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Modeling of the mechanobiological adaptation in muscular arteries

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Abstract

The growth and remodeling of arteries, as controlled by the local stress state and the sensory input from the endothelial cells of the artery wall, is given a novel theoretical framework incorporating the active behavior of vascular smooth muscle. We show that local sensory input maps uniquely to the ratio between a target arterial wall cross-section area corresponding to homeostatic conditions and the current arterial wall area. A growth law is formulated by taking the production rates of individual constituents of the arterial wall to be functions of this target-to-current wall area ratio. We find that a minimum active stress response of vascular smooth muscle is necessary to achieve stable adaptation of the artery wall to dynamic flow conditions. With a sufficient active stress alteration in response to stretch, stable growth toward a homeostatic state can be observed for finite step changes or ramp changes in the transmural pressure or the flow rate.

Keywords: arterial adaptation, finite elasticity, growth and remodeling

1. Introduction

1.1. Background and motivation

Arteries grow and remodel to adapt to changing conditions in the human body, whether these changes are through injury, disease or normal aging. During this growth and remodeling (G&R) process, the constituents of the artery, including collagen, elastin and vascular smooth muscle (Boron and Boulpaep, 2008, pp. 473-481), display different rates of turnover, where the balance between degradation and production rates is purposefully controlled to maintain functionality of the cardiovascular system. At the level of individual arteries, the arterial wall remodels in response to changes in blood pressure (Matsumoto and Hayashi, 1996; Fridez et al., 2002; Hu et al., 2007a,b) or blood flow rate (Langille and O'Donnell, 1986; Lehman et al., 1991; Langille et al., 1989; Brownlee and Langille, 1991). Instantaneous contraction or dilation is achieved by changes in vascular smooth muscle cell tone, which is combined with matrix remodeling at the longer time-scale of G&R (Rodbard, 1975; Dajnowiec and Langille, 2007). While a qualitative picture of the G&R of arteries has been elucidated though experiments and previous modeling efforts, quantitative predictability of the G&R response to, *e.g.*, surgery, injury or vascular deformities remains elusive. This is likely to preclude many advances in the diagnosis and treatment of vascular diseases. For instance, being able to describe the growth response of the arterial wall of an aneurysm would be highly useful for projecting the evolution of the shape of the aneurysm in mechanobiological models.

In this work, we combine thin-wall tube theory with a finite elasticity mechanical model for multiple constituents that deform together as a *constrained mixture* (Humphrey and Rajagopal, 2002; Gleason and Humphrey, 2004; Valentín and Humphrey, 2009a; Valentín et al., 2009). These constituents are continually degraded and produced, as modulated by mechanical stimulation. The constrained mixture theory permits for using different natural configurations for different constituents, which is necessary for modeling their continuous turnover. This is in contrast to a theory based on the multiplicative split of the deformation gradient which, in the case of growth, is usually attributed to Skalak et al. (1996). In this approach one single natural configuration is used, instead of one such for each constituent as in the constrained mixture theory. For a normally functioning artery at physiologically constant conditions, G&R controls the evolution of the artery toward a steady-state, which is referred to as the *homeostatic state*. The constituents of the artery are deposited at a certain prestretch, which is also their homeostatic stretch. Consequently, each constituent carry a known circumferential stress in the homeostatic state (Satha et al., 2014). We assume that G&R is controlled *locally*. By this, we mean that each small through-thickness element of the arterial wall (Fig. 1a) grow and remodel according to the sensory input of that element. It is assumed that this sensory input originates from stress-transduction mechanisms in embedded cells as well as the endothelial cells that line the interior wall of the artery.

A range of novel concepts and ideas are introduced in this work: we formulate an energy density functional for the active stress contribution of smooth muscle, capturing the long-time scale phenotypic switching between the contractile and the synthetic state of smooth muscle (Halayko and Solway, 2001; Albinsson et al., 2014); we consider how the stimuli and the mechanical model can be combined to derive information about the current wall cross-section area and lumen radius of the artery, and thus pinpoint the appropriate direction of growth; we identify the stress measure that appears naturally in the governing equations of the system as a growth stimulus.