A Multiscale Framework for Understanding Arterial Tissue Mechanics: Coupling Cellular Dynamics and Macroscopic Behavior

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Abstract

Introduction

Arterial tissue dynamically regulates mechanical tension to maintain stability under varying physiological conditions (Cyron 2014). A key short-term regulatory mechanism, vasoconstriction, involves smooth muscle cells (SMCs) contracting or relaxing through actin-myosin interactions, resulting in rapid, inelastic deformation (Karkhaneh Yousefi 2023). This microscopic vasoactive response governs the macroscopic mechanical behavior of the tissue. However, despite its importance, the short-term effects of vasoconstriction are underexplored compared to long-term mechanisms such as extracellular matrix (ECM) remodeling, which dominate current research on arterial mechanics.

Understanding the mechanical state of arterial tissue-shaped by the interplay of short- and long-term mechanisms-is essential for addressing pathological conditions characterized by instability. While existing studies predominantly focus on the non-linear behavior of collagen fibers and their contribution to passive mechanics, the active mechanical role of SMCs in vivo remains largely overlooked. Recent advances, however, highlight the importance of explicitly modeling SMC activity at the microscopic level to bridge the gap between cellular and tissue-scale mechanics (Eichinger 2021).

In this context, we present a novel multiscale approach to arterial tissue mechanics, designed to assess mechanical interactions among tissue components and elucidate the coupling between cellular and tissue-level behavior. This framework aims to provide insights on the cellular mechanical behavior, a first step toward modelling the multiscale cellular driven homeostatic regulation of the arterial tissue.

Methods

We implement a previously developed multiscale micromechanical model (Morin 2018) within a Finite Element framework using FeniCSx. This methodology employs analytical homogenization of a Representative Volume Element (RVE) to capture the microscale heterogeneity

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of arterial tissue, including collagen fibers, elastin, smooth muscle cells, and ground substance. Homogenization is based on the Eshelby's theory and Mori-Tanaka method, adapted for finite strain mechanics. This approach allows estimation of mean mechanical fields (stress and strain) within microscopic inclusions and the homogenized macroscopic behavior of the tissue.

For validation, we simulate a cylindrical arterial segment under pressure, representing experimental ex-vivo inflation tests on rat carotid arteries. The arterial wall is modeled as a two-layer structure-media and adventitia. The media comprises collagen fibers, SMCs, and ground substance, with collagen fibers helically arranged around the circumference and SMCs modeled as spheroids with a 1:6.2 shape ratio (O'Connel 2008). The adventitia consists of axially oriented collagen fibers and the ground substance.

To enhance the model, we incorporate a detailed sensitivity analysis of stress distribution within the SMC population, assessing how ECM stiffness and fiber orientation influence mechanical loading on cells. The model is validated against macroscopic experimental data by reproducing the pressure-radius curve from inflation tests, ensuring consistency between predicted and observed behavior. Additionally, we track collagen fiber and SMC kinematics during deformation to provide insights into their orientation and mechanical contributions under physiological loading conditions.

Results and Discussion

The model parameters were calibrated to align with experimental data at both macro- and microscopic scales, reproducing the non-linear pressure-radius curve and collagen fiber kinematics. Preliminary results revealed non-homogeneous circumferential tension in SMCs, varying with their radial position within the arterial wall. This finding underscores the significance of multiscale coupling between tissue macrostructure and microstructure.

Sensitivity analyses highlighted the influence of collagen stiffness on SMC stress distribution, showing that stiffer fibers reduce stress on SMCs. Pre-stretched fibers, in particular, mitigate cellular stress, emphasizing their potential role in mechanical stabilization.

This multiscale approach offers a robust framework for analyzing mechanical interactions between heterogeneous tissue components and understanding how macroscopic geometry affects cellular mechanics. The results demonstrate the critical role of cellular mechanics in driving regulatory processes and tissue behavior, where macrostructure induces non-homogeneous cellular activity.

Future work will incorporate an active feedback loop for SMCs to model vasoactive short-term regulation, advancing our understanding of the complex interplay between cellular and tissue-level processes. Comprehensive validation at both scales will further refine the model's accuracy, providing deeper insights into the mechanobiology of arterial tissue under physiological and pathological conditions.

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