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## VASCULAR MECHANICS, MECHANOBIOLOGY, AND REMODELING<sup>1</sup>

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### Abstract

Arteries exhibit a remarkable ability to adapt in response to sustained alterations in hemodynamic loading as well as in response to disease, injury, and clinical treatment. A better understanding of such adaptations will be aided greatly by formulating, testing, and refining appropriate theoretical frameworks for modeling the biomechanics and associated mechanobiology. The goal of this brief review is to highlight some recent developments in the use of a constrained mixture theory of arterial growth and remodeling, with particular attention to the requisite constitutive relations, and to highlight future directions of needed research.

### Keywords

vascular growth; remodeling; adaptation; extracellular matrix turnover; stress-strain

### 1. Introduction

Vascular disease continues to be a leading cause of morbidity and mortality in the U.S.A. and its prevalence is expanding worldwide. The past four decades have revealed that many vascular diseases cause, or are caused by, marked changes in the associated mechanics. Similarly, many methods of treatment, as, for example, intravascular stents and coils, implanted grafts, and even many surgical interventions, rely largely on mechanical effects. There is, therefore, a pressing need to understand better both the mechanics of the arterial wall and the hemodynamics, with particular attention to the underlying mechanobiology. The goal of this brief review is to outline some recent developments in arterial biomechanics and modeling in mechanobiology in order to highlight future directions of needed research. Toward this end, recall that 40+ years ago Fung (1967) astutely observed that,

“the greatest need lies in the direction of collecting data in multiaxial loading conditions and formulating a theory for the general rheological behavior of living tissues...”

Based upon and motivated by the early work of Y.C. Fung as well as R.N. Vaishnav, B.R. Simon, R.P. Vito, H. Demiray, R.H. Cox, P.B. Dobrin, K. Hayashi, and many others, there have been tremendous advances in our understanding of arterial wall mechanics since the mid-1960s (cf. Fung, 1990; Humphrey, 2002). Nevertheless, two conspicuous shortcomings have remained: the need to account explicitly for separate contributions by the diverse

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structurally significant constituents within the arterial wall and the need to describe mathematically the remarkable ability of arteries to adapt to changing hemodynamic conditions as well as in response to disease, injury, and clinical treatment. These shortcomings are the focus of this review.

It has long been accepted that the five fundamental postulates of continuum mechanics hold for living tissues just as they do for traditional engineering materials. Hence, any theory of arterial growth and remodeling (G&R) should find its foundations in equations for balances of mass, linear momentum, energy, and angular momentum as well as the entropy inequality. In other words, our primary focus should be on constitutive formulations, as noted early on by Y.C. Fung. There are, in general, five basic steps in any constitutive formulation: Delineate general characteristic behaviors, Establish an appropriate theoretical framework, Identify specific functional forms of the requisite relations, Calculate values of the associated material parameters, and Evaluate the predictive capability of the final relations. A former student noted that one can easily remember these five steps via the acrostic DEICE. Notwithstanding the general applicability of these fundamental postulates and basic steps to formulating constitutive relations for biological growth and remodeling, as noted by Y.C. Fung we must remember to focus our attention on *living* tissue. Hence, we should not expect merely to apply classical engineering approaches directly to arteries; rather, we should seek to develop and extend classical approaches to account for the distinguishing characteristics of living tissues, particularly their ability to adapt in response to changing mechanical loads. For this reason, continuum biomechanics is probably better defined as the development, extension, and application of the principles of mechanics for purposes of answering questions of importance in biology and medicine. Let us now consider, within the context of the acrostic DEICE, new approaches for understanding arterial G&R.

## 2. Delineate General Characteristic Behaviors

Constitutive relations describe the response of a material to applied loads under conditions of interest, which depend of course on the internal constitution (make-up) of the material. That is, constitutive relations do not describe materials per se; they describe the behavior of materials under particular conditions and we should thus expect multiple relations to hold equally well for the same material subjected to different conditions. A simple example is water, for which we have different constitutive relations depending on the temperature – for ice (solid-like behavior), liquid water (fluid-like behavior), and steam (gas-like behavior). Arteries exhibit primarily a solid-like behavior under conditions of interest *in vivo* and *in vitro*.

Many of the general characteristic material behaviors of arteries were reported in the remarkable work of Roy (1880). Consistent with his findings, it is now well accepted that, under physiologic conditions, arteries exhibit a highly nonlinear, nearly elastic (or, as called by Fung (1990), pseudoelastic), anisotropic, incompressible behavior under finite deformations; moreover, the arterial wall is heterogeneous due primarily to its medial and adventitial layers even though physiologic responses may be dominated by the former. The underlying polymeric structure of the tensile bearing constituents of the wall endows arteries with a primarily entropic, not energetic, elasticity similar to that of elastomers. Like all soft tissues and cells, arteries also consist of abundant water. Under some conditions, therefore, the mechanical behavior of the arterial wall should be considered as either nonlinearly viscoelastic or poroelastic, or in some cases poroviscoelastic, but our focus will be on the nearly elastic behavior.

Whereas these general characteristic mechanical behaviors dominated the search for arterial constitutive relations for nearly 30 years (mid-1960s to mid-1990s), and gave rise to nonlinear stress-strain relations that remain useful for stress analyses (cf. Fung, 1990; Humphrey,

2002), there was actually little attention to the “living” characteristic. Consider, therefore, a simple definition of life (The American Heritage Dictionary of the English Language, 1976): “The property or quality manifested in functions such as metabolism, growth, response to stimulation, and reproduction, by which living organisms are distinguished from dead organisms or from inanimate matter.” It has long been known, for example, that arteries enlarge in response to sustained increases in blood flow (e.g., in development) and they thicken in response to sustained increases in blood pressure (e.g., in hypertension). In addition to such physiologic responses, the advent of balloon angioplasty in the 1960s and 1970s revealed an aberrant response by the arterial wall (restenosis) to the balloon-induced mechanical injury. Yet, such “growth” responses to altered mechanical “stimulation” were not considered within the context of continuum mechanics until the mid-1990s (Taber, 1995) as discussed more below.

The first clues into the mechanobiology underlying arterial responses to altered loading came from *in vitro* experiments using cell culture. Rosen et al. (1974) showed that altered fluid flow on endothelial cells resulted in the production of an enzyme (histidine decarboxylase) essential for the production of histamine, an effector of vascular permeability and smooth muscle tone. Leung et al. (1976) showed that altered cyclic stretch of vascular smooth muscle cells resulted in the production of extracellular matrix proteins and proteoglycans, which are essential to the structural integrity of the arterial wall. In other words, altered mechanical stimuli can result in altered gene expression, which in turn can cause important biological, biochemical, and biomechanical changes. Since then, myriad experiments and observations have confirmed that all vascular cells (endothelial, smooth muscle, fibroblasts, and even macrophages) are mechano-sensitive (e.g., Davies, 1995; Chien et al., 1998; Grinnell, 2003; Lehoux et al., 2006; Li and Xu, 2007), thus revealing that constitutive relations for arterial G&R must account for characteristic cell-mediated responses.

One of the most important discoveries in arterial wall mechanics was the existence of residual stresses, that is, stresses that exist independent of external loading. Observed independently in 1983 by Y.C. Fung and R.N. Vaishnav and their colleagues, residual stresses were thereafter shown to reduce significantly the previously predicted large transmural gradients in wall stress (Fung, 1990). That is, due to both kinematic and material nonlinearities, residual stresses on the order of 3 kPa appear to reduce the otherwise large intimal circumferential wall stresses by hundreds of kPa. An important implication of this observation is that it appears that arteries grow and remodel during development so as to achieve a nearly uniform and equibiaxial distribution of wall stress in maturity, which in turn suggests a homeostatic target value of stress. Indeed, observations at multiple length and time scales, from sub-cellular to tissue, similarly suggest the existence of a ubiquitous mechanical homeostasis in vascular biology and pathobiology (Humphrey, 2008). This simple example of effects of residual stress on the computed distribution of stresses across the arterial wall reveals well how detailed biomechanical analyses can lead to important mechanobiological hypotheses.

Although early investigators recognized that different extracellular proteins contributed differently to overall wall mechanics (e.g., that elastin dominates behavior at low pressures and collagen dominates behavior at high pressures; Fung, 1990), there was little attempt until recently to model arteries as materially nonuniform (i.e., consisting primarily of elastic fibers, fibrillar collagens, reticular collagens, proteoglycans, and contractile smooth muscle in addition to abundant water), that is, a mixture. In particular, there was little attempt to account for the observation that the different structurally significant constituents not only exhibit different stiffnesses, they also possess different natural (i.e., stress-free) configurations and they turnover at different rates and to different extents at different times during development, maturity, and aging. Such general characteristics should play a central role in any theory of arterial G&R.

### 3. Establish an Appropriate Theoretical Framework

Because of the aforementioned characteristic nonlinear, nearly elastic, anisotropic, nearly incompressible mechanical behaviors, many approaches from finite strain elasticity have played key roles in arterial wall mechanics (Fung, 1990; Humphrey, 2002). One example is the use of stored energy functions  $W(\mathbf{F})$ , where  $\mathbf{F}$  is the deformation gradient tensor, to quantify the stress response to transient loading. Again, however, we shall focus here on the growth and remodeling. To date, there have been two primary approaches to modeling soft tissue G&R, one based primarily on large deformation kinematics and one based primarily on mass production and removal. Not surprisingly, these two approaches were proposed by two of the pioneers of modern biomechanics: R. Skalak and Y.C. Fung (see pages 12-13 in Humphrey (2002) for their pictures). Briefly, the concept of kinematic growth introduced by Skalak in 1981 was championed by Rodriguez et al. (1994) and thereafter applied to arterial mechanics by A. Rachev and L.A. Taber (see, e.g., Taber, 1998; Rachev, 2000). The basic idea is that growth can be modeled by imagining an original stress-free body to be divided into small stress-free parts, each of which is allowed to grow independently based on an evolution relation for a kinematic “growth tensor”  $\mathbf{F}_g$  that changes as a function of differences in stresses from their homeostatic targets. The different parts need not grow compatibly, however, hence there can be a need to assemble the parts elastically, via a tensor  $\mathbf{F}_a$ , to form a continuous body. This assembly process may introduce residual stresses, which were thus anticipated theoretically by R. Skalak before they were computed by Y.C. Fung and colleagues based on empirical observations. Nevertheless, the assembled traction-free body can be deformed further by applied loads, thus resulting in an elastic deformation  $\mathbf{F}_e$ . The stress response is then given in terms of a stored energy function  $W = \hat{W}(\mathbf{F}_e \mathbf{F}_a)$ , which allows stresses to be computed as usual:  $\mathbf{t} = (2 / \det \mathbf{F}) \mathbf{F} (\partial W / \partial \mathbf{C}) \mathbf{F}^T$  where  $\mathbf{t}$  is the Cauchy stress tensor,  $\mathbf{F} (= \mathbf{F}_e \mathbf{F}_a)$  is the overall deformation gradient tensor, and the right Cauchy-Green tensor  $\mathbf{C} = \mathbf{F}^T \mathbf{F}$  (Truesdell and Noll, 1965). Note that  $W$  is assumed to be independent of  $\mathbf{F}_g$  because growth is assumed to occur in stress-free parts even though the evolution equations depend explicitly on changing stresses. Although Y.C. Fung suggested the need for a “mass-stress” formalism to model G&R, he did not propose a particular framework. Here, therefore, we focus on that introduced by Humphrey and Rajagopal (2002). They suggested that the concept of kinematic growth could predict many consequences of growth and remodeling, but could not account for the underlying mechanobiological mechanisms. Hereafter, growth implies a change in mass and remodeling a change in structure; the two generally occur together in arterial adaptations and require cell and matrix turnover.

Briefly, Humphrey and Rajagopal (2002) suggested that full continuum mixture relations be used for mass balance (see below), but a rule-of-mixtures relation be used for the stress response and thus linear momentum balance (i.e., solve the classical relation for Cauchy stress, namely,  $\text{div} \mathbf{t} = \rho \mathbf{a}$  where  $\rho$  is the mass density and  $\mathbf{a}$  the acceleration for the mixture as a whole, and conceptually let  $W = \sum \phi^k W^k$  where  $\phi^k$  are mass fractions and  $W^k$  are stored energy functions for individual constituents  $k$ ). This rule-of-mixtures approach allows one to account for contributions of different structurally significant constituents while avoiding potential difficulties associated with identifying both appropriate boundary conditions for partial tractions and momentum exchanges between different constituents as they turn over. Later it was recognized that the mass balance relations could be separated into two classes:  $i = 1, 2, \dots, N-n$  non-structurally significant constituents that can diffuse (e.g., vasoactive, mitogenic, proteolytic, and inflammatory molecules) and  $k = 1, 2, \dots, n$  structurally significant constituents that cannot diffuse (e.g., elastic fibers, collagen fibers, and smooth muscle). It can be shown that mass balance for the former can be written in the form of the standard reaction-diffusion equation, namely

$$\frac{dC^i}{ds} = R^i + D^i \nabla^2 C^i, \quad (1)$$

where  $C^i$  are molar fractions (i.e., concentrations),  $R^i$  are reactions, and  $D^i$  are diffusivities; moreover,  $s$  represents a G&R time that is much longer than the time associated with transient loading over the cardiac cycle. In contrast, for a quasi-static, 2-D, membrane framework, Baek et al. (2006) postulated the following form for mass balance for the structurally significant constituents

$$M^k(s) = M^k(0) Q^k(s) + \int_0^s m^k(\tau) q^k(s-\tau) d\tau \quad (2)$$

where  $M^k(s)$  is an apparent mass density for constituent  $k$  defined per reference area of the mixture (artery),  $Q^k(s) \in [0,1]$  represents the fraction of constituent  $k$  that was produced at or before  $s=0$  that survives to time  $s$ ,  $m^k(\tau)$  is an apparent mass density production rate at G&R time  $\tau \in [0, s]$ , and  $q^k(s-\tau) \in [0,1]$  represents the fraction of constituent  $k$  that was produced at  $\tau$  that survives to time  $s$ . This form for constituent mass density motivated the following form for the stored energy function for constituent  $k$ , noting that each constituent is allowed to turnover at different rates at different times  $\tau \in [0, s]$ :

$$W^k(s) = \frac{M^k(0)}{\rho(s)} Q^k(s) \widehat{W}^k(\mathbf{C}_{n(0)}^k(s)) + \int_0^s \frac{m^k(\tau)}{\rho(s)} q^k(s-\tau) \widehat{W}^k(\mathbf{C}_{n(\tau)}^k(s)) d\tau, \quad (3)$$

where  $\widehat{W}^k(\mathbf{C}_{n(\tau)}^k(s))$  is the energy stored in constituent  $k$  at time  $s$ , which depends on the deformation experienced by that constituent relative to its individual natural configuration  $\kappa_n^k(\tau)$ . It can be shown that such a formalism recovers a standard rule-of-mixtures relation prior to G&R (i.e., at  $s=0$ ) and in the case of tissue maintenance (i.e., balanced production and removal of material in unchanging configurations) – see Valentin et al. (2009). More importantly, however, equation (3) allows one to consider contributions to overall structural integrity by both different classes of constituents (e.g., elastic versus collagen fibers) and the same class of constituent produced at different times within different configurations.

Three assumptions fundamental to this G&R theory are: (1) that individual constituents  $k$  are constrained to move with the mixture as a whole despite possessing individual natural configurations (i.e., motions  $\mathbf{x}^k(s) = \mathbf{x}(s)$  despite original positions  $\mathbf{X}^k(\tau) \neq \mathbf{X}(\tau)$  for all  $\tau \in [0, s]$ ), whereby  $\kappa_n^k(\tau)$ ; (2) constituents are incorporated within extant extracellular matrix at preferred stretches (called homeostatic deposition stretches and denoted by the tensor  $\mathbf{G}_h^k(\tau)$ ) that relate to the homeostatic target stresses; and (3) the overall mixture mass density remains the same ( $\rho(s) = \rho(0)$ ; Rodriguez et al., 1994) despite the apparent constituent mass densities changing during G&R. The first two assumptions allow one to relate deformations experienced by individual constituents, relative to individual natural configurations, to those experienced by the mixture as a whole (Baek et al., 2006):  $\mathbf{F}_{n(\tau)}^k(s) = \mathbf{F}_o(s) \mathbf{F}_o^{-1}(\tau) \mathbf{G}_h^k(\tau)$ , where  $\mathbf{F}_o(s)$  represents the standard deformation gradient for the artery relative to a convenient reference

configuration at  $s = 0$  and similarly for  $\mathbf{F}_o(\tau)$ , thereby enabling one to use the classical relation for stress,

$$\mathbf{t}(s) = \frac{2}{\det \mathbf{F}_o(s)} \mathbf{F}_o(s) \frac{\partial \sum W^k(s)}{\partial \mathbf{C}_o(s)} \mathbf{F}_o^T(s) \tag{4}$$

and similarly linear momentum balance for quasi-static G&R:  $\text{div} \mathbf{t}(s) = \mathbf{0}$ . For more details on the fundamental development of this theory, see Baek et al. (2006) and Valentin et al. (2009). The main observation is that the rule-of-mixtures relation allows one to retain, indeed build upon, many of the advances in nonlinear arterial biomechanics by simply writing the net stored energy function in terms of the energies stored in individual constituents as they are produced; the survival functions ensure that energy is stored in a constituent only until it is removed (e.g., by proteolytic degradation or apoptosis). It is the accounting for changing rates of production (protein synthesis and cell proliferation) and associated half-lives that enables basic mechanisms of G&R to be modeled mathematically rather merely modeling the kinematic consequences of such turnover. Changes in geometry are computed naturally in the constrained mixture model of G&R simply by satisfying linear momentum balance at each time  $s$ .

#### 4. Identify Specific Functional Forms

As noted earlier, many different phenomenological stored energy functions  $W$  have been proposed to describe the nonlinear, nearly elastic, anisotropic, nearly incompressible behavior exhibited by arteries independent of G&R (Fung, 1990; Humphrey, 2002); among these, the forms proposed by Y.C. Fung and G.A. Holzapfel are used most commonly today (cf. Holzapfel et al., 2000; Gasser et al., 2006). Such relations are useful not only for standard stress analyses, they also provide important guidance for the identification of new forms of relations useful in modeling the biomechanical behaviors during G&R.

Recall that the G&R framework represented by equations (2) to (4) reveals the need for three fundamental classes of constitutive relations:

$$\begin{aligned} & \widehat{W}^k(\mathbf{C}_{n(\tau)}^k(s)) \\ & , \quad m^k(\tau) \\ & , \quad q^k(s - \tau) \quad \forall \tau \in [0, s], \end{aligned} \tag{5}$$

that is, stored energy functions, rates of mass density production, and survival functions for each family of structurally significant constituents. Although it is not easy to test mechanically the individual constituents, forms for their stored energy functions can now be prescribed with some confidence, as, for example, neo-Hookean forms for elastin and Fung-exponentials for fibrillar collagens and passive smooth muscle (Holzapfel et al., 2000; Gleason et al., 2004; Valentin et al., 2009). Nevertheless, it is clear that the behavior of individual constituents in vivo depends, in part, on their interactions with other constituents (e.g., collagen with proteoglycans or elastin with microfibrils such as fibrillin-1), hence such relations should be thought of as “constituent dominated” not “constituent only.”

Less obvious, but equally important, are appropriate functional forms for the rates of mass density production and survival – it is here that the mechanobiology surfaces prominently. Whereas the degradation of proteins is driven enzymatically (e.g., by matrix metalloproteinases) and thus likely obeys Michaelis-Menten type kinetics, it appears that first order type kinetics can be used to a good first approximation. Specific functional forms for mass density production remain less clear despite clear evidence of their mechano-control (e.g.,

Leung et al., 1976; Li et al., 1998). To date, rates of mass density production have typically been assumed to depend linearly on differences in stress from homeostatic targets, yet there is a pressing need for more data and more appropriate functional forms (cf. Humphrey (2008) wherein I call for “mechanical dose response curves”). The complexity of such relations is revealed easily by an illustrative observation: vascular smooth muscle cell production of fibrillar collagen depends in part on changes in cyclic circumferential stress ( $\sigma_\theta$ ), or stretch, but it is also influenced by vasoactive molecules that are produced by endothelial cells in response to changes in wall shear stress ( $\tau_w$ ). For example, nitric oxide, a potent vasodilator, is an inhibitor of smooth muscle production of collagen whereas endothelin-1, a potent vasoconstrictor, is a promoter of smooth muscle cell production of collagen (Rizvi et al., 1996; Rizvi and Myers, 1997). Moreover, cellular production of other molecules, such as tissue-transglutaminase (tTG), can affect collagen production through its relation to the cytokine transforming growth factor – beta, as well as collagen cross-linking, hence we can imagine forms like  $m^k(\tau) = f(\sigma_\theta - \sigma_\theta^h, \tau_w - \tau_w^h, C^1, \dots)$  where  $C^1$  may be computed from equation (1) and represent tTG or other important effectors of matrix turnover or structural integrity.

We conclude, therefore, that just as noted by Y.C. Fung over 40 years ago, the primary need in biomechanics remains the identification of appropriate constitutive relations, which largely means identification of specific functional forms based on data, once an appropriate theoretical framework is in place.

## 5. Calculate values of the material parameters

In many ways, this step of a constitutive formulation is the easiest provided that the specific functional form is well known. For example, material parameters in constituent stored energy functions can be determined using standard methods of nonlinear regression (e.g., Marquardt-Levenberg), provided that appropriate data are available. Recalling the quote by Y.C. Fung from Introduction, such data must be multiaxial for arteries, with combined finite inflation and axial extension being preferred. Recall, too, that although such energy functions are often ascribed to individual constituents, actual behaviors depend in part on inter-constituent interactions, thus it is best to determine best-fit values of the material parameters from data on intact vessels as well as possibly those wherein certain constituents have been removed selectively (e.g., elastin has been removed using elastase and elastin has been isolated by autoclaving, yet neither method is perfectly selective). Although mixture based relations necessarily contain many more parameters than traditional phenomenological relations, the microstructural motivation of such relations provides many important physical bounds on the parameter values that restrict the parameter search space. A good example is the recent work by Masson et al. (2008) wherein 14 best-fit parameters were determined for human carotid arteries based on clinically available pressure-diameter data collected at high frequency over the cardiac cycle. See, too, the work by Stalhand and Klarbring (2005) who further introduce the physical constraint of constancy of axial force in vivo to aid in the parameter estimation. These examples are good reminders of the importance of extensive in vitro studies and testing – parameter estimation is relatively easy only if the functional forms are reliable (which can only be determined using comprehensive multiaxial data collected under well controlled conditions in vitro) and appropriate bounds or initial guesses are known.

In addition to bounds imposed on the parameter search space by microstructural motivations (e.g., mass fractions must be less than 1 and deposition stretches appear to be between 1 and 2), such best-fit values of the parameters should also respect standard continuum restrictions such as convexity, Baker-Ericksen type inequalities, and so forth (cf. Holzapfel et al., 2000; Humphrey, 2002; Balzani et al., 2006). Moreover, standard parameter sensitivity studies can play important roles in identifying bounds for the parameter search space that ensure physically

realistic predictions, computing the correlation matrix for the parameters can help ensure that the relation is not overparameterized, and nonparametric methods such as bootstrapping can help determine statistical significance of parameter values (Humphrey, 2002). Finally, note that Valentin and Humphrey (2009a) also showed another potential utility of performing parameter sensitivity studies for arterial G&R relations. Such studies can guide the much needed experimental work by suggesting those parameters the model is most sensitive to, and thereby which data should be measured with greater precision.

## 6. Evaluate predictive capability

All aspects of a constitutive formulation are important, but evaluating the predictive capability is essential for gaining confidence in the use of any relation for computational simulations and modeling. Indeed, this step in the overall DEICE formulation is fundamental to much needed validation and verification (cf. Anderson et al., 2007). Such evaluations can take many forms, first of which is simply ensuring that the overall model captures salient features of the behaviors of interest. With regard to the constrained mixture model discussed herein (equations (2) to (4)), salient features of arterial growth and remodeling in response to sustained changes in pressure (e.g., thickening over periods of weeks), flow (e.g., changing caliber over weeks and a resetting of the active force-length behavior), and axial extension (e.g., a lengthening of the vessel), the development of idealized intracranial aneurysms, and the development and resolution of cerebral vasospasm have been captured by the same basic framework (Gleason et al., 2004; Gleason and Humphrey, 2004, 2005; Baek et al., 2005, 2006, 2007a; Humphrey et al., 2007; Valentin et al., 2009)<sup>1</sup>. There is a pressing need, however, for data sufficient for a rigorous testing of these models in each case. Cardamone et al. (2009) also showed that the basic rule-of-mixtures model for wall behavior captures two of the most fundamental aspects of arterial mechanics, the existence of residual stresses and axial prestretches. That is, whereas most prior computational models have sought to quantify the consequences of residual stresses on transmural distributions of stress in arteries based on assumed kinematic (e.g., opening angles; Fung, 1990) – which as noted above was vital in identifying the fundamental mechanobiological hypothesis of the existence of a target homeostatic stress – results in Cardamone et al. (2009) suggest a possible means by which residual stresses arise. That is, they showed that differences in constituent prestretches (resulting primarily from the deposition of highly stable elastin primarily in the perinatal period and the continual turnover of collagen and smooth muscle in evolving configurations) can explain the existence of residual stress and axial prestretch (which is revealed easily upon transection of an artery and which likely represents a balance between highly elastic and extended elastin that tries to recoil fully and slightly extended collagen which is put into compression upon transection by the recoiling elastin; cf. Zeller and Skalak, 1998). Moreover, the radial gradients in elastin prestretches that one would expect based on normal developmental processes appear to play a key role in dictating the degree of residual stress (i.e., opening angle).

Humphrey et al. (2009) recently suggested that axial prestretch plays a much more fundamental role in arterial adaptations than previously thought, perhaps being the least constrained geometric change available to an artery (with local geometry defined primarily via radius, thickness, and length and assuming that the caliber is dictated largely by changes in wall shear stress and thickness is dictated largely by changes in transmural pressure, both of which are controlled by distal means – the heart and resistance vessels). Evaluating predictive capability can thus mean correspondence with prior observations or identifying new hypotheses that can then be evaluated. Valentin and Humphrey (2009b) suggest further that computational models based on assumed functional forms of constitutive relations can also be used to evaluate

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<sup>1</sup>Na et al. (2007) showed further that a similar approach may be useful from modeling cellular growth and remodeling, which could facilitate multiscale modeling via a common framework.



fundamental hypotheses upon which G&R theories are based. For example, by testing the null hypotheses that cells do not incorporate new matrix material within extant matrix at a preferred deposition stretch, that cells cannot alter their rates of production of structurally significant constituents in response to changes in mechanical loading, and that arteries cannot vasoregulate during G&R, it was shown that these hypotheses allow one to capture salient features of actual behaviors.

## 7. Discussion and future directions

Development of this new constrained mixture model of arterial growth and remodeling over the past six years has been based primarily on a 2-D formulation (i.e., an assumed 2-D uniform state of stress, with the artery endowed with a 3-D geometry). There were four primary reasons for this: (1) a 2-D formulation is much simpler than a 3-D formulation, thus it enables much more insight initially, which is important as one develops and refines a new theory; (2) a 2-D formulation provides information that is of most importance clinically, that is, changes in arterial caliber and structural stiffness; (3) many of the associated experimental studies utilized mouse carotid arteries, which consist of a 2 to 3 layers of smooth muscle cells and thus are likely less sensitive to radial gradients in stress; and (4) the initial motivation was the need to understand better the biomechanics and mechanobiology of intracranial aneurysms, which can be treated mechanically as membranes and thus a 2-D formulation. Given the ability of this simple 2-D formulation to capture salient trends in diverse cases of arterial G&R, however, there is now a need to extend the basic ideas to 3-D. Prior implementations also examined primarily the simple cases wherein hemodynamic loads changed once and remained constant thereafter. There is a pressing need to couple directly computational models of hemodynamics and arterial wall mechanics including growth and remodeling. Baek et al. (2007b) showed that the theory of small deformations superimposed on large could be helpful in this regard. That is, although fully nonlinear (kinematically and materially) theories are needed for G&R, cyclic deformations over the cardiac cycle are often small in comparison to those induced by diastolic loading or gross adaptations. The theory of small on large thus allows information from G&R computations to be linearized appropriately for inclusion in standard fluid-solid interaction (FSI) codes that solve unsteady, 3-D flows in complex (including patient-specific) geometries based on small strain elastic deformations of the wall. An approach to coupling FSI and G&R codes to form fluid-solid-growth (FSG) models was reported by Figueroa et al. (2009). The need for such FSG models to understand disease progression, such as the development and potential rupture of abdominal aortic and intracranial aneurysms, is discussed by Humphrey and Taylor (2008).

Although long ignored, the biomechanics and mechanobiology of arterial responses to altered hemodynamic loading as well as in disease progression, injury responses, device tissue interactions, and interventional therapies is now beginning to attract significant attention. Due to the complexity of these problems, and the continuing lack of sufficient data and well accepted constitutive relations, much remains to be accomplished. Indeed, even the best theoretical framework remains unclear. This review focused primarily on a constrained mixture model for G&R that is based on constitutive relations for cell and matrix turnover and a rule-of-mixtures description of the mechanical behavior of the wall, but emphasized the importance of a general five step formulation of the requisite constitutive relations. Many other approaches to modeling arterial growth and/or remodeling have been proposed, however, including Taber (1998), Rachev (2000), Watton et al. (2004, 2009), Hariton et al. (2007), Kuhl et al. (2007), Kroon and Holzapfel (2007, 2008), Dreissen et al. (2008), Alastrue et al. (2008), Alford et al. (2008), Olsson and Klarbring (2008), and others. The interested reader is encouraged to consult these important works as well. Indeed, the ultimate theory of arterial growth and remodeling will likely synthesize different ideas from many of these different approaches.

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