# Chapter 9
# Multiscale Modeling of Arterial Adaptations: Incorporating Molecular Mechanisms Within Continuum Biomechanical Models

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**Abstract** Continuum level biomechanical models of arterial adaptations are proving themselves vital both for understanding better the progression of disease and for improving the design of clinical interventions. Although these models are most appropriate to the clinical scale of observation, the underlying mechanisms responsible for such remodeling occur at the molecular scale. The goal of this chapter is to review a validated continuum level model of arterial adaptations and to suggest a straightforward approach to incorporate molecular level information within such models. In particular, it is shown that continuum mixture models reveal naturally a means to incorporate molecular information within fundamental constitutive relations within the continuum theory. There is, therefore, significant motivation to continue to formulate molecular level models that are necessary to inform models at scales that address the Physiome.

## 9.1 Introduction

The past four decades have brought forth tremendous advances in the continuum biomechanics of arteries (Humphrey, 2002). Nevertheless, three conspicuous shortcomings have persisted. First, most constitutive relations and stress analyses have focused on conditions at a single instant, not how the arterial properties and stress fields evolve due to normal development or in response to perturbed loads, disease, injury, or clinical treatment. Second, biomechanical analyses have been based on the assumption that arteries are materially uniform rather than consisting of many different constituents that turnover at different rates and to different extents while collectively defining the whole. Third, continuum biomechanical models have employed phenomenological constitutive relations that have not directly accounted for the many classes of molecules that control arterial adaptations, including vasoactive, mitogenic, proteolytic, and inflammatory molecules. The primary goal herein is to encourage a new direction in arterial research whereby one develops multiscale

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models that can predict time-dependent changes in composition, structure, geometry, and properties that occur in response to changes in the biochemomechanical environment. Although much more data will be needed to model precisely many of the underlying mechanisms that are responsible for such growth and remodeling (G&R), expanding data bases provide sufficient guidance on salient aspects of development, adaptation, and disease progression for us to begin to interpret these data within mathematical frameworks. Toward this end, here we consider a constrained mixture model of tissue-level arterial adaptations that can incorporate molecular information related to the underlying mechanisms. Areas requiring further research are then highlighted to encourage continued development of these models.

## 9.2 Continuum Framework

By growth, we mean a change in mass; by remodeling, we mean a change in structure. Notwithstanding the many associated complexities at different spatial and temporal scales, we begin by assuming that G&R occurs via quasi-static isothermal processes, which focuses our attention on equations of mass balance and linear momentum balance. Moreover, let us assume that the arterial wall can be modeled as a mixture consisting of $N$ constituents, including $\alpha = 1, 2, \ldots, n$ insoluble but structurally significant constituents and $i = 1, 2, \ldots, N - n$ soluble but structurally insignificant constituents. Examples of the former are elastic fibers, fibrillar collagens, muscle fibers, and proteoglycans; examples of the latter include vasoactive, mitogenic, proteolytic, and inflammatory molecules. We have previously discussed the utility of employing full mixture equations to describe mass balance for both classes of constituents, but a rule-of-mixtures relation for the stress response that can be used to satisfy overall linear momentum balance (Humphrey and Rajagopal, 2002).

Mass balance, in spatial form, can be written as

$$\frac{\partial \rho^i}{\partial \tau} + \operatorname{div}\left(\rho^i v^i\right) = \bar{m}^i, \quad i = 1, 2, \ldots, N - n, \tag{9.1}$$

$$\frac{\partial \rho^\alpha}{\partial \tau} + \operatorname{div}\left(\rho^\alpha v^\alpha\right) = \bar{m}^\alpha, \quad \alpha = 1, 2, \ldots, n, \tag{9.2}$$

where $\rho^i$ and $\rho^\alpha$ are so-called apparent mass densities (constituent mass per mixture volume) and $\bar{m}^i$ and $\bar{m}^\alpha$ are the so-called net rates of mass density production/removal (which can be positive, zero, or negative); $\tau \in [0, s]$ is the G&R time, which is typically much greater than the cardiac cycle timescale $t$.

Focusing first on the $N - n$ soluble constituents, i.e. Eq. (9.1), it is convenient to introduce the mass flux $\boldsymbol{j}^i = \rho^i(\mathbf{v}^i - \mathbf{v})$ where $\mathbf{v}^i - \mathbf{v}$ is sometimes called the 'diffusion velocity.' Regardless, Eq. (9.1) can be written at G&R time as

$$\frac{\partial \rho^i}{\partial \tau} + \operatorname{div}\left(\rho^i \mathbf{v}\right) = \bar{m}^i - \operatorname{div}\left(\boldsymbol{j}^i\right), \tag{9.3}$$

or if the mixture velocity $\mathbf{v}$ is negligible (consistent with a quasi-static assumption that is used for the structurally significant constituents)

$$\frac{\partial \rho^i}{\partial \tau} = \bar{m}^i - \operatorname{div}\left(\boldsymbol{j}^i\right). \tag{9.4}$$

Noting that we have $N-n$ equations to determine $N-n$ constituent mass densities $\rho^i$, we clearly must introduce additional (constitutive) relations for $\bar{m}^i$ and $\boldsymbol{j}^i$. For dilute solutions, the mass flux for diverse molecular species is often approximated by Fick's law, which is typically written in terms of molar, not mass, densities. Note, therefore, that the molar density $C^i \equiv \rho^i / MW^i$ where $MW^i$ are molecular masses. Hence, the mass balance equation for the soluble constituents can be written

$$\frac{\partial C^i}{\partial \tau} = R^i - \operatorname{div}\left(\boldsymbol{J}^i\right), \tag{9.5}$$

where $C^i$ are also called concentrations, $R^i$ are reactions responsible for production/removal, and by Fick's law $\boldsymbol{J}^i = -D^i \operatorname{grad} C^i$, where $D^i$ are the diffusivities. Hence, we obtain the classical reaction-diffusion equation

$$\boxed{\frac{\partial C^i}{\partial \tau} = R^i + D^i \nabla^2 C^i, \quad i = 1, 2, \ldots, N-n} \tag{9.6}$$

for all soluble constituents at G&R times $\tau \in [0, s]$.

The situation is very different for the insoluble, structurally significant, constituents, i.e. Eq. (9.2). We previously introduced an additional assumption that all structural constituents are constrained to move with the mixture (Humphrey and Rajagopal, 2002). This assumption coupled with the quasi-static assumption thus requires that the motions $\mathbf{x}^\alpha = \mathbf{x} = \mathbf{0}$, whereby velocities are similarly constrained: $\mathbf{v}^\alpha = \mathbf{v} = \mathbf{0}$. Equation (9.2) thus can be written

$$\frac{\partial \rho^\alpha}{\partial \tau} = \bar{m}^\alpha \quad \text{or} \quad \int \frac{\partial \rho^\alpha}{\partial \tau} \mathrm{d}\tau = \int \bar{m}^\alpha \mathrm{d}\tau. \tag{9.7}$$

We thus have $n$ equations to determine $n$ mass densities, which again necessitates the introduction of additional (constitutive) relations for the net production/removal function. Yet, because $\bar{m}^\alpha = 0$ during periods of tissue maintenance (i.e., balanced production and removal in unchanging configurations), we have shown previously that it is convenient to assume a separable representation $\bar{m}^\alpha(\tau) = m^\alpha(\tau) q^\alpha(s, \tau)$, where $m^\alpha(\tau) > 0$ is the true rate of mass density production and $q^\alpha(s, \tau) \in [0, 1]$ is a survival function that accounts for the fact that all cells and proteins have a finite half-life (Valentín et al., 2009). Hence, the survival function represents the percentage of constituents produced at time $\tau$ that survives to current time $s$.

It can be shown that use of the separable form for the net production term allows Eq. (9.7) to be written in a reduced form, namely

$$\boxed{\rho^\alpha(s) = \rho^\alpha(0) Q^\alpha(s) + \int_0^s m^\alpha(\tau) q^\alpha(s, \tau) \mathrm{d}\tau, \quad \forall \alpha = 1, 2, \ldots, n,} \tag{9.8}$$

which is to say that the current apparent mass density depends on its original value $\rho^\alpha(0)$ and the kinetic loss of the original material via $Q^\alpha(s) \in [0,1]$, as well as both the subsequent true production $m^\alpha(\tau)$ and associated loss $q^\alpha(s,\tau) \in [0,1]$ of material after $s = 0$ (the time at which a perturbation initiates G&R). Because the constituent mass densities are apparent, not true, densities, the total mass density is computed easily via

$$\rho(s) = \sum \rho^\alpha(s) \rightarrow 1 = \sum \phi^\alpha(s), \tag{9.9}$$

where $\phi^\alpha(s) = \rho^\alpha(s)/\rho(s)$ are usual mass fractions. Of course, we must recover $\rho^\alpha(0)$ at $s = 0$, which reveals that $Q^\alpha(0) = 1$ in Eq. (9.8).

Because we employ a rule-of-mixtures relation for the stress, linear momentum for quasi-static G&R is simply the same as that in classical continuum mechanics, namely $\operatorname{div}\mathbf{t} = \mathbf{0}$, where $\mathbf{t}$ is the Cauchy stress. As in most of biomechanics, therefore, the significant challenges lie first in formulating appropriate constitutive relations and second in solving initial-boundary value problems of interest.

Although it is natural to seek constitutive relations for stress directly (Humphrey and Rajagopal, 2002), it proves useful to follow advances in nonlinear elasticity and alternatively seek constitutive relations for the stored energy $W^\alpha(s)$, whereby a rule-of-mixtures approach can be written conceptually as

$$W(s) = \sum_{\alpha=1}^{n} \phi^\alpha(s)\hat{W}^\alpha(s), \tag{9.10}$$

noting of course that the stored energy depends on the (finite) deformation experienced by the material, which is to say each of its load-bearing constituents. Prior studies have suggested, however, that such an approach is limited in its ability to capture contributions of individual constituents that may turnover continuously at different rates and to different extents. Hence, following Baek et al. (2006), we let

$$W(s) = \sum_{\alpha=1}^{n} W^\alpha(s), \tag{9.11}$$

where we postulated, constituent-specific, forms motivated by Eq. (9.8) (which was derived directly), namely

$$\boxed{\begin{aligned} W^\alpha(s) = {} & \frac{\rho^\alpha(0)Q^\alpha(s)}{\rho(s)}\hat{W}^\alpha\left(\mathbf{C}^\alpha_{n(0)}(s)\right) \\ & + \int_0^s \frac{m^\alpha(\tau)q^\alpha(s-\tau)}{\rho(s)}\hat{W}^\alpha\left(\mathbf{C}^\alpha_{n(\tau)}(s)\right)\mathrm{d}\tau, \end{aligned}} \tag{9.12}$$

where the energy stored in individual constituents is assumed to depend on deformations experienced by those constituents, which by the principle of material frame indifference requires dependence on the deformation gradient through the

right Cauchy-Green tensor: $\mathbf{C}^{\alpha}_{n(\tau)}(s)$. In particular, $n(\tau)$ reminds us that this deformation is referred to the natural configuration $\kappa^{\alpha}_{n}(\tau)$ for that individual constituent at its time of deposition $\tau \in [0, s]$. To appreciate the assumed form in Eq. (9.12), note that if there is no G&R, then $s = 0$ and this equation reduces to

$$W^{\alpha}(0) = \frac{\rho^{\alpha}(0)\, Q^{\alpha}(0)}{\rho(0)}\, \hat{W}^{\alpha}\big(\mathbf{C}^{\alpha}_{n(0)}(0)\big) = \phi^{\alpha}(0)\, \hat{W}^{\alpha}\big(\mathbf{C}^{\alpha}_{n(0)}(0)\big) \tag{9.13}$$

(recalling that $Q^{\alpha}(0) \equiv 1$ by definition), which recovers a simple rule-of-mixtures relation as desired. It can be shown similarly that the simple rule-of-mixtures relation is recovered in the case of tissue maintenance, that is, balanced production and removal in unchanging configurations (Valentín et al., 2009).

Most importantly, Eqs. (9.8) and (9.12) reveal the need to determine three basic types of constitutive relations for each structurally significant constituent $\alpha = 1, 2, \ldots, n$, namely

$$m^{\alpha}(\tau), \qquad q^{\alpha}(s - \tau), \qquad \hat{W}^{\alpha}\big(\mathbf{C}^{\alpha}_{n(\tau)}(s)\big). \tag{9.14}$$

In our prior implementations (e.g., Baek et al., 2006; Valentín et al., 2009), we have used phenomenological constitutive relations motivated by tissue level observations of mechanobiological responses by arteries in response to diverse mechanical loads (Humphrey, 2008b). For example, we have modeled the energy stored in the elastin dominated amorphous matrix using a classical neo-Hookean relation and the energy stored in collagen fibers and passive smooth muscle using classical Fung-type exponential relations. For the present discussion, it is important to note that the neo-Hookean relation was first derived based on micromechanical arguments and exponential relations have been shown to capture well the net mechanical response of collections of fibers having linear behaviors but a distribution of undulations. It is suggested that increased attention should be given to the derivation of microstructurally based constitutive relations for the energy stored in individual constituents as well as interaction energies between constituents. Such relations would enable better modeling of many disease processes wherein either particular constituents are absence because of genetic mutations (e.g., fibrillin-1, which stabilizes elastic fibers, or collagen III, as in Marfan and Ehlers–Danlos IV syndromes, respectively) or chemomechanical injury (e.g., degradation or fatigue of elastic fibers in aging). Below, however, let us focus on constitutive relations for mass production and removal, which are unique to G&R theories.

## 9.3 Towards Multiscale Constitutive Relations

Two of the best studied arterial adaptations are responses to sustained alterations in blood pressure and flow, the former of which is particularly relevant to hypertension research. It is well accepted that large arteries tend to grow and remodel so as to keep the mean circumferential stress $\sigma_{\theta} = Pa/h$ and the wall shear stress

$\tau_w = 4\mu Q/\pi a^3$ each near target/homeostatic values (e.g., $\sigma_\theta^h$ and $\tau_w^h$, respectively, where $P, a, h, \mu$ and $Q$ are blood pressure, luminal radius, wall thickness, blood viscosity, and volumetric flow, respectively). As shown previously (Humphrey, 2008a), if we let parameterize the change in blood pressure from normal and parameterize the change in blood flow from normal (e.g., $\gamma = 1.5$ for a 50 % sustained increase in pressure), then it is easy to show that $a \to \varepsilon^{1/3} a_h$ and $h \to \gamma \varepsilon^{1/3} h_h$ (where the subscripts $h$ denote homeostatic values) to maintain/restore the stresses to homeostatic targets in response to modest alterations in blood pressure or flow. Whereas these simple relations describe the extent of the morphological adaptations, they cannot describe the time-course of such changes or the associated changes in structure or properties. In contrast, the G&R framework described by Eqs. (9.8) and (9.12) can address both the extent and rate of each of these changes.

Fundamental to geometric and structural changes in arteries are changes in rates of turnover of structurally significant constituents such as the smooth muscle and fibrillar collagens. For example, we have shown that the following constitutive relations (cf. Eq. (9.14)) provide a good description of large artery adaptations to both altered blood pressure and flow:

$$m^\alpha(\tau) = m_B^\alpha \left(1 + K_\sigma^\alpha \Delta\sigma - K_{\tau_w}^\alpha \Delta\tau_w\right), \tag{9.15}$$

$$q^\alpha(s-\tau) = \exp\left[-\int_\tau^s K_q^\alpha \left(1 + \Delta\sigma(\tilde{\tau})^2\right) \mathrm{d}\tilde{\tau}\right], \tag{9.16}$$

where the stress differences are given by

$$\Delta\sigma = \frac{\sigma - \sigma^h}{\sigma^h}, \qquad \Delta\tau_w = \frac{\tau_w - \tau_w^h}{\tau_w^h}, \tag{9.17}$$

with $\sigma$ an appropriate scalar metric of intramural stress. Note, too, that the gain-type parameters $K$ in Eqs. (9.15) and (9.16) modulate the stress-mediated changes in mass production and removal. Although these particular functional forms are among the simplest possible, basal rates are recovered ($m_B^\alpha$ and $K_q^\alpha$) when the stresses equal their homeostatic targets, as desired, and associated simulations have captured many salient aspects of observed adaptations (Valentín and Humphrey, 2009a,b). Note, too, that the survival function recovers first order kinetic decays as suggested by much of the data (cf. Humphrey, 2008b).

At this juncture, it is important to recognize that these constitutive relations are motivated by mechanobiological observations, yet they are phenomenological. For example, it is well known that collagen synthesis is increased by increases in cyclic stretch/stress of smooth muscle cells. It is also well known that increases in wall shear stress increase endothelial cell production of the vasodilator nitric oxide (NO) and decreases in wall shear stress increase endothelial cell production of the vasoconstrictor endothelin-1 (ET-1); see Fig. 9.1 and Humphrey (2008b). Moreover, NO decreases the production of collagen by smooth muscle cells whereas ET-1 increases the production rate (hence the minus sign in Eq. (9.15) for the shear stress mediated

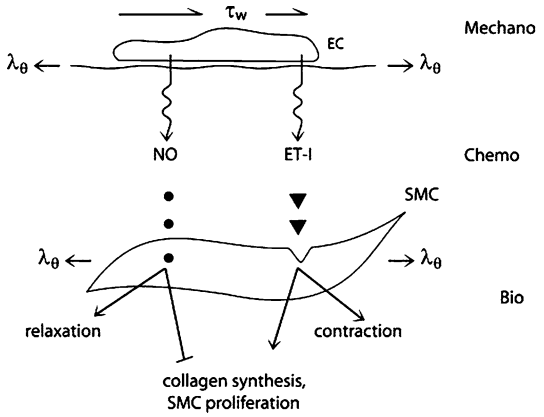


**Fig. 9.1** Schema of possible mechano-induced production of vasoactive molecules, nitric oxide (NO) and endothelin-1 (ET-1), by endothelial cells (EC) in response to changes in cyclic wall shear stress and circumferential wall stretch. Diffusion and consumption of the vasoactive molecules results in stimulation of smooth muscle cell (SMC) vasoactivity and proliferation as well as synthesis of extracellular matrix proteins

term). It is also becoming increasingly clear that altered stress affects the production, activation, and effectiveness of proteolytic enzymes (e.g., matrix metalloproteinases; Humphrey, 2008b).

Whereas phenomenological equations can be very useful for simulations, as we learn more and more about the mechanobiology, there is an opportunity—indeed a responsibility—to move toward more mechanistic modeling. For example, it is now known that the increase in collagen synthesis by smooth muscle cells in response to increased mechanical stress/stretch (cf. Fig. 9.1) is mediated by complex signaling pathways that involve multiple vasoactive molecules and cytokines. For example, it appears that increased cyclic stress (as in hypertension due to increased pulse pressure) causes smooth muscle cells to increase their production of angiotensin-II and possibly to change associated receptor-ligand binding, which in turn stimulates the production of latent transforming growth factor beta (TGF-$\beta$) that can be activated by mechanical stress and ultimately lead to collagen production. Hence, there is an opportunity to use reaction-diffusion equations (9.6) to quantify local changes in 'effector molecules' that in turn influence directly the rates of mass production and removal (cf. Fig. 9.1). For example, one could consider mass density production for collagen ($\alpha = c$) such as

$$m^c(\tau) = m^c_B\big(1 + K^c_{\mathrm{TGF}}\Delta C^{\mathrm{TGF}} + K^c_{\mathrm{ET1}}\Delta C^{\mathrm{ET1}} - K^c_{\mathrm{NO}}\Delta C^{\mathrm{NO}} + \cdots\big). \quad (9.18)$$

Similarly for smooth muscle ($\alpha = m$), which depends in part on the concentration of platelet-derived growth factor (PDGF), one could consider

$$m^m(\tau) = m^m_B\big(1 + K^m_{\mathrm{PDGF}}\Delta C^{\mathrm{PDGF}} + K^m_{\mathrm{ET1}}\Delta C^{\mathrm{ET}} - K^m_{\mathrm{NO}}\Delta C^{\mathrm{NO}} + \cdots\big). \quad (9.19)$$

In other words, rather than purely phenomenological forms represented by Eq. (9.15), molecular level information could be used to inform the continuum level analysis. Similar relations could be determined for the survival function, which should include terms accounting for concentrations of active proteases. Moreover, relations for changes in molecular production can be derived from appropriate experiments, as, for example, studies of the effects of changing wall shear stress on the production of NO, as, for example (Humphrey, 2008b)

$$C^{\mathrm{NO}} = C_B^{\mathrm{NO}}\left\{\zeta + \beta\left[1 - \exp\left(-\delta\tau_w^2\right)\right]\right\}, \tag{9.20}$$

where $(\zeta, \beta, \delta)$ are parameters required to fit the data (e.g., $\zeta, \beta, \delta = 0.37, 0.63$, and $-8.89$ as reported in Humphrey, 2008b). In this way, molecular level (mechanistic) relations can be combined simply with continuum level models that have already proven useful in modeling diverse aspects of arterial G&R.

## 9.4 Discussion

Bioengineers and clinicians must similarly address arterial adaptations at a macroscopic scale—including normal changes due to development or exercise as well as disease progression, responses to treatment, and so forth. Classical examples include quantification of wall thickening and stiffening in hypertension, changing caliber in exercise or arterio-venous fistulas, stenoses in vein grafts, evolving atherosclerotic plaques, aneurysms, and so forth (Taylor and Humphrey, 2009). Continuum level biomechanical modeling has proven fundamental to studying such tissue-level changes and will likely remain so for purposes of diagnosis, interventional planning, medical device design, and many other daily activities. Nevertheless, we must also exploit our growing understanding of the molecular level mechanisms that dictate macroscopic manifestations. We submit here that a consistent mixture theory framework for growth and remodeling allows one to account naturally for spatial and temporal changes in effector molecules via classical reaction-diffusion equations, which in turn can be used to inform improved constitutive relations for cell and matrix turnover that are fundamental to the tissue-level analyses that are vital for so many aspects of research and clinical care. Indeed, we emphasize that the present G&R framework, which focuses on changes to the arterial wall, is also easily coupled to sophisticated computational fluid dynamics simulations of the hemodynamics (Figueroa et al., 2009), thereby permitting both multiscale and multi-physics studies. Moreover, we emphasize that the multiscale approach presented here (focused mainly on informing continuum level constitutive relations with molecular level information) is but one possible multiscale approach. Hayenga et al. (2011), recently showed that agent based models can similarly be integrated with continuum level G&R models, hence providing yet another level of multiscale modeling.

In summary, there is a pressing need for continued research on the molecular mechanisms responsible for arterial adaptations and disease progression, particularly given the complex multifunctional capabilities of the large number of effector

molecules, including vasoactive, mitogenic, proteolytic, and inflammatory. Discovery of appropriate mechanobiological relations can and should be incorporated in continuum level models.

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