A RULE-OF-MIXTURES MODEL FOR FLOW-INDUCED ALTERATIONS IN THE GEOMETRY, STRUCTURE, AND PROPERTIES OF ARTERIES

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ABSTRACT
Evidence from diverse investigations, including studies on vein grafts, hypertension, flow-induced remodeling and the effects of microgravity, strongly suggests that vascular growth and remodeling (G&R) correlates well with changes in mechanical stresses from their homeostatic values [1]. From a basic science perspective, there is a need for a comprehensive theory that accounts for changes in the complex three-dimensional distribution of stress within the vascular wall, including residual stresses, and their relation to underlying mechanisms of mechanotransduction. Unfortunately, current technology does not provide sufficient information to compute the in vivo stress field. Information is typically available only on the lumen and intraluminal pressure, from which one can infer the structural stiffness of the wall, and sometimes the wall thickness and tortuosity of the vessel. A simpler theory that accounts for gross effects of stress-mediated G&R could thus be useful clinically as well as in supporting computations on solid-fluid interactions in the vasculature and providing direction for future efforts to develop a comprehensive theory of vascular G&R. In this paper, therefore, we present a simple rule-of-mixtures model of a vascular adaptation to an altered flow. To render the problem tractable, we consider a membrane model of a cylindrical vessel, a simple rule-of-mixtures model for the stress response function, and first order kinetics for the production and removal of constituents within the wall.

INTRODUCTION
It is now generally accepted that hemodynamically altered wall shear and intraluminal stresses (or strains) correlate well with changes in the production of vasoactive, growth regulatory, inflammatory, degradatory, and adhesive molecules by vascular cells (endothelial, smooth muscle, and fibroblasts). In the case of acute changes in flow, the vessel merely seeks to vasodilate or vasoconstrict to restore the wall shear stress to its homeostatic value. In cases of sustained increases or decreases in flow, it appears that an altered turnover of cells (via proliferation and apoptosis), collagen (via synthesis and degradation), and possibly some elastin results in G&R at the vaso-altered configuration. Such changes alter material properties, biological function, and the underlying microstructure; for example, there are shifts in both the passive and the active mechanical response curves. Hence, an appropriate model must account for the two-step process of adaptation and predict changes in the lumen, wall thickness, and structural properties.

METHODS
Because the individual load-bearing constituents may turnover at different rates, there is a need to account for the mechanics of each separately. Toward this end, we employ a simple rule-of-mixtures description for the mean Cauchy stress of the form

$$\sigma_i = \sum_{j \in A} \phi^i(s) \sigma_i^j(\lambda^j_0(s), \lambda^j_s(s))$$

(1)

where \(\phi^i(s)\) is the potentially changing mass fraction of constituent \(k\) as a function of G&R time \(s\), and \(\sigma_i^j(\lambda^j_0, \lambda^j_s)\) is the mean stress of constituent \(j\) as a function of the stretch ratios \(\lambda^j_0(s)\) and \(\lambda^j_s(s)\) that are experienced separately by each constituent due to their separate evolving natural configurations. Moreover, the free index \(i\) in equation (1) can take values \(i = \theta\) or \(i = z\), thus yielding the two in-plane stresses, circumferential and axial respectively, in the membrane model. The superscripts \(j\) represent the constituents, which we take to be \(j = e, c, o, m\) for elastin, collagen, and smooth muscle, respectively. The subscript \(k\) similarly identifies these constituents but also their natural configuration – we will have two natural configurations for each constituent, original and new. By original, we mean configurations associated with constituents that were produced at or before \(s = 0\); by new, we mean those associated with constituents that were produced after \(s = s_o\), the time at which the initial vasoactive response that seeks to restore the wall shear stress to its homeostatic value in the presence of the altered flow. Thus, \(k = oe, ne, oc, nc, om,\) and \(nm\) denote original and new elastin, collagen, and smooth muscle,
respectively. Finally, note that $\phi^k(s)$ can be described by simple kinetic functions, the rate parameters of which depend on differences between the current state of stress and the homeostatic values. Hence, we not only assume that multiple types of constituents (elastin, collagen, and muscle) co-exist at a point (i.e., within a homogenized neighborhood), we also assume that constituents produced at different times, having different natural configurations, can co-exist.

We will present an illustrative example of this model for a single step change in blood flow rate. Specific applications require one to specify deformations between the configurations and states of interest as well as the functional forms of the material response functions and kinetic relations. These must come from data – data that are not currently sufficient. For purposes of illustration, therefore, we will consider the ramifications of simple forms for these functions. Thus, for the stress-response functions, we will assume that elastin exhibits a neo-Hookean type of behavior describable via a strain-energy function of the form $W = 2b_1(I_C - 3)$, where $I_C$ is the first invariant of the right Cauchy-Green tensor $C^e$ for the elastin and $b_1$ is a material parameter. Collagen can be modeled as a sub-class of transversely-isotropic materials ($W = f_1(I_C, IV_C)$ where $I_C$ and $IV_C$ are invariants of $C^c$ for the collagen), with the $z$-direction as the preferred direction. Smooth muscle exhibits both active and passive responses - the passive response will be modeled as a sub-class of transversely-isotropic materials ($W = f_2(I_C, IV_C)$ where the invariants are for deformations of the smooth muscle), with the $\theta$-direction as the preferred direction; the active response will be modeled as a nonlinear-polynomial, consistent with Rachev and Hayashi [2].

**CLOSURE**

It will be shown that a simple rule-of-mixtures membrane model with first order kinetics of the changing mass fractions can mimic observed alterations in the lumen, thickness, and structural stiffness of the wall without requiring a complicated description of the residual stress field or material heterogeneity, which are not currently measurable in the clinical environment. We further show that, by simply adjusting physiologic constraints (e.g., changing the rate of elastin turnover), our model can predict seemingly contradictory results from the literature that arise due to the use of different age animals (e.g., different basal rates of turnover and turnover of different constituents) and different degrees of change in the altered flow.

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**REFERENCES**
