, constrained mixture, mechanobiology, finite elements, artery.

# 1 Introduction

A distinguishing feature of soft biological tissues is their ability to grow (change mass) and remodel (change microstructure) in response to diverse stimuli. Multiple approaches for mathematically modelling such growth and remodelling (G&R) have proved useful in describing diverse situations for many different tissues [1]. In particular, a constrained mixture model has proved useful when there is a need to account for the different material properties and rates of turnover of the individual constituents that define the tissue [2]. The heredity integral-based formulation of this mixture approach is computationally expensive, however, with past implementations focused on simple geometries.

Herein, we show computational advantages for illustrative cases by exploiting a recent concept of mechanobiologically equilibrated G&R [3,4]. The kinematics accounts for general three-dimensional G&R with finite deformations and possible rotations. This 3D framework can be implemented easily within existing finite element solvers, though with a non-symmetric tangent stiffness matrix. This new formulation enables fast, reliable finite element simulations of many G&R problems while accounting for critical differences in the behaviour of the different constituents that exist in soft tissues as, for example, their different turnover characteristics [5].

Local balance equations at both constituent and mixture levels are first reviewed and then particularized under mechanobiological equilibrium conditions. When these algebraic equations are complemented with an equilibrium value for a given stimulus function for mass production, they furnish a set of equations to compute fully resolved states at any material point and G&R time $s$.

# 2 Methods

Consider an in vivo loaded configuration $\kappa$ of a soft tissue, modeled here as a constrained mixture [2] of multiple solid constituents $\alpha = 1,\dots,\mathrm{N}$ (e.g., various cell types and extracellular matrix proteins). One key difference between conventional and biological materials is the ability of the latter to grow in response to diverse stimuli, which one can describe with mass balance relations in spatial form

$$\frac{d\rho^\alpha}{ds} + \rho^\alpha \nabla\cdot\mathbf{v}^\alpha = m^\alpha - n^\alpha = n^\alpha(\Upsilon^\alpha - 1)\,, \qquad \alpha = 1,\dots,\mathrm{N} \tag{1}$$

where $\rho^\alpha$ is the homogenized mass density, with $\rho = \sum\rho^\alpha$ the mass density of the tissue, $\mathbf{v}^\alpha = \mathbf{v}$ the common velocity, and $m^\alpha > 0$ and $n^\alpha > 0$ rates of mass density production and removal. Furthermore, $\Upsilon^\alpha = m^\alpha/n^\alpha > 0$ in Equation (1) defines a stimulus function that enhances ($> 1$), reduces ($< 1$), or balances ($= 1$) mass production with respect to removal, which is to be correlated to specific stimuli (e.g., stress, stretch, or their rates).

Spatial linear momentum balance relations read

$$\rho^\alpha \frac{d\mathbf{v}}{ds} = \nabla\cdot\boldsymbol{\sigma}_{\mathrm{t}}^\alpha + \rho^\alpha\mathbf{b}^\alpha\,, \qquad \alpha = 1,\dots,\mathrm{N} \tag{2}$$

where $\boldsymbol{\sigma}_{\mathrm{t}}^{\alpha}$ is the Cauchy stress tensor and $\mathbf{b}^{\alpha}$ the constituent body force, with additional exchanges of momentum typically negligible in soft tissue G&R. Summation of mass (1) and momentum (2) balances over all constituents yields associated relations for the mixture.

Considerer here cases where the tissue adapts rapidly relative to the imposed perturbations (e.g., slowly evolving aneurysms or slow arterial wall thickening in hypertension). The growth evolution becomes quasi-equilibrated, with $\Upsilon^{\alpha} \approx 1$ in Equation (1) to be solved quasi-statically along with mechanical equilibrium (Equation (2) with $d\mathbf{v}/ds \approx \mathbf{0}$), constitutive, and compatibility equations subject to boundary conditions [4,5].

During a mechanobiologically equilibrated evolution of this type, a deformation gradient $\mathbf{F}_h$ describes deformations between an initial in vivo configuration $\kappa_o$ and an evolved one $\kappa_h$, where natural configurations of different constituents either evolve ($\alpha = \xi$, which turnover continuously) or remain fixed ($\alpha = \zeta$). The equilibrated Cauchy stress for the mixture, computed from constituent-specific strain energies and deformation gradients, reads

$$\boldsymbol{\sigma}_h = \sum \boldsymbol{\sigma}_{\mathrm{t}h}^{\alpha} = \sum \phi^{\zeta} \boldsymbol{\sigma}_h^{\zeta} + \sum \phi^{\xi} \boldsymbol{\sigma}_h^{\xi} - p_h \mathbf{I} \tag{3}$$

where, importantly, the mass fractions $\phi^{\alpha}$ depend only on the Jacobian $J_h = \det \mathbf{F}_h$, $\boldsymbol{\sigma}_h^{\zeta}$ represents an elastic contribution, and $\boldsymbol{\sigma}_h^{\xi}$ remains constant (except for possible rotations). Hence, only the equilibrated Lagrange multiplier $p_h$ at the current in vivo state remains to be determined. Importantly, an equilibrated stimulus function for constituents $\xi$ driven by changes in stress relative to homeostatic baseline values introduces a constraint for the stress in Equation (3), from which

$$\Upsilon_h\big(\boldsymbol{\sigma}_h(p_h)\big) = 1 \;\Rightarrow\; p_h \tag{4}$$

Finally, tangent tensors for load-bearing constituent stresses, including $p_h$, all of them evolving consistent with the mechanobiologically equilibrated constraint $\Upsilon_h = 1$, yield an exact linearization of the rate-independent G&R formulation, which can be implemented easily within existing finite element solvers (we implemented it as a user material plugin in the open source software FEBio), though with non-symmetric (Lagrangian) tangent contributions arising from the constant Cauchy (pre)stresses $\boldsymbol{\sigma}_h^{\xi}$.

## 3 Results

We specialize the previous rate-independent constrained mixture framework to G&R experienced by arteries during maturity, for which the main load-bearing constituents are an amorphous elastin-dominated matrix ($\zeta = e$), circumferentially oriented passive smooth muscle ($\xi = m$), and circumferentially, axially, and diagonally oriented fibrillar collagen ($\xi = c$). To compute constituent-specific equilibrated stresses in Equation (3), we consider a four-fibre family model, with a neo-Hookean stored energy function for elastin and Fung-exponentials for the other oriented passive constituents. Furthermore, the stimulus function in Equation (4) is assumed to depend

on local changes in the volumetric Cauchy stress at the tissue level relative to its initial homeostatic value.

Elastin, however, may be removed (or degraded) in aneurysms. In particular, Fig. 1 shows the effects of elastin degradation, either axisymmetric (left) or asymmetric (right), on an arterial segment under initial in vivo conditions (pressurized and axially stretched; top). As it can be seen, localized losses of elastic fibre integrity result in growth and remodelling responses that cause marked dilatations of the aortic wall. Shown are deformed meshes and contour plots of circumferential stiffness, a particularly important indicator of aneurysmal presence, computed for a maximum localized degradation of elastin of 60% for the axisymmetric aneurysm and 75% for the asymmetric one, both showing also marked localized increases in mass (i.e., volume) ratios. Each finite element simulation was advanced quasi-statically and computed in 10 incremental time steps, which showed quadratic rates of convergence during global Newton-Raphson iterations and elapsed CPU times ≈ 1min on a single CPU processor Intel® Xeon® E5 at 3GHz in a Workstation Dell Precision 5810 with 32GB RAM. The FE model comprised $\mathrm{N}_r\mathrm{N}_\theta\mathrm{N}_z = 1 \times 20 \times 20 = 400$ displacement-based 3D quadratic elements with full $3 \times 3 \times 3$ Gauss integration.

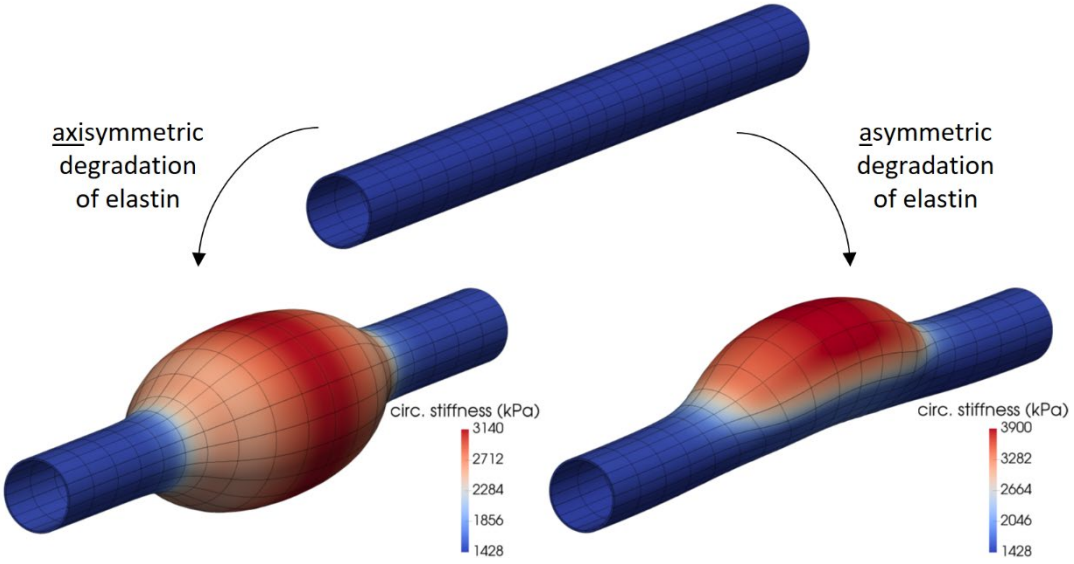


Figure 1: Initial (top) and evolved in vivo states for an arterial segment with axisymmetric (left) or asymmetric (right) loss of elastic fibre integrity, with constant blood pressure and fixed axial displacements at the ends.

## 4 Conclusions and Contributions

In this work, we presented results computed with a new constrained mixture formulation that enables computational tractability while retaining the biologically important characteristic of individual constituent properties, including rates of production and removal. This efficiency was achieved by using a mechanobiologically equilibrated framework, which avoids the heredity integral basis of a full constrained mixture model while providing precise information on the long-

term “relaxed” solution [3,6]. This approach is also particularly useful when time scales associated with G&R are shorter than those associated with perturbations in mechanical or chemical stimuli to which the cells respond [4,6]. Importantly, the formulation is easily implemented within available finite element solvers, though for non-symmetric tangent stiffness matrices. Results were presented for a modified open source code, FEBio, with solutions revealing quadratic convergence with computational efficiency comparable to that for a nonlinear hyperelastic computation, though here for the simultaneous solution of mechanical and mechanobiological equilibrium at load steps that capture evolving geometries, compositions, and properties of interest.

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