Introduction

This special issue of *Journal of Biomechanical Engineering* (JBME) highlights young investigators and their scientific contributions to emerging frontiers and challenges in musculoskeletal biomechanics. In particular, the work showcased in this issue addresses the following key areas for musculoskeletal biomechanics:

1. Advances in assessment of tissue function in vivo,
2. Integrating physiological processes and systems within the context of mechanical function,
3. Sophisticated assessments of tissue structure and function, and
4. Emerging uses of rodent models to study musculoskeletal systems.

By highlighting young investigators working on these critical frontiers, we describe research of emerging leaders and laboratories working in musculoskeletal biomechanics. In particular, these papers introduce new ideas, innovative solutions, and novel approaches to key challenges in musculoskeletal biomechanics. This commentary summarizes these contributions, while discussing future challenges in these topics.

**Advances in Assessment of Tissue Function In Vivo.** Taking the considerable knowledge, we have gained over the last several decades in biomechanics, and applying it in vivo represents the next critical frontier for our field. Three of our authors have made strides toward bridging this gap, and by doing so elegantly demonstrate the kind of tools and advances needed (Foltz; Pickle; Kloserhoff). First, advancing and harnessing noninvasive imaging, as the laboratory of Arin Ellingson has done by applying quantitative magnetic resonance imaging and T2 mapping in asymptomatic volunteers to predict the in vivo biomechanical and biochemical properties of the intervertebral disk (Foltz). Ellingson’s laboratory shows that by correlating in vivo measures from magnetic resonance imaging with ex vivo data, the sulfated glycosaminoglycan and residual stress throughout in the disk can be predicted. This approach provides a potential tool for diagnostics of disk health. Computational modeling and simulation will continue to be an essential tool to advance assessment of tissue function in vivo, as nicely demonstrated by the laboratory of Anne Silverman (Pickle). Silverman and her group applied musculoskeletal modeling to experimental kinematic and kinetic data and quantified the mechanical power delivered by passive and powered prostheses and validated the models with electromyographic data. The team addressed important hypotheses about prostheses design, concluding that hamstring power in amputees is larger than nonamputees, with implications for overuse injuries, and that powered prostheses reduce the hamstring contributions and thus their need to compensate for the lost ankle function. Finally, in addition to imaging and modeling, implantable sensors are a critical tool to quantify in vivo biomechanics, as shown by the laboratory of Nick Willett (Kloserhoff). Willett and his team developed and demonstrated the capabilities of an implantable strain sensor for noninvasive monitoring of axial strain across a femoral defect during functional activity. They rigorously evaluated the capabilities of the sensor and then demonstrated its function in a rodent bone defect model during ambulation. This technology shows tremendous promise for quantifying in vivo tissue function over the course of bone healing and remodeling.

These diverse tools developed by the young investigators demonstrate ways in which the field can harness our knowledge gained over the last several decades of tissue mechanics and apply it to in vivo subjects and patients. Advancement of in vivo assessments of mechanical function will require continuing to develop imaging modalities and implantable sensors, which will require a sophisticated bridging of mechanics, imaging, and sensor development in the biological environment. These in vivo measurements and trends, by matching boundary conditions and preloads, will provide the keystone to link in vivo measures with the extensive ex vivo studies in the literature. Of course, continued efforts and development will be required to rigorously validate these in vivo assessments and models. Finally, a key application of assessing in vivo mechanics is the ability to evaluate the integration of complex mechanical structures across tissue interfaces and address physiological function and how the musculoskeletal tissues interact and affect each other and the milieu in which they exist.

**Integrating Physiological Processes and Systems.** In vivo biomechanical assessment described previously, including clinical and translational studies and animal models, in vitro tissue and cell culture models, and in silico computational models all provide a context to integrate physiological processes and systems of musculoskeletal tissue in order to advance beyond isolated tissue assessment. Three of our young investigators in this issue assess a musculoskeletal system within the context of its physiological system (Pickle; Rahman; Bakker), proving excellent examples for this critical frontier in our field. The lab of Anne Silverman, as described in the Advances in Assessment of Tissue Function In Vivo section, integrated active and passive muscles and prostheses with and without ankle power to study sloped walking in amputees and nonamputees (Pickle). Her simulation considered the entire system’s function and implications for fatigue, overuse, muscle weakness, and socket instability. At the next scale down, the review article from the lab of Marianna Kersh considered the role of all of the tissue structures working together in order to address the secondary effects of rotator cuff tears for the entire shoulder joint and function, including the role of joint cartilage, bone, ligaments, as well and remaining tendons (Rahman). Her group’s study addresses the impact of the timing of the injury and secondary anatomic system consequences that are critical to treatment approaches and algorithms. Finally, at the next scale down, the laboratory of Sherry Liu quantified the load carried by trabecular bone and the bone alterations during pregnancy, lactation, and postweaning recovery (Bakker). Liu’s study is an elegant integration of key life-cycle events and their biological contributions toward key musculoskeletal functions. Recent National Institutes of Health (NIH) emphasis on considering gender effects in...
research is supported by studies such as Liu’s that address reproductive impact on musculoskeletal structure and function.

An integrated approach to address musculoskeletal systems within the human body system, where these tissues have frequently been studied in depth but in isolation, is thus another critical frontier for the field. Advances integrating physiological processes and systems with musculoskeletal research will require stretching our interdisciplinary collaborations across the fields of biology, immunology, neurology, biochemistry, physiology, and more. The influence of a myriad of life-cycle events such as reproduction, aging, injury, cancer, and the mechanics and mechanotransduction of the cell in the complex inhomogeneous and three-dimensional tissue context all remain key open questions for future research and challenging technological developments.

**Sophisticated Assessments of Tissue Structure and Function.**

The evaluation of structure–function relationships has been a focus of musculoskeletal biomechanics for decades. These relationships are critical to understanding how the musculoskeletal system supports movement, dissipates load, and allows for energetically efficient movements. In particular, understanding the structure and function of musculoskeletal tissues is critical for the design of replacements (either synthetic or biologic) and for understanding how musculoskeletal structures fail during aging and injury. This issue highlights three novel studies in the failure mechanics of the annulus fibrosus and tendon (Werbner; Locke; Eekhoff). Work by Grace O’Connell’s laboratory examines the effects of notched geometries in the annulus fibrosus both experimentally and via finite element model (Werbner). This work features the development and validation of novel, reliable experimental methods to study failure properties. Megan Killian’s laboratory also investigated the effects of localized defects, but at the interface of tendon and bone (Locke). Using novel methods to track tissue scale strain, strain concentrations at the attachment were warped by the defect—critical information for determining mechanisms for how this region resists failure. Spencer Lake’s group evaluated the contribution of elastin to structure and function in tendons (Eekhoff). This work extends our understanding of failure mechanics across multiple scales, down to tissue level defects in extracellular matrix. These sophisticated structure–function studies by young investigators highlight how our understanding of tissue mechanics has advanced from the classic work of the last several decades. Today, mechanical modeling of tissue anisotropy, nonlinearity, and viscoelasticity is being extended to the measurement and modeling of failure mechanisms, rather than bulk tissue mechanics. These experiments are critical for understanding tissue growth, remodeling, and repair. Nonetheless, developing robust experiments and models for failure mechanics remains a significant challenge given the complexity of biological tissues. Clearly, new opportunities to study the effects of micro and macroscale defects exist in biological tissues. Understanding how stress and strain fields are altered in the presence of these defects and how micro- and nanoscale mechanics translate to the cellular context will be an important challenge for addressing mechanical failure processes and the role of mechanics on tissue growth and remodeling in musculoskeletal tissues for years to come.

**Emerging Use of Rodent Models to Study Musculoskeletal Systems.** While rodents and humans have distinct differences, rodent models allow biological and environmental variables to be controlled in a manner that is not possible in humans. As such, rodent models provide an opportunity to study fundamental relationships in musculoskeletal biomechanics, allowing sophisticated insights and hypotheses to be generated for human biomechanics. Half of the studies in this special issue used rodent models to explore tissue function and dysfunction (Klosterhoff; Bakker; Eekhoff; Locke), and a key to the success of these studies is the development of sophisticated mechanical and structural assessments that allow for accurate assessment of mechanics at the rodent scale. Work by Nick Willett’s group investigated the role of the mechanical environment for dynamic bone healing and remodeling, demonstrating that a wireless implantable sensor can measure axial strain noninvasively and across time (Klosterhoff). Sherry Liu’s laboratory investigated how load is carried by trabecular bone during pregnancy, lactation, and post-weaning recovery, integrating micro computed tomography scans with microstructural and microfinitely element analysis (Bakker). Spencer Lake’s laboratory investigated the effects of elastin on tendon mechanics by leveraging mouse models of haploinsufficiency, combining traditional tissue mechanics with quantitative microscopy of fiber size and orientation in a genetic mouse model (Eekhoff). Finally, Megan Killian’s laboratory investigated the mechanics of the rat infraspinatus tendon-to-bone attachment, using advanced methods to track tissue level strain near a mechanical defect, preparing the landscape for future in vivo studies of the biological response to injury (Locke). Each of these studies demonstrates the use of robust mechanical modeling in the rodent model, with the goal of understanding fundamental mechanical and physiological principles in musculoskeletal tissues in a preclinical setting.

Understanding how mechanical principles scale from the rodent to the humans remains a challenge, not just with the scales of geometry but also with changes in physiological systems. Nonetheless, the findings from rodent work are invaluable for their ability to apply treatments, assess in vivo tissue function, and integrate physiological processes. Work from rodent models should be viewed as hypothesis generating for larger scale organisms, allowing fundamental relationships in musculoskeletal biomechanics to be investigated with a level of biologic and environmental control that is not possible in humans. Moreover, rodents have been and will remain to be a critical preclinical model of musculoskeletal systems and disorders; thus, understanding how musculoskeletal tissue mechanics scale from rodents to humans will remain a critical step for the development of new musculoskeletal therapies.

**Funding and Outlook.**

As noted in the Guest Editorial by Holmes and Wagensiehl in last year’s JBME special issue: Spotlight on the Future of Cardiovascular Engineering: Frontiers and Challenges in Cardiovascular Biomechanics, funding of new faculty in biomechanics continues to be a challenge for the field and the funding agencies. This representative microcosm of young investigators has primarily relied on faculty development awards (NIH K01, K12, K25 and VA Career Development Awards), National Science Foundation graduate student fellowships, and foundation grants as the critical funding mechanisms to move beyond institutional funding. In addition, some faculty in this issue are funded by NIH R03, NIH R21, and National Science Foundation grants, but in small numbers. Nonetheless, the situation is not without hope, as at the time of this writing, the two most senior young faculty in this issue have very recently been awarded NIH R01 single investigator grants. In order to maintain new ideas and innovative solutions for the translational and basic science questions plaguing human health, including musculoskeletal function, it is contingent upon the academic and governmental leadership to ensure that we provide opportunities and pathways for outstanding young faculty to thrive in the research and the funding infrastructures available to them. This special issue, highlighting the work of eight outstanding young faculty in musculoskeletal biomechanics, demonstrates the strengths in our young investigators and the emerging, vibrant, and important research impact these and others in the field promise to have.

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