Modeling biological growth and remodeling: contrasting methods, contrasting needs

Marcos Latorre

Department of Biomedical Engineering
Yale University, New Haven, CT, USA

Abstract

Biological growth and remodeling processes are necessarily time dependent due to the finite periods needed for the material to be synthesized, deposited, degraded, and/or reorganized and, hence, so have been predominantly modeled for the past 20+ years. However, a full-spectrum examination of the timescales present in these processes reveals the need to explore a new class of models for which time-dependent effects are negligible. These mechanobiologically (quasi-) equilibrated formulations not only appear to apply well in many cases but provide the modeler with those additional pieces of information, and intuition, always needed when modeling complex time-dependent responses. Material model determination, optimization involving long-term adaptations, and mechanobiological stability analyses could be leveraged by the simplicity and computational efficiency of time-independent models. Although this concept is general, we address it by means of two particular theories for which we also highlight crucial differences entailed by their diametrically different material memory and heterogeneity descriptions.

Keywords: kinematic growth, constrained mixture, mechanobiology, homogenization, rate-independent

1. Introduction

Because of their inherently heterogeneous nature, the mechanics of biological materials are frequently studied from two viewpoints: as a mixture of material constituents or as a homogenized material. A theory of mixtures examines the individual properties and interactions of constituents to determine their effects on overall properties, which allows an essential understanding. In a homogenized material, the effects of the constituents are detected only as averaged macroscopic properties, which allows computationally more tractable analyses though less detail.

This distinction is particularly relevant for biological growth and remodeling (G&R), where internal distributions and mechanical properties, but also masses, of the constituents, hence the mixture, may evolve. Two representative approaches are a theory of constrained mixtures (CM) and a theory of finite kinematic growth (FG). In this brief review, we highlight specific salient features of and differences between both approaches regarding evolution equations for mass/volume growth and stress that aim to stimulate future work on both sides. We also identify promising new modeling areas based on a naturally introduced concept of a stimulus function for mass growth and its different physical interpretations and mathematical treatments in mechanobiology.

Email address: marcos.latorre@yale.edu (Marcos Latorre)

2. Balance Laws for Open Systems: Still Open

One key difference between conventional and biological materials is the ability of the latter to grow (i.e., change mass) in response to diverse stimuli, which one typically describes with a mass balance relation $\dot{\rho} + \rho \operatorname{div} \mathbf{v} = \bar{m}$, where ρ is the spatial mass density, $\dot{\rho}$ its material time derivative, $\mathbf{v}$ the velocity, and $\bar{m} \neq 0$ a net rate of mass density production or removal. Let $\bar{m} = m - n$ be defined in terms of true rates of mass density production $m > 0$ and removal $n > 0$. Then, define a stimulus function $\Upsilon := m/n > 0$. Finally, $\operatorname{div} \mathbf{v} = \dot{J}/J$, with $J = \det \mathbf{F}$ the Jacobian determinant of a deformation gradient $\mathbf{F}$ that describes deformations between associated reference and current configurations, thus leading to an equivalent form

$$\frac{\dot{\rho}}{\rho} + \frac{\dot{J}}{J} = \frac{n}{\rho}(\Upsilon - 1) \ , \tag{1}$$

whereupon Υ enhances (> 1), reduces (< 1), or balances ($= 1$) mass production with respect to removal. Hence, the task of modeling mass growth reduces to correlate n and Υ with specific stimuli; whether one uses stress, stretch, or their rates is a controversial matter from a mechanobiological perspective [1], with other factors possible too [2].

Besides exchanging mass, biological materials also exchange momenta, energy, and entropy with their surrounding. Thus, additional terms need to be considered in balance relations extended for open systems [3–7], which have found extensive application to G&R of biological tissues. However, because the intent of the second law of thermo-

dynamics is not to enforce restrictions on processes associated with open systems [8], it is not surprising that the specific form and nature of the extra terms, whether sources or fluxes, reversible or irreversible, are subject to controversy as well. Indeed, the fact that the current "thermodynamic approach fails to restrict universally the functional form of evolution laws for growth" [9] encourages additional theoretical work on the thermodynamic foundations of mechanobiology.

In what follows, we will refer to the linear momentum balance relation, which, for slow growth processes, adopts the classical form

$$\rho\dot{\mathbf{v}} = \operatorname{div}\boldsymbol{\sigma} + \rho\mathbf{b} \ , \tag{2}$$

with Cauchy stress $\boldsymbol{\sigma}$ and body force $\mathbf{b}$.

3. Kinematics and Constitutive Relations

Because of its intricate nature, biological G&R admits multiple mechanobiological interpretations and modeling approaches. Naturally, many have extended successful kinematic relations and evolution equations from allied fields.

3.1. Theory of finite growth

Rodriguez et al. [10] proposed the multiplicative decomposition of the deformation gradient $\mathbf{F} = \mathbf{F}_e\mathbf{F}_g$ for FG, with $\mathbf{F}_g$ the inelastic part of the deformation that represents the addition or subtraction of mass to a local volume element and $\mathbf{F}_e$ the elastic part that generates mechanical stresses.

3.1.1. Rate-dependent, viscous-type evolution

Even though $\mathbf{F} = \mathbf{F}_e\mathbf{F}_g$ is often related to the Bilby–Kröner–Lee multiplicative decomposition for elastoplasticity, evolution equations for $\mathbf{F}_g$ of viscous type are ubiquitous in the literature. To illustrate, consider the conceptual form $\dot{\vartheta}/\vartheta = kK_\sigma\sigma/\sigma_o$, with ϑ a growth multiplier, σ a given stress measure, σ_o a reference value, k a rate parameter, and K_σ a gain. When compared to Eq. (1) with, for example, ρ constant (for a soft tissue that tends to preserve its overall mass density), $n = k\rho$ (first-order kinetics for removal), and $\vartheta = J_g = J$ (incompressible elastic behavior), yields a stimulus function $\Upsilon = 1 + K_\sigma\sigma/\sigma_o$. Further refinements have been proposed in [11] to prevent unlimited growth at non-zero stress, in [12] to let the growth response be activated beyond physiological threshold levels, and, more recently, in [13] to endow the reference configuration with residual stresses.

Consistent with Cannon's idea of homeostasis [14], observations of the mechanobiology suggest that both mass production and removal are governed by feedback mechanisms that depend on perturbations from physiological targets [15], which many FG models fail to incorporate. Attempts in this direction have consisted in deriving rate-dependent evolution equations for growth depending on an overstress in terms of an Eshelby-like tensor [16] or additional internal variables of elastic nature [17].

3.1.2. Rate-independent, plastic-type evolution

In contrast to previous models, a formulation for FG extended from rate-independent plasticity was presented in [18]. Even though numerical simulations appear to agree well with results documented in the literature, this approach has been less popular in the field, perhaps, among other reasons, because soft tissue G&R requires consideration of rate-dependent effects (e.g., one expects a tissue to grow gradually, not instantaneously, after a step change in external loading). A reconsideration of the timescales involved in G&R adaptations, as explained below, could confer more relevance to rate-independent models, either path-dependent or -independent.

3.1.3. Extended evolution equations

As put forward in [19] after deriving a CM formulation in rate form, additional strain- or stress-like internal variables could be incorporated in multiplicative models to extend, and test, their predictive capabilities. In this sense, Soleimani [20] models finite strain viscoelastic (nutrient diffusion-driven) growth for biofilms through an additional linear evolution equation for a stress-like internal variable. After recognizing that viscoelasticity alone may be insufficient to account for irreversible deformations in some tissues (e.g., stress-driven rearrangements of cells and their adhesion network in tumors), Grillo et al. [21] borrow concepts from strain-gradient plasticity and propose an extended multiplicative decomposition $\mathbf{F} = \mathbf{F}_e\mathbf{F}_p\mathbf{F}_g$, with $\mathbf{F}_p$ an additional internal deformation gradient describing distortional plasticity-like remodeling processes.

3.2. Theory of constrained mixtures

Alternatively, Humphrey and Rajagopal [22] let the mass supply and free energy of different load-bearing constituents be expressed through heredity integrals to formalize a conceptually different CM theory. This approach allows consideration of constituent-specific rates of production and removal, with constituents α, deposited with pre-stretch $\mathbf{G}^\alpha$ from evolving natural configurations at deposition time τ, constrained to deform with the mixture through $\mathbf{F}^\alpha_{\mathrm{n}(\tau)}(s) = \mathbf{F}(s)\,\mathbf{F}^{-1}(\tau)\,\mathbf{G}^\alpha(\tau)$ at G&R time $s \geq \tau$. Evolution equations for mass growth are motivated by Fung's call for mass-stress relations and afford tensional homeostasis by means of the pre-stresses generated by the pre-stretches.

3.2.1. Heredity-integral, viscous-type evolution

To review salient features of this model associated with its integrals, let us consider a homogenized mixture in what follows (see [23] for a wider discussion). With $\rho_{\mathrm{R}} = J\rho$ the mass density per unit reference volume and $n/\rho = k$, Eq. (1) yields $\dot{\rho}_{\mathrm{R}} + k\rho_{\mathrm{R}} = m_{\mathrm{R}}$, where $m_{\mathrm{R}} = k\rho_{\mathrm{R}}\Upsilon = n_{\mathrm{R}}\Upsilon$. Mass balance is thus integrable and yields $\rho_{\mathrm{R}}(s) =$

$\int_{-\infty}^{s} m_{\mathrm{R}}(\tau)\, q(\tau, s)\, d\tau$ based on a survival function $q(\tau, s)$. A strain energy per unit reference volume of soft tissue $W_{\mathrm{R}}(s) = \frac{1}{\rho}\int_{-\infty}^{s} m_{\mathrm{R}}(\tau)\, q(\tau, s)\, \hat{W}(\mathbf{F}_{\mathrm{n}(\tau)}(s))d\tau$ is additionally postulated, with $\hat{W}$ the energy function defined from the evolving natural configuration.

3.3. A comparison in rate form

By homogenizing the material in the CM formulation, one can elucidate key differences with a theory of FG associated exclusively with their postulated multiplicative decompositions and strain energies. Let the strain energy per unit current volume for the conventional FG model depend on $\mathbf{F}_e$. Its material time derivative, for an isochoric elastic response without additional internal variables, yields $\dot{W} = \boldsymbol{\sigma}^x : \mathbf{d}$, with $\boldsymbol{\sigma}^x$ the part of the stress that derives from the strain energy and $\mathbf{d}$ the rate of deformation tensor. For the heredity integral model, one obtains $\dot{W} = \boldsymbol{\sigma}^x : \mathbf{d} - k\Upsilon(W - W_{\mathrm{dep}})$, with the second term naturally providing a self-stabilizing, relaxation-like contribution for W towards its homeostatic value (i.e., $W \to W_{\mathrm{dep}}$) associated with the fact that the energy $W_{\mathrm{dep}} = \hat{W}(\mathbf{G})$ of the newly deposited mass is different from the current (average) energy W of the tissue. Hence, because a full CM theory is currently considered to provide a much richer mechanobiological interpretation of the intricate G&R processes in biological tissues [9], but at the same time becomes computationally expensive for complex cases, there is a need for enhanced kinematic decompositions [13, 20, 21, 24] that provide closer descriptions to the more general evolution equations for mass and stress provided by associated theories of CM, as well as, in parallel, a need for computationally more efficient and tractable formulations for the latter [25, 26], currently afforded only by its temporally homogenized variants [27, 28].

4. Stimulus Functions for (mal)adaptive G&R

Cannon's concept of homeostasis seems to work reasonably well for normal adaptations of mature tissues with constant "set points" (or homeostatic stresses), but may not apply in other developmental or pathological processes. For example, Taber [15] assumed that homeostatic stresses increase with blood pressure during development to eventually reach preferred values in maturity. Conceptually, $\Upsilon(s) = 1 + K_\sigma(\sigma(s) - \sigma_h(s))/\sigma_h(s)$ in Eq. (1) with homeostatic stresses $\sigma_h(s)$ evolving during development, consistent with a redefined concept of "adaptive homeostasis" [29].

Homeostatic mechanisms may be highly dysregulated in diseases where inflammation plays a crucial role [30]. For example, Bersi et al. correlated increased inflammation with failed restoration of wall stresses to normal values in the descending thoracic aorta (DTA) of wild-type [31] and *Apoe*$^{-/-}$ [32] mice rendered hypertensive via infusion of AngII. This maladaptation for target stresses may be accounted for by considering both mechanobiological and immunobiological contributors to aortic wall G&R. Conceptually, $\Upsilon(s) = 1 + K_\sigma(\sigma(s) - \sigma_o)/\sigma_o + K_\varphi \Delta\varrho_\varphi(s)$ in Eq. (1). Once the inflammatory response has achieved its protective goal, for which $\Delta\varrho_\varphi = 1$ is maximum, a new equilibrium state $\Upsilon = 1$ is reached, which leads to a new homeostatic stress $\sigma_h = \sigma_o(1 - K_\varphi/K_\sigma)$ lower than σ_o for $K_\varphi \in (0, K_\sigma)$, consistent with experimental observations in [31, 32] and model predictions in [33, 34]. The coupling between stress and inflammatory stimuli, however, remains largely unexplored and not even simple functional forms have been proposed. Network models are a promising venue in this regard.

5. Loading and Adaptation Timescales Revisited

In a seminal review [35], Cowin recognized two timescales in living tissue mechanics that differ by many orders of magnitude: a short timescale for (typically fast) loading and a long timescale for (typically slow) adaptations.

The adaptation timescale in biological tissue is inherently related to the turnover, or combined deposition and degradation, of its constituents [36]. It ranges from minutes (e.g., for certain cells) to days to months (e.g., for constituents within the extracellular matrix). Recently, a thermodynamically inspired, intrinsic timescale associated with growth, termed "internal time" was determined [37]. Consistent with a shorter loading timescale, G&R models have included rate-dependent, relaxation-like effects for the growth response (e.g., $\mathbf{F}_g$ in FG models) but also the stress response (e.g., W in CM models). However, because an adaptation process is not necessarily driven by external loads, the concept of "short loading timescale" could be broadened. There exist, in fact, situations for which the period over which the stimulus that drives G&R varies is comparable to, or even longer than, the response timescale: slowly evolving aneurysms stimulated by slow degradation of elastin laminae, or slow neovessel formation and adaptation stimulated by slow degradation of the polymer within tissue-engineered vascular grafts (TEVG). One can also think of a slow arterial wall thickening in hypertension stimulated by a gradual increase in (perhaps systolic) blood pressure. Because pressure represents an external load, but elastin or polymer degradation do not, we submit that a "stimulation timescale" could be a broader term to define the characteristic "external" time that is to be compared to an "internal" time to allow for more precise modeling.

Therefore, contrary to the observation in [35] that motivated the enhancement of rate-dependent theories of adaptive elasticity, the present observation about comparable timescales in other problems of interest aims to stimulate further development on rate-independent G&R theories. In this regard, if the tissue adapts rapidly (relative to the stimulation timescale), the growth evolution becomes quasi-equilibrated and requires $\Upsilon \simeq 1$ in Eq. (1), which can be solved quasi-statically with mechanical equilibrium (Eq. (2) with $\mathbf{v} \simeq \mathbf{0}$), constitutive, and compatibility

equations subject to boundary conditions [38]. Since G&R time is absent, a generalization of this formulation for CM models well-suited for computational implementation in finite element solvers would signify a significant reduction in computational time and memory needs and enable (so far impractical) complex non-linear finite element simulations for a host of soft tissues. Of course, a comparison between the involved timescales should dictate the appropriate formulation to use for each application [38].

6. Mechanobiological Equilibrium

Cells attempt to establish, maintain, or restore a homeostatic mechanical state and eventually reach a biological equilibrium under stable physiological conditions [36]. Very few researchers have addressed how to determine mechanobiological equilibrium states following a direct approach. Among them, Rachev was the first in studying, theoretically, the final adaptation of an artery under sustained hypertension [39]. Recently, a CM model for cylindrical arteries was pre-integrated to yield a system of algebraic equations which solution, consistent with $\Upsilon = 1$ in Eq. (1) and $\mathbf{v} = \mathbf{0}$ in Eq. (2), is equivalent to the long-term solution of its respective heredity integral model [40]. If "G&R models represent a fundamentally new capability to predict the single thing that matters most to doctors and patients: long-term outcomes" [41], a formalization of these, and others that may emerge, formulations that give rise to efficient and reliable computational methods for parameter sensitivity, uncertainty quantification, and optimization of material parameters or geometries, subject to complex loads and boundary conditions, should be pursued.

The formulation in [40] gives a path-independent, reversible solution for given blood pressure, flow rate, and axial stretch, which is consistent with the conceptual analysis performed in [42] for a hypertensive adaptation. It seems also consistent with recent experimental evidence on common carotid arteries of Wistar rats [43]. Similar to rate-independent plasticity, however, an actual mechanobiologically equilibrated evolution might be path-dependent and require to account for irreversible deformations of the tissue, as in [18, 21]. There is a need, thus, for more experimental evidence to elucidate the (ir)reversibility of biological G&R within different environments. Extended CM models that incorporate possible irreversible effects for specific constituents promise to provide additional insight.

7. Mechanobiological Stability

When studying mechanobiological equilibrium, there are two properties that stand out, namely, existence and uniqueness of solutions. Regarding G&R evolutions, another property should be assessed, namely, dynamical stability. These three properties can be analyzed from initial-boundary value problems involving Eqs. (1) and (2) complemented with a constitutive equation for stress.

Dynamic stability analyses of G&R were first performed in [44, 45] using CM models and in [46] using FG. The concept was formalized mathematically in [47] based on an enhanced theory of "small on large" [48]. Further insight was given in [19] based on a full CM model in rate-form well-suited for stability analyses. In particular, derivations in [19] showed a natural separation of, e.g., the Truesdell rate of the Cauchy stress into elastic, growth, and remodeling parts, the last reading, conceptually, $\mathring{\boldsymbol{\sigma}}_r = -k\Upsilon(\boldsymbol{\sigma} - \boldsymbol{\sigma}_{\text{dep}})$, which, consistent with the one for W, is a self-stabilizing, relaxation-like contribution for $\boldsymbol{\sigma}$ towards its homeostatic, pre-stress value (i.e., $\boldsymbol{\sigma} \to \boldsymbol{\sigma}_{\text{dep}}$) absent in the conventional FG theory. In fact, an "active stress recovery" of this type was originally derived in [24] based on constituent-specific decompositions $\mathbf{F} = \mathbf{F}_e^\alpha \mathbf{F}_r^\alpha \mathbf{F}_g^\alpha$ meant to rely on micromechanical ideas from CM models. Since mass and stress evolutions are necessarily coupled for materials subjected to stress-driven turnover, this contribution could be critical in analyzing their mechanobiological stability.

Besides analyzing the *dynamic stability* of perturbed responses around equilibrium states (see [23]), the study [19] also brought up the importance of analyzing the *static stability* of equilibrium states themselves, that is, assessing their existence and uniqueness under mechanobiologically quasi-equilibrated evolutions. In this respect, non-existence of an equilibrium state could associate with an asymptotic growth response, whereas non-uniqueness could associate with mechanobiological (i.e., not just mechanical) limit point instabilities or bifurcations. Other model parameters could similarly give rise to static instabilities of this kind [49].

This is an emerging field where much work needs to be done, particularly on distinguishing static from dynamic instabilities in complex pathologies (e.g., in unstable expansions of aneurysms) and neutral from asymptotic stability in different adaptations, nonlinear stability analyses (with possible vanishing real eigenvalues or limit cycles), as well as experimental, theoretical, and computational stability studies for formed neovessels after graft implantation [50, 51].

8. Conclusions

Since early pioneering works by Skalak, Fung, and colleagues, many advanced formulations to model G&R of living tissues have been proposed. We have briefly examined a few particular features of two remarkably different theories: finite growth based on time and material homogenizations and constrained mixtures based on heredity integrals. However, precisely because of their intrinsic differences, we submit that both formulations present complementary modeling assets that make them natural companions to progress on the continuum modeling of biological G&R.

We suggested the need to systematically incorporate additional internal variables in future implementations of a (computationally favorable) theory of finite growth to

reproduce responses otherwise predicted by a constrained mixture model (even if materially homogenized). On other hand, noting that with a theory of mixtures one gains an understanding for why and how biological materials grow and remodel, full modeling power will be demonstrated when its computational performance additionally improves. This may indeed be attainable, as a starting point, by rate-independent theories that may find a place in G&R applications after a reconsideration of the time-scales involved in practical cases. Further advancement should bring robust and efficient, mechanobiologically inspired, computational models that will be essential to analyze mechanobiological equilibrium and stability properties of living tissues, which mechanoadapt, or not, to the myriad stimuli that drive their G&R.

Conflict of Interest. The authors declare no conflict of interest.

References

[1] J. D. Humphrey, Stress, strain, and mechanotransduction in cells, Journal of Biomechanical Engineering 123 (6) (2001) 638–641.

[2] E. Kuhl, Growing matter: a review of growth in living systems, Journal of the Mechanical Behavior of Biomedical Materials 29 (2014) 529–543.

[3] S. C. Cowin, D. H. Hegedus, Bone remodeling I: theory of adaptive elasticity, Journal of Elasticity 6 (3) (1976) 313–326.

[4] M. Epstein, G. A. Maugin, Thermomechanics of volumetric growth in uniform bodies, International Journal of Plasticity 16 (7-8) (2000) 951–978.

[5] E. Kuhl, P. Steinmann, Mass– and volume–specific views on thermodynamics for open systems, Proceedings of the Royal Society of London. Series A: Mathematical, Physical and Engineering Sciences 459 (2038) (2003) 2547–2568.

[6] K. Garikipati, E. M. Arruda, K. Grosh, H. Narayanan, S. Calve, A continuum treatment of growth in biological tissue: the coupling of mass transport and mechanics, Journal of the Mechanics and Physics of Solids 52 (7) (2004) 1595–1625.

[7] G. A. Ateshian, On the theory of reactive mixtures for modeling biological growth, Biomechanics and Modeling in Mechanobiology 6 (6) (2007) 423–445.

[8] K. R. Rajagopal, A. R. Srinivasa, Some remarks and clarifications concerning the restrictions placed on thermodynamic processes, International Journal of Engineering Science 140 (2019) 26–34.

[9] A. Goriely, The mathematics and mechanics of biological growth, Springer, 2017.

[10] E. K. Rodriguez, A. Hoger, A. D. McCulloch, Stress-dependent finite growth in soft elastic tissues, Journal of Biomechanics 27 (4) (1994) 455–467.

[11] V. A. Lubarda, A. Hoger, On the mechanics of solids with a growing mass, International Journal of Solids and Structures 39 (18) (2002) 4627–4664.

[12] S. Göktepe, O. J. Abilez, E. Kuhl, A generic approach towards finite growth with examples of athlete's heart, cardiac dilation, and cardiac wall thickening, Journal of the Mechanics and Physics of Solids 58 (10) (2010) 1661–1680.

[13] Y. Du, C. Lü, W. Chen, M. Destrade, Modified multiplicative decomposition model for tissue growth: beyond the initial stress-free state, Journal of the Mechanics and Physics of Solids 118 (2018) 133–151.

[14] W. B. Cannon, Organization for physiological homeostasis, Physiological Reviews 9 (3) (1929) 399–431.

[15] L. A. Taber, A model for aortic growth based on fluid shear and fiber stresses, Journal of Biomechanical Engineering 120 (3) (1998) 348–354.

[16] D. Ambrosi, F. Guana, Stress-modulated growth, Mathematics and Mechanics of Solids 12 (3) (2007) 319–342.

[17] M. B. Rubin, An Eulerian formulation of inelasticity: from metal plasticity to growth of biological tissues, Philosophical Transactions of the Royal Society A 377 (2144) (2019) 20180071.

[18] C. Vignes, P. Papadopoulos, Material growth in thermoelastic continua: theory, algorithmics, and simulation, Computer Methods in Applied Mechanics and Engineering 199 (17-20) (2010) 979–996.

[19] M. Latorre, J. D. Humphrey, Mechanobiological stability of biological soft tissues, Journal of the Mechanics and Physics of Solids 125 (2019) 298–325.

[20] M. Soleimani, Finite strain visco-elastic growth driven by nutrient diffusion: theory, FEM implementation and an application to the biofilm growth, Computational Mechanics 64 (5) (2019) 1289–1301.

[21] A. Grillo, S. Di Stefano, A. Ramírez-Torres, M. Loverre, A study of growth and remodeling in isotropic tissues, based on the Anand-Aslan-Chester theory of strain-gradient plasticity, GAMM Mitteilungen (2019) e201900015.

[22] J. D. Humphrey, K. R. Rajagopal, A constrained mixture model for growth and remodeling of soft tissues, Mathematical Models and Methods in Applied Sciences 12 (3) (2002) 407–430.

[23] D. Ambrosi, M. Ben Amar, C. J. Cyron, A. DeSimone, A. Goriely, J. D. Humphrey, E. Kuhl, Growth and remodelling of living tissues: perspectives, challenges and opportunities, Journal of the Royal Society Interface 16 (157) (2019) 20190233.

[24] C. J. Cyron, R. C. Aydin, J. D. Humphrey, A homogenized constrained mixture (and mechanical analog) model for growth and remodeling of soft tissue, Biomechanics and Modeling in Mechanobiology 15 (6) (2016) 1389–1403.

[25] N. Horvat, L. Virag, G. A. Holzapfel, J. Sorić, I. Karšaj, A finite element implementation of a growth and remodeling model for soft biological tissues: verification and application to abdominal aortic aneurysms, Computer Methods in Applied Mechanics and Engineering 352 (2019) 586–605.

[26] W. J. Lin, M. Iafrati, R. A. Peattie, L. Dorfmann, Non-axisymmetric dilatation of a thick-walled aortic aneurysmal tissue, International Journal of Non-Linear Mechanics 109 (2019) 172–181.

[27] F. A. Braeu, A. Seitz, R. C. Aydin, C. J. Cyron, Homogenized constrained mixture models for anisotropic volumetric growth and remodeling, Biomechanics and Modeling in Mechanobiology 16 (3) (2017) 889–906.

[28] S. J. Mousavi, S. Farzaneh, S. Avril, Patient-specific predictions of aneurysm growth and remodeling in the ascending thoracic aorta using the homogenized constrained mixture model, Biomechanics and Modeling in Mechanobiology 18 (6) (2019) 1895–1913.

[29] K. J. A. Davies, Adaptive homeostasis, Molecular Aspects of Medicine 49 (2016) 1–7.

[30] M. E. Kotas, R. Medzhitov, Homeostasis, inflammation, and disease susceptibility, Cell 160 (5) (2015) 816–827.

[31] M. R. Bersi, C. Bellini, J. Wu, K. R. Montaniel, D. G. Harrison, J. D. Humphrey, Excessive adventitial remodeling leads to early aortic maladaptation in angiotensin-induced hypertension, Hypertension 67 (5) (2016) 890–896.

[32] M. R. Bersi, R. Khosravi, A. J. Wujciak, D. G. Harrison, J. D. Humphrey, Differential cell-matrix mechanoadaptations and inflammation drive regional propensities to aortic fibrosis, aneurysm or dissection in hypertension, Journal of The Royal Society Interface 14 (136) (2017) 20170327.

[33] M. Latorre, J. D. Humphrey, Modeling mechano-driven and immuno-mediated aortic maladaptation in hypertension, Biomechanics and Modeling in Mechanobiology 17 (5) (2018) 1497–1511.

[34] M. Latorre, M. R. Bersi, J. D. Humphrey, Computational modeling predicts immuno-mechanical mechanisms of maladaptive

aortic remodeling in hypertension, International Journal of Engineering Science 141 (2019) 35–46.
[35] S. C. Cowin, Tissue growth and remodeling, Annual Review of Biomedical Engineering 6 (2004) 77–107.
[36] C. J. Cyron, J. D. Humphrey, Growth and remodeling of load-bearing biological soft tissues, Meccanica 52 (3) (2017) 645–664.
[37] A. Grillo, S. Di Stefano, S. Federico, Growth and remodelling from the perspective of Noethers theorem, Mechanics Research Communications 97 (2019) 89–95.
[38] M. Latorre, J. D. Humphrey, Critical roles of time-scales in soft tissue growth and remodeling, APL Bioengineering 2 (2) (2018) 026108.
[39] A. Rachev, Theoretical study of the effect of stress-dependent remodeling on arterial geometry under hypertensive conditions, Journal of Biomechanics 30 (8) (1997) 819–827.
[40] M. Latorre, J. D. Humphrey, A mechanobiologically equilibrated constrained mixture model for growth and remodeling of soft tissues, ZAMM Journal of Applied Mathematics and Mechanics 98 (12) (2018) 2048–2071.
[41] J. W. Holmes, J. E. Wagenseil, Spotlight on the future of cardiovascular engineering: frontiers and challenges in cardiovascular biomechanics, Journal of Biomechanical Engineering 138 (11) (2016) 110301.
[42] J. D. Humphrey, Mechanisms of arterial remodeling in hypertension: coupled roles of wall shear and intramural stress, Hypertension 52 (2) (2008) 195–200.
[43] K. Hayashi, D. Kakoi, A. Makino, Remodeling of the arterial wall: response to restoration of normal blood flow after flow reduction, Biorheology 54 (2-4) (2018) 95–108.
[44] G. Satha, S. B. Lindström, A. Klarbring, A goal function approach to remodeling of arteries uncovers mechanisms for growth instability, Biomechanics and Modeling in Mechanobiology 13 (6) (2014) 1243–1259.
[45] J. Wu, S. C. Shadden, Stability analysis of a continuum-based constrained mixture model for vascular growth and remodeling, Biomechanics and Modeling in Mechanobiology 15 (6) (2016) 1669–1684.
[46] A. Erlich, D. E. Moulton, A. Goriely, Are homeostatic states stable? Dynamical stability in morphoelasticity, Bulletin of Mathematical Biology (2018) 1–26.
[47] C. J. Cyron, J. D. Humphrey, Vascular homeostasis and the concept of mechanobiological stability, International Journal of Engineering Science 85 (2014) 203–223.
[48] S. Baek, R. L. Gleason, K. R. Rajagopal, J. D. Humphrey, Theory of small on large: potential utility in computations of fluid–solid interactions in arteries, Computer Methods in Applied Mechanics and Engineering 196 (31-32) (2007) 3070–3078.
[49] J. D. Humphrey, M. Latorre, Biomechanics and mechanobiology of extracellular matrix remodeling, in: Y. Zhang (Ed.), Multi-scale Extracellular Matrix Mechanics and Mechanobiology. Studies in Mechanobiology, Tissue Engineering and Biomaterials, Vol. 23, Springer, Cham, 2020.
[50] R. Khosravi, K. S. Miller, C. A. Best, Y. C. Shih, Y.-U. Lee, T. Yi, T. Shinoka, C. K. Breuer, J. D. Humphrey, Biomechanical diversity despite mechanobiological stability in tissue engineered vascular grafts two years post-implantation, Tissue Engineering Part A 21 (9-10) (2015) 1529–1538.
[51] J. M. Szafron, A. B. Ramachandra, C. K. Breuer, A. L. Marsden, J. D. Humphrey, Optimization of tissue-engineered vascular graft design using computational modeling, Tissue Engineering Part C: Methods 25 (2019) 10.

Annotated References

[13] (*) Finite kinematic growth model based on an enhanced multiplicative decomposition for biological tissues endowed with residual stresses in an initial state.

[19] (*) Full constrained mixture model in rate form suitable for studying mechanobiological equilibrium and stability of soft tissues, clearly delineating static from dynamic instabilities.

[20] (*) Finite kinematic growth model including an additional stress-like internal variable to model finite strain viscoelastic growth.

[33] (*) Growth and remodeling model including mechanical stress and inflammatory cell density as determinants of matrix turnover to model maladaptative adventitial fibrosis in hypertension.

[38] (*) A revisited examination of the timescales present in biological growth and remodeling reveals the need to explore a new class of models for which time-dependent effects are negligible over the adaptation timescale.

[40] (*) Mechanobiologically equilibrated constrained mixture model developed for arterial G&R with enhanced rules of mixtures for local mass and stress for which constituent-specific mass fractions, and perhaps other properties, may change.

[43] (*) The authors report reversible adaptations in common carotid arteries of Wistar rats following restoration of normal blood flow after prior reduction, as predicted by current mechanobiologically equilibrated models.

[46] (*) A mechanobiological stability analysis performed with a finite kinematic growth model.