An Integrative Multi-Scale Model of Extracellular Matrix Mechanics in Vascular Remodeling

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Motivation

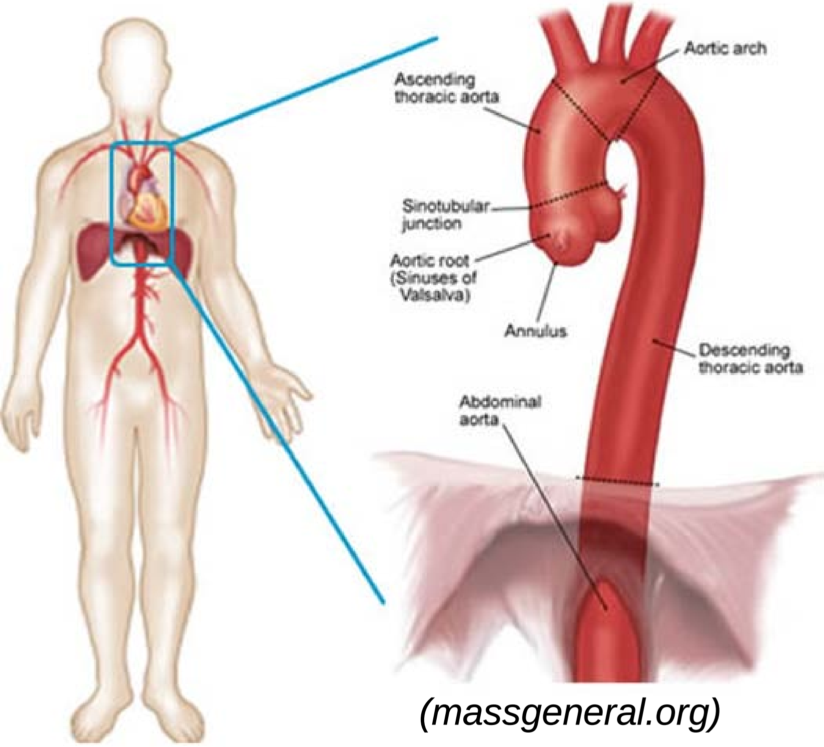
- Cardiovascular diseases (CVDs) are responsible for 40 percent of all deaths in the U.S.
- Many CVDs involve arteriosclerosis, or hardening of the arteries due to structural changes in blood vessel walls.
- Lack of understanding on the mechanisms that control structural and functional changes in blood vessel walls.

Objectives

- To develop a multi-scale predictive mechanobiology model of extracellular matrix (ECM) mechanics that integrates *biomechanical integrity*, *biochemical composition stability*, and *microstructure of the ECM*.
- To better understand the underlying physics of arterial stiffness—and ultimately, CVDs.

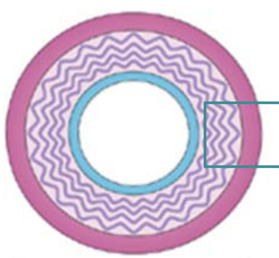
Structure of the arterial wall

- Arteries are large diameter vessels that move blood away from the heart to the body
- Elastic to accommodate cardio-respiratory function and pulsatile blood flow
- Three layers



(massgeneral.org)

- Tunica intima
- Tunica media
- Tunica adventitia



Media (elastic fibers, SMCs, collagen, proteoglycan)

Adventitia (collagen, fibroblasts, nerves, capillaries)

Intima (Endothelial cells, basal lamina)

Importance of elastin and collagen in the mechanics of arterial Wall

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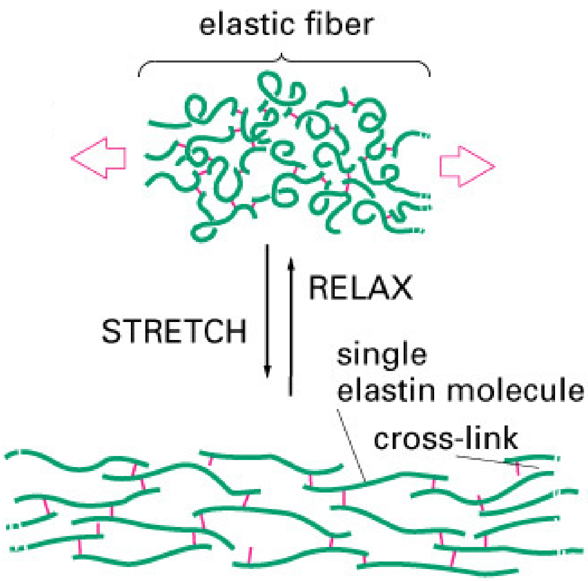
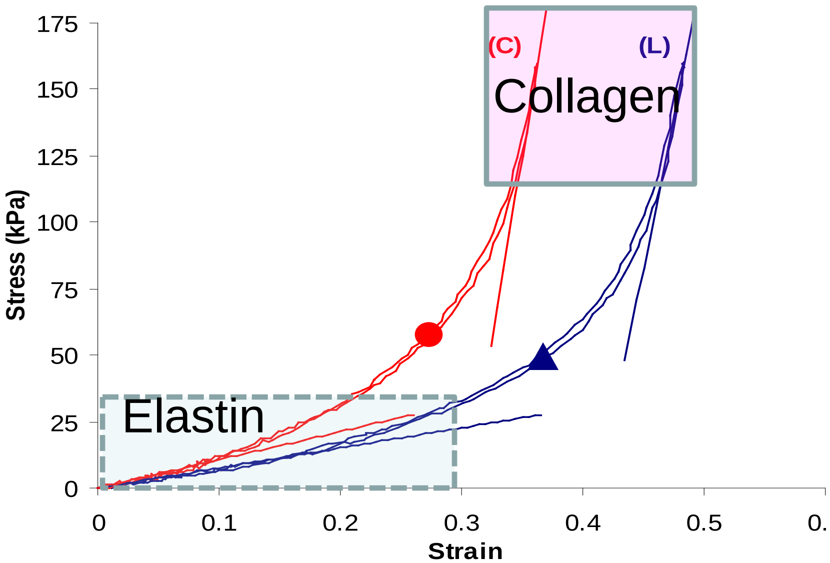
- Majority of the passive mechanical behavior is due to the collagen and elastin
- Elastin is essential to provide the elasticity of dynamic tissues
- Collagen fibers support the load in the stiff region

Mechanically recoil 3×10⁹ times over a 70-year life!

(Sherratt, *Age*, 2009)

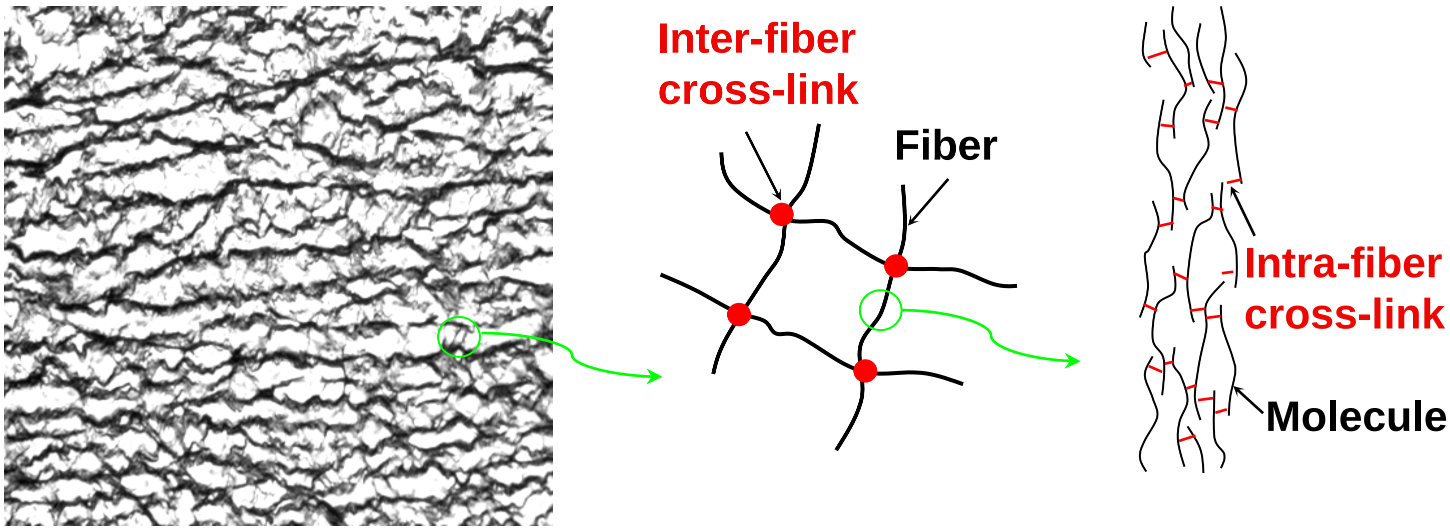


Molecular Biology of the Cell, 2002, Alberts et al.



Hierarchical ultrastructure within the ECM

- Mechanical function of ECM at the tissue level is highly dependent on its structure (fiber distribution/orientation) and its biochemical composition (ECM content and cross-linking)



Tissue level **Fiber level** **Molecular level**

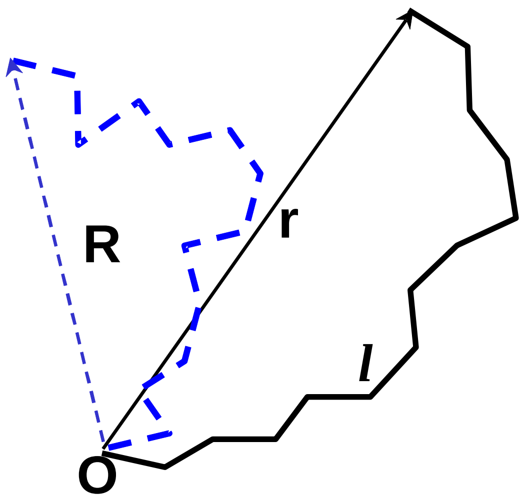
- Fundamental mechanics perspective coupled with critical biophysical input

Fiber-level mechanical function (cross-linking)	Structural/histological information (fiber content, distribution)	Tissue-level mechanical function (normal vs. disease)

Statistical mechanics based constitutive model

Freely Jointed Chain

(Kuhn and Grün, 1942)



Strain energy dW = Internal energy dU (→ 0) − Entropy change TdS

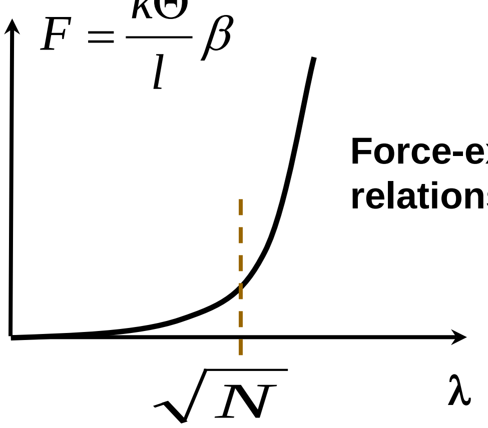
$$dW = -TdS$$

Material parameter:

N – number of links within each chain

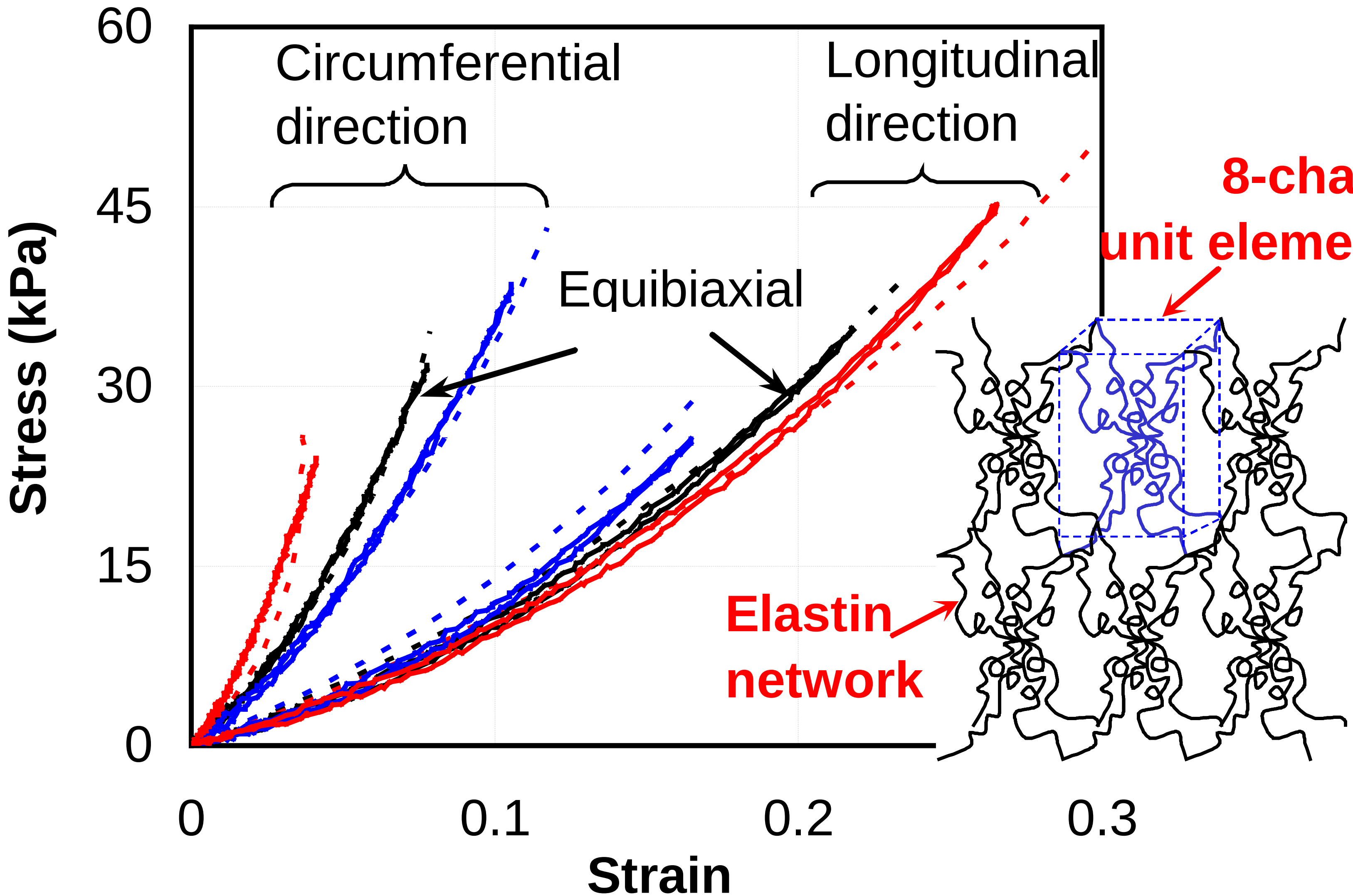
Locking stretch of the chain; chain length between cross-links

$$F = \frac{k\Theta}{l}\beta$$



Force-extension relationship

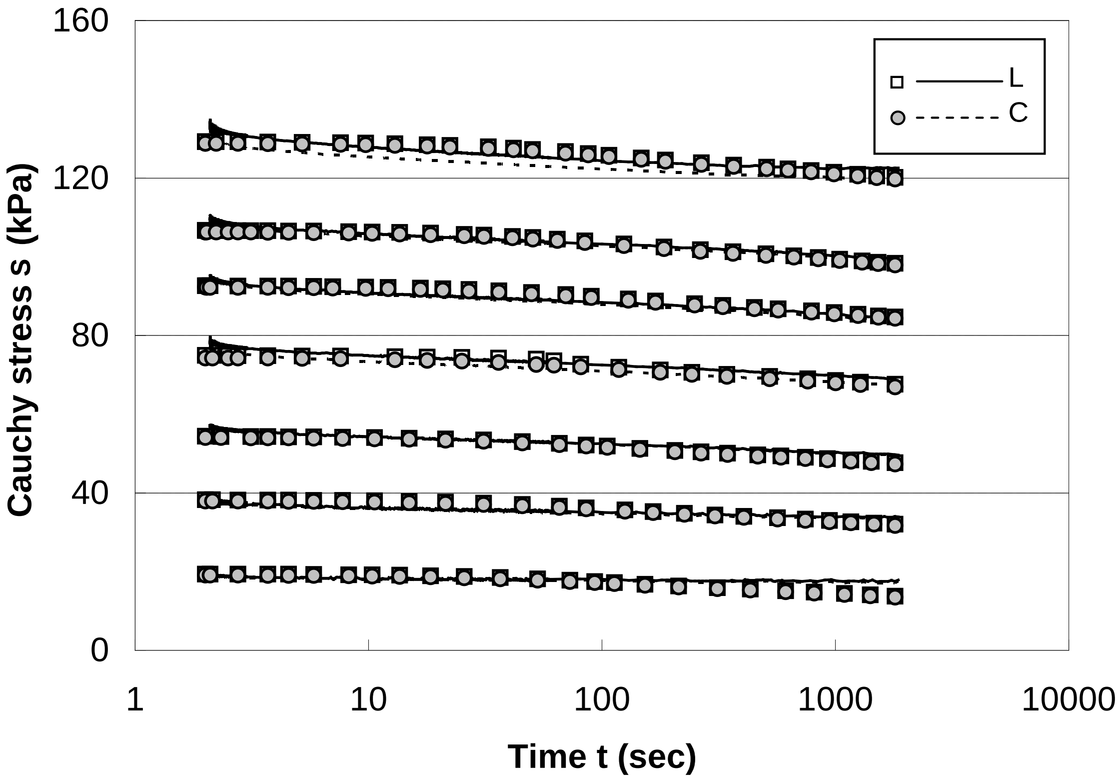
Orthotropic hyperelasticity of elastin



Material parameters: a=1.8011, b=1.31, c=1.2, $n=5.8\times10^{15}(1/mm^3)$

(Zou and Zhang, Ann Biomed Eng, 2009)

Viscoelastic behavior of elastin



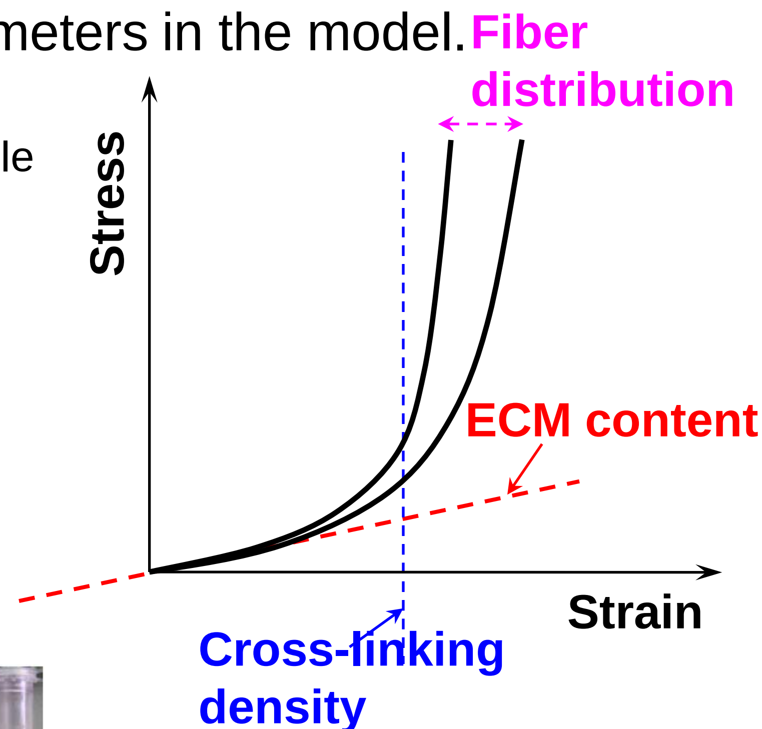
$n = 1.75\times10^{16}$ (1/mm^3)
$a = 1.53$
$b = 1.44$
$c = 1.3$
$N = 1.6$
$G_e = 0.89$
$G_o = 1.0$
$N_d = 6$
$I_o = 2$

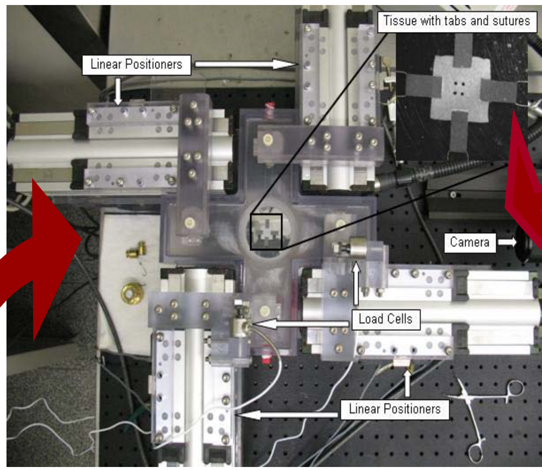
- The dependence of the rate of stress relaxation on the initial stress level is small at physiological load.
- Mterial parameters fitted from one test can be used to simulate the stress relaxation behavior of elastin under different initial stress levels and provide reasonable predictions.

(Zou and Zhang, J Biomech Model Mechanobiology, 2011)

Experiment validation

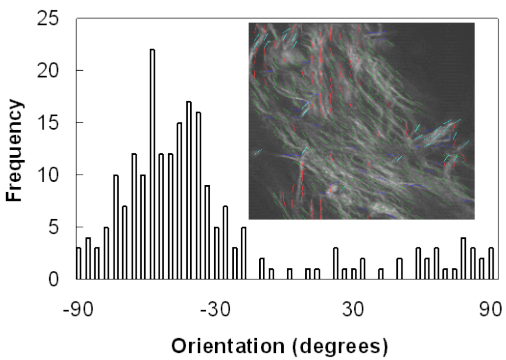
- Provide validation of the model.
- Determine corresponding material parameters in the model.





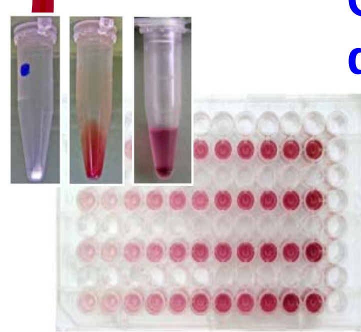
- Biaxial tensile testing

Tissue-level stress-strain relationship



- Confocal microscopy

Fiber distribution function

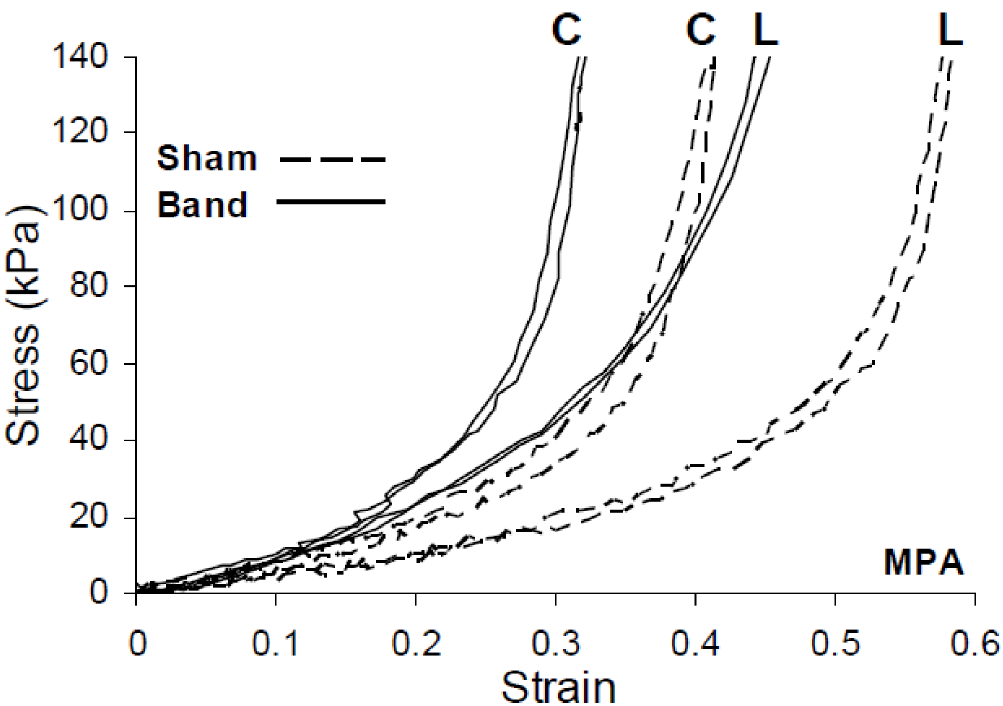


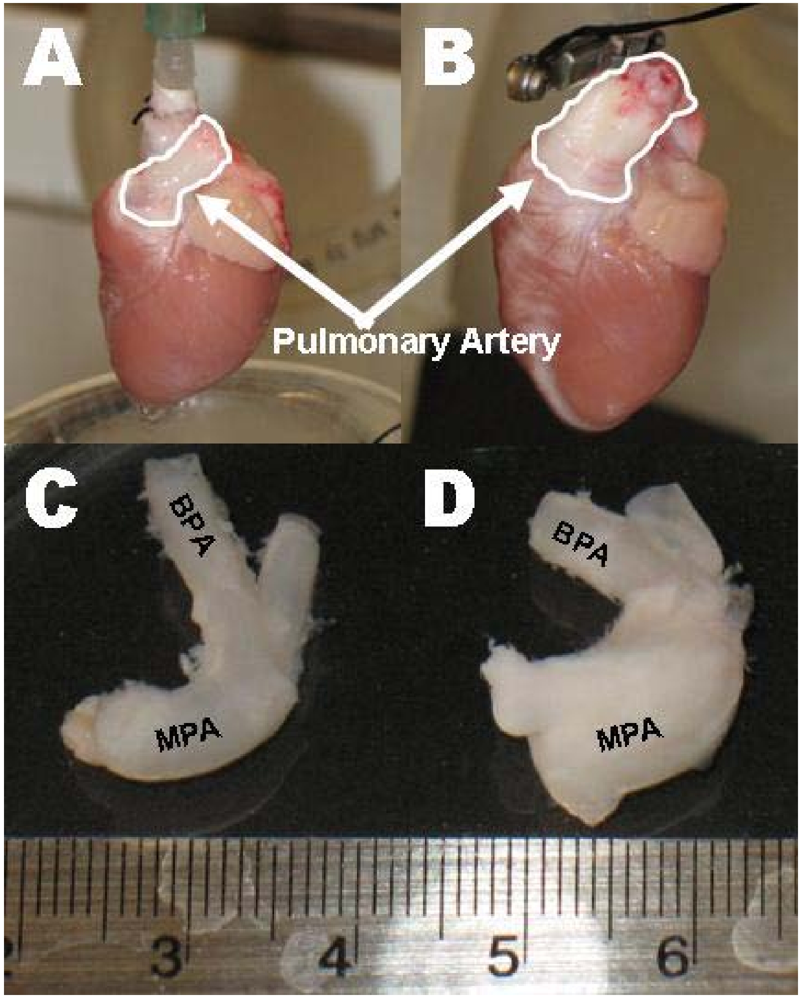
- Collagen and elastin assay
- Histology study

Biochemical
ECM content,
cross-linking

Obstruction Induced Pulmonary Vascular Remodeling

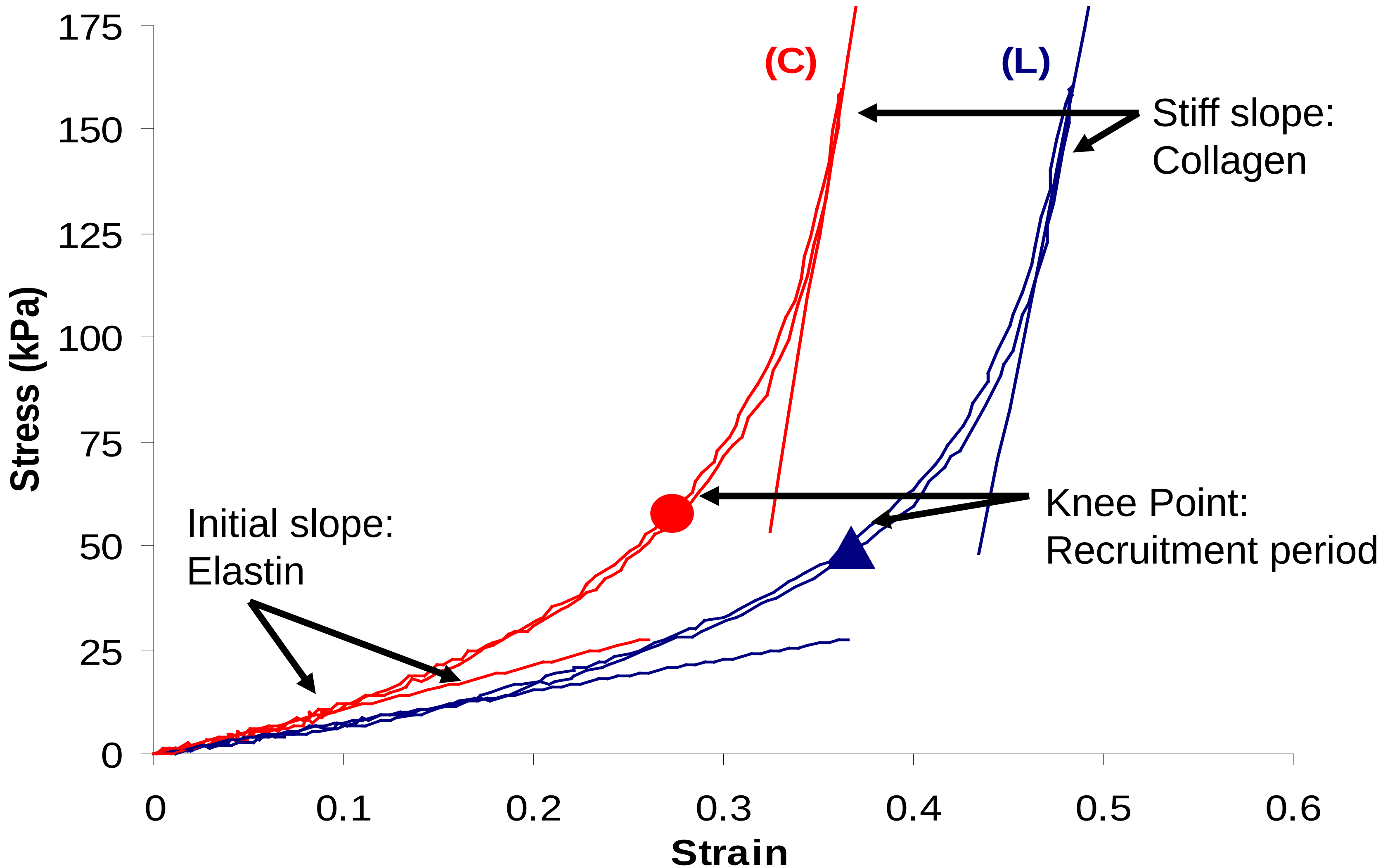
- In collaboration with Boston's Children's Hospital





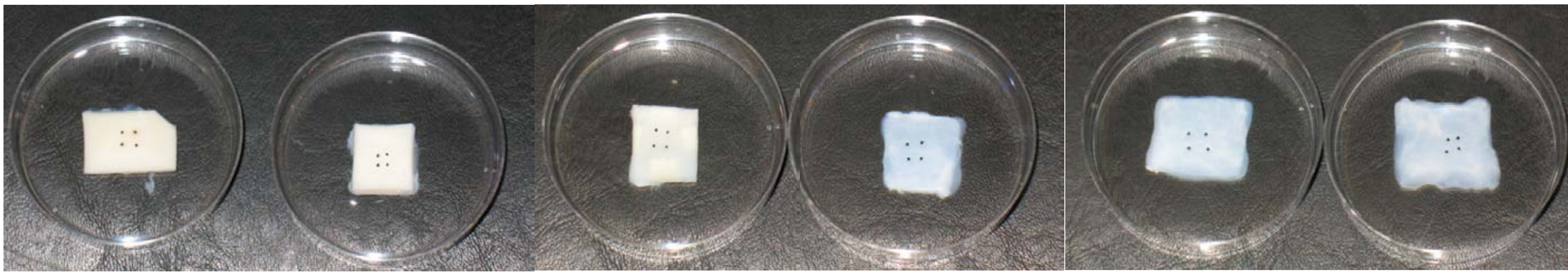
(Chow et al., J Biomech Eng, accepted)

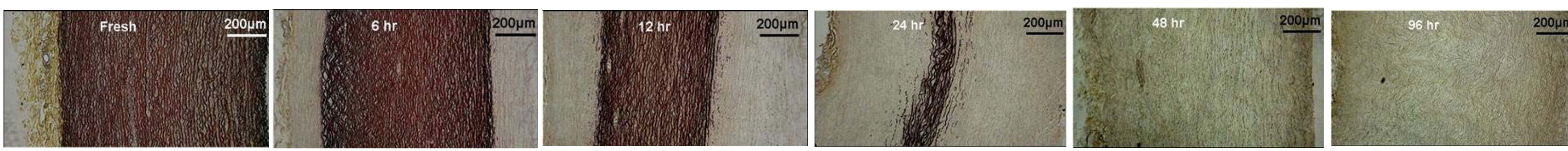
Structural functional changes



(Chow et al., J Biomech Eng, accepted)

Structural and Mechanical Changes in Elastin Degraded Arteries

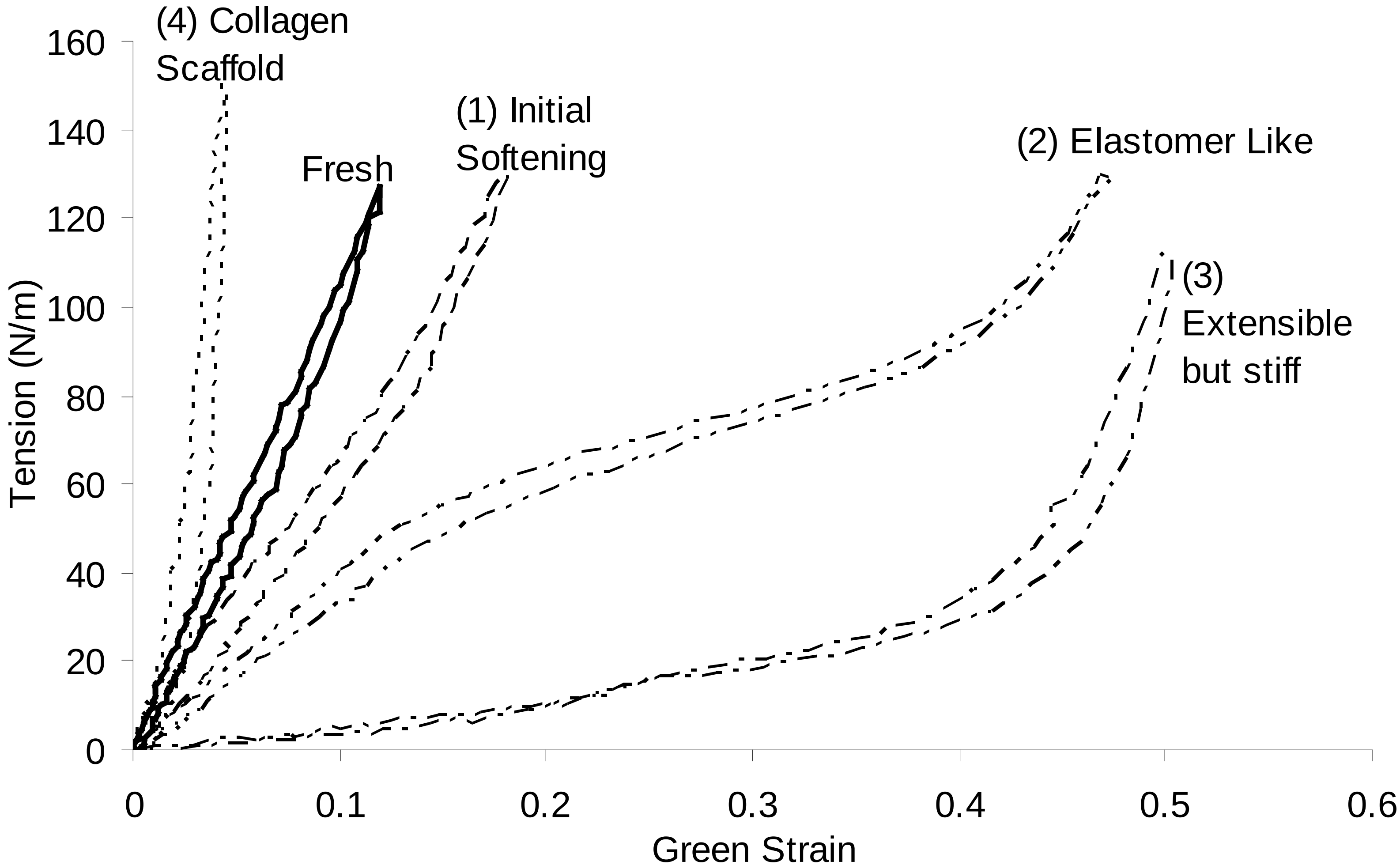




- Elastic solid → Translucent gel with size increase
- Elastin decreases with longer digestion time
- Size increases due to elastin degradation

(Chow et al., J Biomech Model Mechanobiology, submitted)

Initial softening ⇨ **Elastomer like** ⇨ **Extensible but stiff** ⇨ **Collagen scaffold**



(Chow et al., J Biomech Model Mechanobiology, submitted)

Summary and Future Evolution

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- Coupled experimental-modeling approach
  - Fiber orientation information of elastin and collagen will be obtained using confocal microscopy and directly incorporated into the model.
  - Content and crosslinking density of elastin and collagen will be measured biochemically through biological assay. Corresponding material parameters in the model will be determined from fits to the biaxial-tensile testing data.
  - Establish relationship between biomechanical integrity, biochemical composition stability, and microstructure of the vessel wall.
- Combine with animal models of vascular remodeling in CVDs and other diseases, this research approach has a great potential to unravel the underlying key mechanisms of vascular remodeling.