

CARDIOVASCULAR SOLID BIOMECHANICS

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Summary

The mammalian cardiovascular system comprises a finely tuned multi-chambered mechano-electrical pump at the center of a dynamic network of circulatory vessels, which, if placed end-to-end, could wrap around the earth twice. Biological function of the heart is to deliver blood to the body, and it has evolved with a helical laminar muscle architecture to optimize pumping efficiency; blood vessels have their own specialized biomechanical adaptations, such as multilayered structures and residual strains, that minimize transmural stress gradients under physiological and pathological conditions. Mechanical characteristics of the cardiovascular system have been studied extensively, for they are key to understanding the development and function of one of the most essential organ systems in the body. This fascinatingly complex system has hierarchical, nonlinear, heterogeneous, anisotropic biomechanical properties that need to be examined over multiple size and time scales. There are numerous computational and experimental methods to study cardiovascular solid biomechanics including finite element analyses, multiaxial tissue testing and atomic force microscopy. It is hoped that, ultimately, this knowledge will translate to improved diagnoses and novel treatments for patients suffering from cardiovascular disease, which in terms of mortality and economics has persisted as the number one health problem in the modern world.

1. Introduction

As simply stated in his classic *Biomechanics* text, Professor Y.-C. Fung defines biomechanics as the application of engineering mechanics to biological systems. Because function of the cardiovascular system has been a source of fascination since the earliest mechanicians like da Vinci and Galileo, biomechanical analysis of cardiac and

vascular tissues has a long and interesting history, as beautifully summarized by Professor Humphrey in his *Cardiovascular Solid Mechanics* text. The study of cardiovascular biomechanics remains of critical importance, as diseases of the cardiovascular system continue to be the number one killer in developed nations around the world. Altered hemodynamic loading and the resultant changes in the properties of cardiovascular tissues play a crucial role in development and progression of most chronic cardiovascular disease processes. For example, pathological cardiac hypertrophy and neointimal vascular wall thickening are both directly linked to structural remodeling resultant from abnormal mechanical forces. Fortunately, the mammalian cardiovascular system has evolved to adapt under physically challenging conditions, utilizing biomechanical feedback mechanisms such as the Frank-Starling Law of the Heart or the transmural residual strain gradient of blood vessels to preserve functional homeostasis. In addition to complex mechanobiological signaling networks that govern such responses, these tissues often exhibit nonlinear, heterogeneous, viscoelastic mechanical properties and rapidly changing cyclic dynamics that impact the functional efficiency and physiological robustness of the system. Therefore, the study of cell and tissue biomechanics provides a unified framework for understanding the complex systems-level interaction of physiological and physical phenomena in the cardiovascular system. In the following section, we provide an overview of the field of cardiovascular biomechanics. For a more comprehensive treatment of this important field, the bibliography lists a number of excellent related textbooks.

2. Biomechanical Hierarchy in Cardiovascular Physiology

Heart and vascular tissues are composed of a variety of cell types and extracellular matrix constituents (Table 1) combined in a complex microenvironment. The resulting meshwork has a highly organized structural hierarchy, which results in heterogeneous biomechanical properties that depend on the scale of observation, necessitating rigorous multiscale measurement and analysis. Several components play a critical role in forming and maintaining this multiscale biomechanical architecture, including extracellular matrix fibers (e.g., collagen, elastin), intracellular components (e.g., actin, microtubules) and highly charged structural molecules (e.g., chondroitin sulfate, heparin sulfate).

<i>Cell type</i>	<i>Location</i>	<i>Description</i>	<i>Modulus</i>
Myocytes	Heart (muscle)	Non-proliferative and contractile muscle cells; main functional unit that comprises 1/3 of the heart cell population	$E = 8\text{-}100\text{kPa}$ Dynamically changes due to cross-bridge cycling
Fibroblasts	Heart (muscle, valves), vasculature (adventitia)	Regulates extracellular matrix composition, distribution and mechanics. Represent bulk of cardiac cell population	$E = 0.5\text{-}8\text{kPa}$ Mainly regulated by actin cytoskeleton
Endothelial cells	Vasculature (intima), heart (capillaries,	Luminal lining of vasculature; play a critical role in vascular dynamics via systemic	$E = 1\text{-}7\text{kPa}$

	valves)	mechanobiological signaling	
Smooth muscle cells	Vasculature (media)	Medial section of large vessels; regulates vascular tone	$E = 1\text{-}3\text{kPa}$

<i>Matrix type</i>	<i>Location</i>	<i>Description</i>	<i>Modulus</i>
Collagen	Heart, vasculature (adventitia)	Mechanical backbone of ECM; type I, III, IV and V present in the cardiovascular system; important in mechanobiology and signaling	$E = 1\text{GPa}$
Elastin	Vasculature (media)	Exceptional extensibility; physiologically relevant for vascular recoil	$E = 0.6\text{MPa}$
Fibrillin	Heart, Vasculature	Creates extensibility and ECM stability. Mutations lead to Marfan's syndrome.	$E = 1\text{MPa}$
Fibronectin	Heart, vasculature	Little or no structural significance; critical in mechanoreponse	
Proteoglycans	Heart, vasculature	Often labeled as "ground substance"; provides fixed charge density; also coats cellular membrane and acts as a mechanosensor	

Table 1. Biomechanical characteristics of different types of cells and extracellular matrix constituents in the cardiovascular system

2.1. Molecular and Subcellular Mechanics

Cells are the fundamental building blocks of biological tissues, and are themselves composite materials (Figure 1). Subcellular biomechanical heterogeneity was first discovered by Kite and Chambers in the early 20th century using microdissection of spermatocytes. After a hundred years of research, numerous structures responsible for such micromechanical heterogeneity have been identified, along with potential molecular mechanisms that utilize this phenomenon in cellular signal transduction. When cellular organelles are isolated or chemically synthesized, and these individual subcellular components are tested *in vitro*, a widely varying spectrum of mechanical properties is observed. For example, individual chemically stabilized actin fibers exhibit an exceptionally stiff linear elastic modulus of 2.2 MPa, whereas isolated endothelial cell nuclei have an equivalent elastic modulus around 8 kPa. The assembly of these components gives rise to intracellular mechanical heterogeneity, which may play a vital role in specialized physiological functions of the cell.

While cytoplasm is a viscous milieu containing numerous organelles, the cytoskeleton gives the cell its characteristic elastic properties. In particular, filamentous actin is the most dominant subcellular component that governs cellular biomechanics. While the exact mechanisms of actin-dependent mechanoresponse have been fiercely disputed, it is well established that actin fibers form the elastic backbone of the cell, and they can rapidly disassemble and reorganize in response to mechanical perturbations. Other cytoskeletal proteins, such as microtubules and intermediate filaments, as well as motor proteins like myosin also contribute to subcellular mechanics. Crosslinkers, such as actinin and filamin, were also shown to modulate actin dynamics and viscoelasticity.

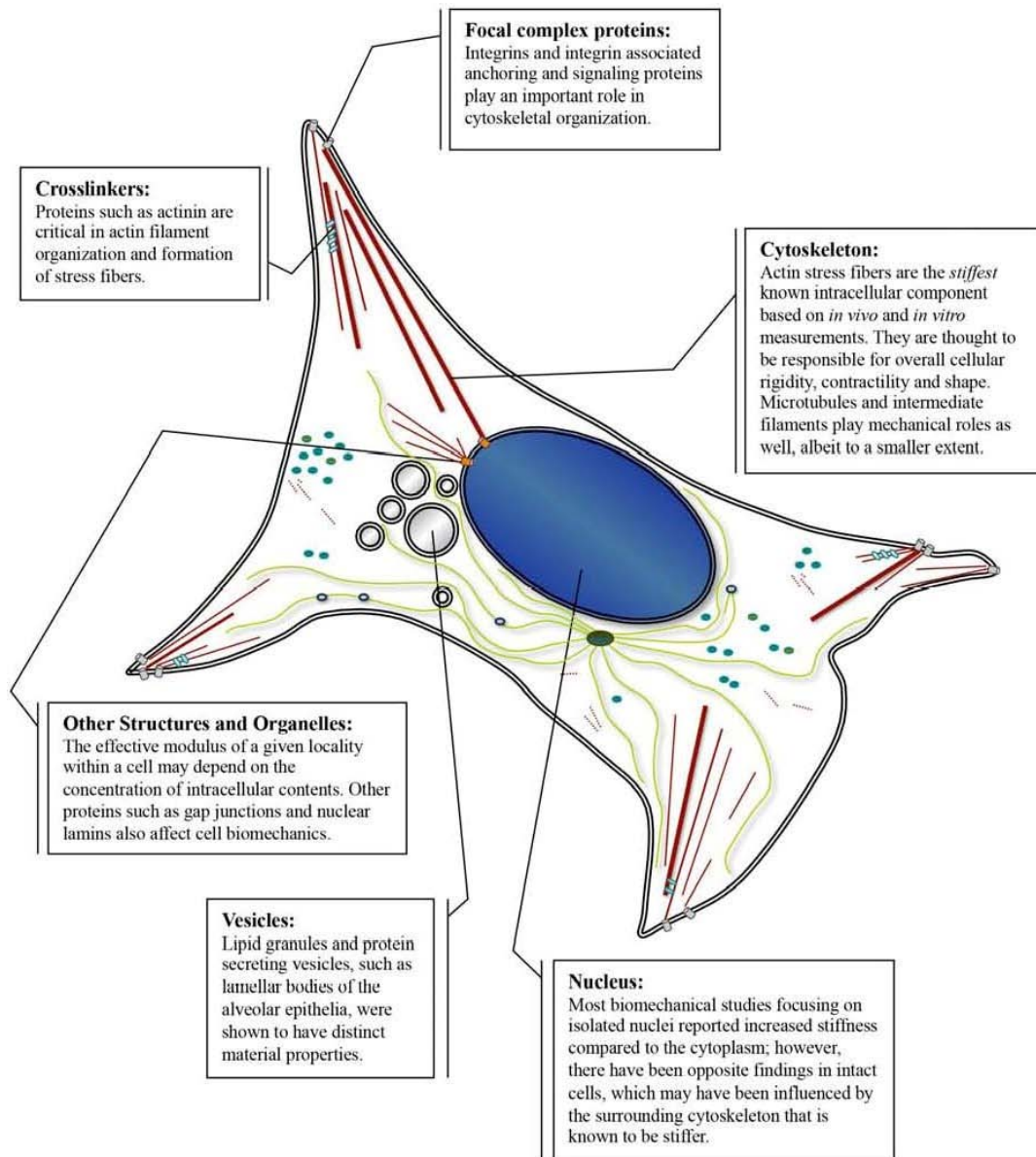


Figure 1. Subcellular and aggregate cell mechanics in the cardiovascular system can be affected by a number of intracellular components with distinct material properties.

Spatial distribution of cytoskeletal fibers, nuclei and certain organelles as well as crosslinkers, adapters and anchoring proteins can contribute to heterogeneity in cellular biomechanics.

In addition to the three major cytoskeletal proteins known to play a universal role in regulating subcellular mechanics (i.e., actin, microtubules and intermediate filaments), cardiomyocytes possess several specialized structural components that affect their biomechanical function. Titin, for example, is one of the most widely studied sarcomeric proteins contributing to myocardial viscoelastic properties. Originally described as connectin, reflecting its structural linkage between the z-disk and sarcomeric myosin thick filaments, titin has become an exemplar for the study of molecular mechanics using force spectroscopy or atomic force microscopy (AFM) techniques due to its enormous size (exceeding 2,000,000 Da) and characteristic patterns of unfolding. Titin filaments, which also contribute to the mechanical heterogeneity of myofibrils, are thought to dominate passive cardiomyocyte elasticity at shorter sarcomeric lengths. While its role in passive tissue stiffness is still controversial, titin represents an exciting potential drug target for biomechanical modulation of chronic cardiac conditions such as dilated cardiomyopathy due to its ability to shift molecular mechanics with posttranslational modifications.

The role of other proteins is slowly being uncovered as more advanced biomolecular modifiers, such as short-hairpin RNAs, are being utilized to modulate accessory proteins such as adaptors and crosslinkers. Upstream signaling proteins that control cytoskeletal dynamics can be just as critical in cardiovascular cell biomechanics as structural proteins. For example, focal adhesion kinase and Abl tyrosine kinase were respectively shown to regulate actin and myosin functionality, affecting cell mechanics and vascular permeability by altering cytoskeletal stability. Clearly, the study of subcellular biomechanics remains a critical area for continued investigation.

2.2. Biomechanics of the Aggregate Cell

As biphasic materials consisting of both solid and fluid components, cells exhibit overall mechanical properties that are similar in many ways to macroscopic tissue biomechanics. Their aggregate (or global) mechanical response seems to stem from a combination of cytoplasm-related viscous attributes along with elastic or hyperelastic properties that are tied to the cytoskeleton and other organelles. Assuming global homogeneity, they have been previously modeled using viscoelastic and hyperelastic material properties based on data from a variety of platforms including atomic force microscope indentation, micropipette aspiration, nanoindentation, compression testing, twisting bead cytometry, and optical tweezers.

Since tissue dynamics play a critical role in cardiovascular function, aggregate mechanical properties of cells are inextricably tied to their physiological function. In red blood cells, viscosity and membrane rigidity increase with sickle cell anemia, making it harder for the cells to pass through small capillaries; treatment with hydroxyurea reverses these anomalous mechanical properties. Leukemia has a similar stiffening effect on white blood cells that can be rectified by chemotherapy. Similarly, cardiac myocytes undergoing some types of hypertrophy exhibit a significant increase in their viscous moduli, which can be reversed by colchicine treatment to inhibit microtubule polymerization. In light of the mounting evidence linking disease conditions with aggregate cell mechanics, biomechanical diagnostics have been suggested as a viable method to search for disease progression. Recent developments in nanotechnology have even allowed markerless sorting of cells purely based on their mechanical properties,

which may soon be utilized to quantitatively classify cell phenotypes based on their aggregate deformability in a high-throughput manner.

2.3. Organ and Tissue-Level Biomechanics

While the distribution of forces within cells plays an important role in modulating cellular behavior, transmission of forces to the cells via extracellular matrix (ECM) is equally important for biomechanical equilibrium and homeostasis. The magnitude of forces transferred to the cell depends on the local matrix properties. In fact, biomechanics at the tissue and organ levels is often dominated by the spatial distribution and individual material properties of ECM proteins. This becomes evident when one compares the elastic moduli of isolated cells with the mesoscale moduli of the corresponding tissues, which can differ by orders of magnitude in elastic and muscular arteries. In mammalian vasculature, collagen and elastin represent the major ECM components, comprising up to 75% of the dry arterial weight. In addition, fibrillin and proteoglycans contribute to the mechanical backbone of the cardiovascular extracellular matrix. Mutations in genes that control these components often lead to human diseases with strong biomechanical phenotypes, such as Alport syndrome (COL4A3, COL4A4, COL4A5 mutations), Williams syndrome (ELN deletion), Marfan syndrome (FBN1 mutation) and vascular Ehlers-Danlos syndrome (COL3A1 mutation).

A common method for characterizing tissue mechanical properties involves phenomenological model fitting of data from biomaterial testing, with the objective of recapitulating the stress-strain behavior of the tissue irrespective of the underlying structural basis. Due to their intrinsic material nonlinearity and the finite deformations they sustain, soft tissues such as those in the cardiovascular system are often modeled as hyperelastic materials that have distinct *strain-energy density* descriptions. The strain energy function, W , of a material can be used to define the stress-strain relationship via

$$\mathbf{S} = 2 \frac{\partial W}{\partial \mathbf{C}} \quad (1)$$

where \mathbf{S} and \mathbf{C} are the second Piola-Kirchhoff stress tensor and the right Cauchy-Green deformation tensor, respectively. Using a strain energy function of a predefined form, an optimal set of material parameters describing the tissue mechanical properties can be obtained using various fitting algorithms with experimental data from multiaxial mechanical tests. Alternatively, a cleverly prescribed set of “constant invariant” biaxial tests can be used to experimentally reveal the mathematical form of the strain energy function. Such an approach yielded the following polynomial strain energy density function to describe the biaxial stress-strain properties of passive myocardium:

$$W = c_1 (\lambda - 1)^2 + c_2 (\lambda - 1)^3 + c_3 (I_1 - 3) + c_4 (I_1 - 3)(\lambda - 1) + c_5 (I_1 - 3)^2 \quad (2)$$

where λ is the extension ratio along the primary fiber direction and I_1 is the first invariant, or trace, of the deformation tensor, \mathbf{C} . This form introduces transverse isotropy of myocardium, with the preferred axis along the local muscle fiber orientation. More recently, fully orthotropic constitutive laws have been proposed to reflect the 3D laminar architecture of myocardium (Figure 2). Expressed in terms of the Lagrangian

Green's strain tensor, $\mathbf{E} = \frac{1}{2}(\mathbf{C} - \mathbf{I})$, with components referred to a structurally based natural coordinate system (X_f, X_s, X_n) aligned with the local fiber, sheet, and sheet-normal axes of the underlying myocardial laminae, the so-called "Costa Law" can be written as follows:

$$W = \frac{1}{2} a (e^Q - 1); \tag{3}$$

$$Q = b_{ff} E_{ff}^2 + b_{ss} E_{ss}^2 + b_{nn} E_{nn}^2 + 2b_{fs} \left(\frac{1}{2} (E_{fs} + E_{sf})^2 \right) + 2b_{fn} \left(\frac{1}{2} (E_{fn} + E_{nf})^2 \right) + 2b_{sn} \left(\frac{1}{2} (E_{sn} + E_{ns})^2 \right) \tag{4}$$

Recent modeling studies have concluded that the constitutive relation in Eq. (4) is superior to a number of alternative formulations for modeling the mechanical behavior of isolated passive myocardium.

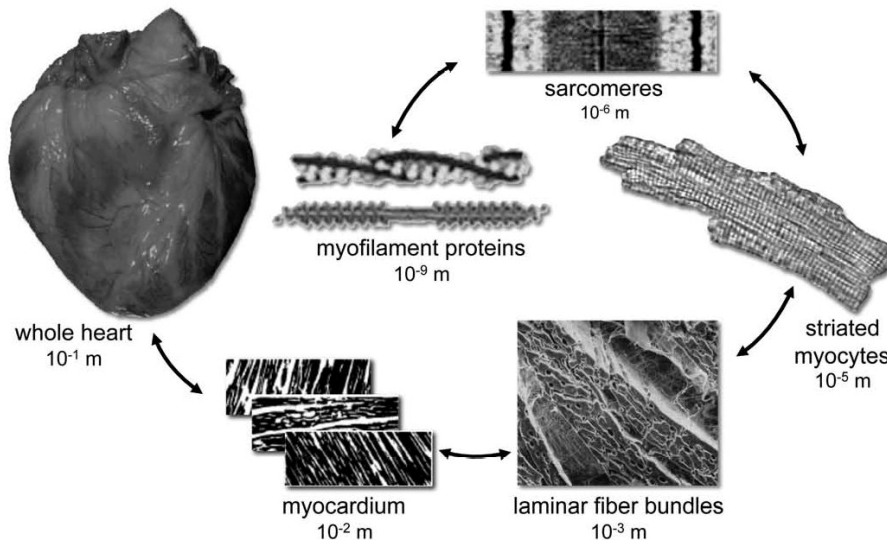


Figure 2. Multiscale structural hierarchy in the heart. Biomechanical properties of the heart depend on a number of structural parameters that span a range from molecular (filamentous or motor proteins, 1-10 nm) to subcellular (sarcomeres and other organelles, 1-2 μm) to cellular (adult mammalian myocytes, 10-100 μm) to ultracellular (laminar sheet architecture, 1 mm) to tissue (myocardium, 1 cm) to whole organ (heart, 10 cm) levels [electron microscope image of laminar fiber bundles adapted from Glass et al., 1991, with permission].

In contrast to the myocardium, vascular tissues need to be modeled as heterogeneous multilayered structures to account for mechanical differences in the intima, media, and adventitia (Figure 3). A Fung-type strain energy function (similar to the one used for the myocardium) can be used to characterize the passive mechanical response of individual layers under inflation or extension as functions of Lagrangian strain components using a cylindrical polar coordinate system aligned with the circumferential, axial, and radial axes of the artery:

$$Q = b_1 E_{\theta\theta}^2 + b_2 E_{ZZ}^2 + b_3 E_{RR}^2 + 2b_4 E_{\theta\theta} E_{ZZ} + 2b_5 E_{ZZ} E_{RR} + 2b_6 E_{RR} E_{\theta\theta} + b_7 E_{\theta Z}^2 + b_8 E_{RZ}^2 + b_9 E_{R\theta}^2 \quad (5)$$

In most cases, shear terms of Eq. (5) have been ignored, or the whole form has been replaced with a 2-D version for simpler analysis. For more detailed information on tissue-level hyperelasticity, refer to relevant texts in the Bibliography.

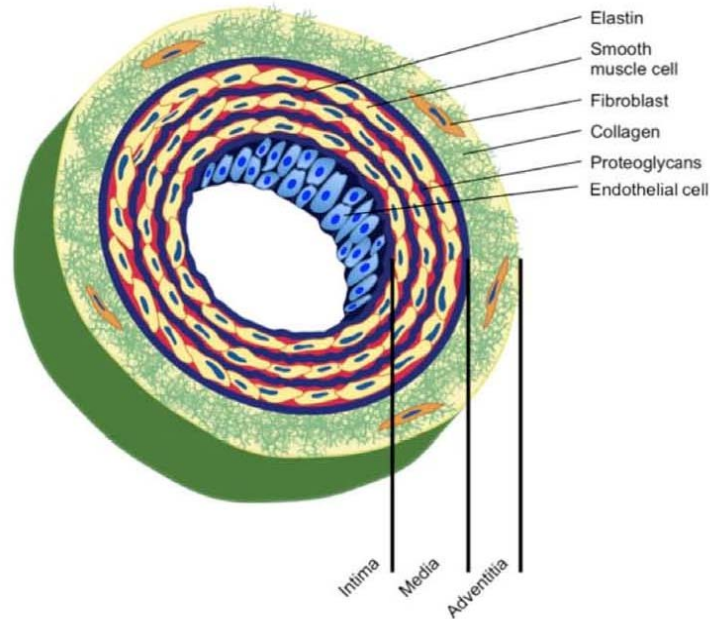


Figure 3. Schematic representation of the multilayered structure of an elastic artery (intima, media, and adventitia), showing key cellular and extracellular structural components that dominate vascular biomechanical properties.

Another approach for stress analysis involves a more detailed structural description of tissue subcomponents, in which properties of individual constituents are determined either in isolation or by observing changes in effective elasticity of whole tissue following selective enzymatic digestion. The resultant information is then used to create a mathematical model based on measured properties of the constituents, aiming to reproduce experimental data from intact tissue. While phenomenological and structural modeling methods each have advantages and drawbacks, the latter are appealing because the model parameters have a more direct physical interpretation (e.g., stiffness, concentration, or distribution of a particular filamentous protein), and the model construction readily accommodates the variety of ECM components known to affect tissue mechanics. The formulation of such a structurally based strain energy function can take the following mathematical form:

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Biographical Sketches

Evren U. Azeloglu received his B.E. in Mechanical Engineering and M.S. in Biomedical Engineering from State University of New York at Stony Brook in 2002 and 2004, respectively. He completed his Ph.D. in Biomedical Engineering from Columbia University in the City of New York in 2009. His main research interests focus on cell and tissue biomechanics, cardiovascular mechanobiology, systems biology and tissue engineering. He was awarded the Yuen-huo Hung & Chao-chin Huang Award from Columbia

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Kevin D. Costa earned B.S. and M.S. degrees in Biomedical Engineering from Boston University in 1988 and 1990, and the Ph.D. in Bioengineering from University of California, San Diego in 1996, under Professor Andrew McCulloch. Following postdoctoral fellowships at Johns Hopkins University and Washington University under Professor Frank Yin, Dr. Costa joined the Biomedical Engineering faculty at Columbia University from 1999 to 2008. In 2009 he was recruited to the Cardiovascular Research Center at the Icahn School of Medicine at Mount Sinai, where he is Associate Professor of Medicine (Cardiology), Director of Cardiovascular Cell and Tissue Engineering, and founding co-Director of the graduate training program in Design, Technology and Entrepreneurship. His research interests are in multiscale cardiovascular biomechanics, AFM elastography, and 3D cardiac tissue engineering. He was awarded the Faculty Early Career Development (CAREER) Award from the National Science Foundation, and has served on editorial boards for *Biophysical Journal*, *Molecular and Cellular Bioengineering*, and *Journal of Biomechanical Engineering*.