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A 3-D framework for arterial growth and remodeling in response to altered hemodynamics

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ABSTRACT

We present a three-dimensional mathematical framework for modeling the evolving geometry, structure, and mechanical properties of a representative straight cylindrical artery subjected to changes in mean blood pressure and flow. We show that numerical predictions recover prior findings from a validated two-dimensional framework, but extend those findings by allowing effects of transmural gradients in wall constituents and vasoactive molecules to be simulated directly. Of particular note, we show that the predicted evolution of the residual stress related opening angle in response to an abrupt, sustained increase in blood pressure is qualitatively similar to measured changes when one accounts for a nonlinear transmural distribution of pre-stretched elastin. We submit that continuum-based constrained mixture models of arterial adaptation hold significant promise for deepening our basic understanding of arterial mechanobiology and thus for designing improved clinical interventions to treat many different types of arterial disease and injury.

1. Introduction

Stimulated in large part by the work of Rodriguez et al. [26], the past decade and a half has seen increasingly greater attention directed toward mathematically modeling soft tissue growth (i.e., changes in mass) and remodeling (i.e., changes in microstructure), particularly in arteries. Such modeling is made challenging by the intrinsic complexities of arterial mechanics, including its composite make-up and associated active smooth muscle contractility plus nonlinear, anisotropic, pseudo-elastic passive behaviors over finite deformations [16]. Whereas the "kinematic growth" approach of Rodriguez and colleagues has been embraced and extended by various investigators to model arterial responses to sustained alterations in blood pressure and flow (e.g., [23,24,28,29]), Humphrey and Rajagopal [15] suggested that this approach focuses primarily on consequences of growth and remodeling (G&R), not underlying mechanisms. Hence, they proposed a fundamentally different approach, one based on modeling changes in the rates and extents of cellular and extracellular matrix turnover in response to perturbations of mechanical stimuli from normal. Moreover, they introduced the concept of a *constrained mixture model* wherein different structurally significant constituents are constrained to move together with the mixture (i.e., artery), but are allowed to possess different natural (stress-free) configurations, material behaviors, and rates of turnover.

The goal of this paper is to extend to 3-D the prior 2-D constrained mixture model for arterial G&R proposed by Baek et al. [2] for cerebral aneurysms and extended by Valentín et al. [32], Valentín and Humphrey [33,34] for cerebral arteries. Whereas 2-D frameworks provide information on arterial adaptations that is of most importance clinically (i.e., changes in caliber and structural stiffness), advantages of a 3-D framework include the ability to account for gradients in the

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distribution and pre-stretch of individual structurally significant constituents, particularly elastin [5], and similarly gradients in the concentration of non-structurally significant constituents (e.g., oxygen, vasoactive molecules, growth factors, and proteases). We confirm the consistency of predictions by the proposed 3-D model with prior 2-D results for sustained alterations in mean blood pressure and flow, and show advantages of a 3-D model in predicting changes in the residual stress related opening angle. Because of a continuing lack of some of the essential data on cell and matrix turnover, many results are presented parametrically based on the best data available.

2. The mass change function – J_m

We assume that the three primary structurally significant constituents comprising the wall of the basilar artery are elastin, four families of fibrillar collagens (oriented axially, circumferentially, and symmetrically oblique; [35]), and smooth muscle. Data consistently reveal that effective elastin cannot be not produced during maturity even though it is removed via normal aging processes as well as in diseases such as hypertension. In contrast, fibrillar collagens and smooth muscle turnover continuously throughout maturity, which emphasizes the importance of tracking individual balances or imbalances in production and removal. For more information on histology, pathology, and mechanobiology of arteries, see [16,17].

Consider first the change of total mass during G&R. Mass balance for individual constituents k that are constrained to move with a mixture that deforms quasi-statically can be written at any G&R time $\tau \in [0, s]$, where s is the current time, as

$$\frac{\mathrm{d}M^k}{\mathrm{d}\tau} = \bar{m}^k, \tag{1}$$

where M^k the mass of constituent k and $\bar{m}^k$ is its net rate of production or removal. Summing Eq. (1) for all constituents, we have

$$\sum_k \frac{\mathrm{d}M^k(\tau)}{\mathrm{d}\tau} = \sum_k \bar{m}^k, \tag{2}$$

which can be used to find the total mass $\sum_k M^k(\tau) = M(\tau)$. Hence,

$$\frac{\mathrm{d}M(\tau)}{\mathrm{d}\tau} = \sum_k \bar{m}^k. \tag{3}$$

Total volumes between two instants, e.g. between $\tau = 0$ and $\tau = s$, are given by the overall Jacobian, $V(\tau) = J_m(\tau)V(0)$ for all $\tau \in [0, s]$. Using this relation and assuming that the mass density of the mixture is constant over all past times and throughout G&R [15], that is, $\rho(\tau) \approx \rho(0)$ for all $\tau \in [0, s]$, Eq. (3) becomes

$$\int_{-\infty}^{s} \frac{\mathrm{d}[J_m M(0)]}{\mathrm{d}\tau}\mathrm{d}\tau = \int_{-\infty}^{s} \sum_k \bar{m}^k \mathrm{d}\tau, \tag{4}$$

or,

$$[J_m(s) - J_m(-\infty)]M(0) = \int_{-\infty}^{s} \sum_k \bar{m}^k \mathrm{d}\tau. \tag{5}$$

The right hand side of Eq. (5) represents the total change in mass over time and gives us relatively simple expression for the mass change function

$$J_m(s) = \frac{M(s)}{M(0)}. \tag{6}$$

3. Kinematics

Consistent with prior 2-D constrained mixture models, we assume that the mechanical properties and "deposition stretches" of newly synthesized constituents (i.e., fibrillar collagens and smooth muscle) remain the same despite changes in overall tissue geometry or loading. We denote individual deposition stretches (or pre-stretch in the case of elastin because it is only produced during the perinatal period) by, $\mathbf{G}^k(\tau)$, which as illustrated in Fig. 1 is defined relative to constituent-specific natural configurations rather than an overall mixture configuration (cf. [19]). That is, $\mathbf{G}^k(\tau)$ quantifies mappings from natural (stress-free for each constituent) to intermediate (*in vivo*, loaded mixture) configurations at each deposition time $\tau \in [0, s]$. Henceforth, $\tau = 0$ denotes the instant at which the mechanical loading is perturbed from normal in maturity and s denotes the current G&R time. Note, too, that the deformation gradient $\mathbf{F}^k_{n(\tau)}(s)$ quantifies mappings from natural configurations of constituent k at time τ to a current mixture configuration at time s, and the deformation gradient ${}^s_\tau\mathbf{F}^k_g$ similarly quantifies mappings for each constituent k between its natural configurations at times τ and s. Moreover, ${}^s_\tau\mathbf{F}$ quantifies mappings within in vivo mixture configurations between τ and s. Because the total mixture mass density is assumed to remain constant, that is, $\rho(s) \cong \rho(0)$, despite expected changes in total mass [15], we have

$$\det {}^s_0\mathbf{F} = J(s). \tag{7}$$