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Integrated Multiscale Biomaterials Experiment and Modeling

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Abstract

The integration of modeling and experimentation is an integral component of all engineering design. Developing the technologies to achieve this represents a critical challenge in biomaterials because of the hierarchical structures that comprise them and the spectra of timescales upon which they operate. Progress in integrating modeling and experiment in biomaterials represents progress towards harnessing them for engineering application. We present here a summary of the state of the art, and outlooks for the field as a whole.

Introduction

The use of metals in structural engineering underwent a transformation in the 20th century, in which empirical design laws were replaced by mathematical models that arose from efforts that integrate experiment and modeling. The outcomes of this transformation were both the set of phenomenological constitutive models that can be fit to simple testing data and used for nearly all engineering design, and a set of tools that can be used for design in the cases where these phenomenological tools fail. Although this phenomenology looks on the surface to be similar to the empirical laws used at the beginning of the 20th century, it is fundamentally different: the careful, quantitative, modeling-based experiments that validate these phenomenological models and establish the underlying deformation mechanisms make these predictive frameworks safe and effective.

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The study of biomaterials has not yet achieved this transformation. However, a concerted, community-wide effort is underway to bring the field to this level. At the core of the challenge is the hierarchical and often fibrous nature of biomaterials, and the vexing contributions of living cells. Accounting for the ways that information travels up and down these hierarchical structures is an ongoing challenge, and our still emerging understanding of how cells react to and adapt this information confounds the problem. From the perspective of hierarchies, the structures and functions of biomaterials are related in ways that often cannot be predicted by considering only a single length scale or time scale. Length scales and time scales that are hidden in one loading scenario can arise with new mechanical, electrophysiological, or biochemical loading, and then vanish. Validating models at these hidden length and time scales poses a widespread challenge because these frequently remain hidden from current technologies for experimental quantification, and because separating contributions of cells and extracellular matrix (ECM) is a persistent challenge.

The working group on Integrated Multiscale Biomaterials Experiment and Modeling has been formed to address these challenges. This working group resides under the umbrella of the Multiscale Modeling Consortium that is part of the Interagency Modeling and Analysis Group. This special issue brings together a collection of papers that represents the efforts of this working group, and that highlights successes, challenges, and opportunities in efforts to develop modeling capacity for a range of important biomaterials. We believe that this collection represents the state of the art in this important endeavor, and highlights critical directions for the field as a whole. This issue collects articles that encapsulate the state of the art in four key areas: hierarchical characterization of musculoskeletal tissues; design of biomaterial scaffolds; cross-scale cell-material interactions; and cell biophysics and mechanobiology. This specific journal was chosen for this compilation because the journal itself provides a snapshot of the field. As we point out, nearly every paper from the past two years that has appeared in this journal represents an effort to quantify hierarchical structure in a way that can be linked to modeling: the effort is essential to the development of the field of biomaterials as a whole, and to the development of the related field engineering mechanobiology.

Hierarchical characterization of musculoskeletal tissues

The first area of focus is musculoskeletal tissues, one of the most heavily studied classes of animal biomaterials, especially from the perspective of biomechanics. Even with these materials, the integration of experiment and modeling is far from complete, and the ability to predict either passive or active functioning of these tissues is limited. The musculoskeletal tissues that comprise the human body are inherently multiscale in nature. The successes and limitations of models of these tissues is perhaps best encapsulated by state of the art efforts to synthesize bone and bone-like materials. The work of the Barber and Wagoner-Johnson groups presented here represent now the state of the art incorporates roles for multiscale effects and characterization in the synthesis of biomimetic and healing-promoting scaffolds.[1,2] The ability to synthesize scaffolds that guide cells to produce bone-like material is advanced and impressive, but the guiding principles for further optimization are still emerging. One of the areas where further development is needed is characterization and replication of the mechanisms that these tissues use to resist injury, failure, and inelastic

deformation. A key component of these mechanisms is energy absorption. The work of the Gupta group reveals that, as the nonlinearity of antler tissue becomes engaged, the specific staggering of lower fibrils that exist at the nano- to micro-scale and the way that they interact at that scale determine the degree of hysteretic energy absorption of these materials.[3] Such cross-scale interactions are difficult to assess experimentally, and integrated experiment and modeling is therefore crucial for dissecting these mechanisms. Understanding these mechanisms in bone is pivotal to dissecting and eventually alleviating critical pathologies such as osteoporosis and the brittle bone pathology osteogenesis imperfecta. The Shefelbine group, leaders in the biophysical characterization of osteogenesis imperfecta, review the state of the art and report a recent breakthrough from their group in applying high energy microscopy to characterize the structural and chemical nanoscale factors the that underlie these pathologies.[4]

From the perspective of muscle, a critical challenge is identifying how the well-understood mechanisms of local actuation, mediated by actomyosin cross-bridging, translate up to muscle force and body motion. The state of the art models at the extremes of cross-bridging behavior and limb motion are well-validated, but linking these scales poses a still unmet challenge. As described in the cellular biophysics and mechanobiology section of this article, the challenge of assembling whole-cell models from our models of protein biophysics is still unmet. Rising up over hierarchical scales, the load transfer and distribution of straining over muscle poses a key challenge. The Neu and Goergen groups encapsulate the state of the art in this field, and report here a recent set of results that substantially advance our understanding of how strain is transferred across hierarchies in skeletal muscle.[5]

Although the cross-scale study of musculoskeletal tissues and their pathologies is reaching a state of maturity, the study of the interfaces between them is still in its early stages. This issue contains contributions that highlight challenges and opportunities in two such tissue systems. The first is the tendon to bone enthesis site, a critical and frequent location of injury. Healing here is poor, and even surgical repair fails frequently. Identification and understanding of the factors that lead to reduced structural integrity with age is a critical need, and is the focus of multiscale analysis reported by the Lu group[6]. The critical analysis of often ineffective repair techniques is a pressing need, and the Killian group undertakes a study of interface repair strategies in the context of multiscale structure-function relations in their contribution.[7] The second is the cartilaginous tissues that resides between healthy bone-to-bone connections, balancing the tensile forces afforded by ligaments with compressive damping and resistance. Although constitutive models for cartilage represent one of the most advanced set of biomaterials models, the Chahine group reports that critical effects of inflammation on multiscale biomechanical properties remain poorly characterized, and report state of the art observations.[8] The ability to understand these mechanisms and then design tissue engineered replacement tissues or palliatives that thwart these effects is a promising direction for the future. As reported by the O'Connell group, a future in which bioprinted cartilage is readily available might not be too far away.[9]

A final aspect considered in this issue is quantification of biophysical properties across scales. This is a challenge not only in musculoskeletal tissues, but also across all tissue systems. The canonical example that we focus on in this issue is bioheat transfer. Unlocking

the thermal properties and distribution of thermal energy across scales and tissue components is essential for a broad range of thermal ablation therapies and for cryopreservation of tissues and organs for transplantation. As reviewed by Natesan and Bischof,[10] thermal conductivity and calorimetric measurements are particularly challenging in anisotropic and layered tissues. This challenge is complicated by the hierarchical nature of the tissues, and by uncertainties in the properties of the interfaces between cells and ECM. The review more broadly encapsulates the challenge across all areas of physics of making measurements to evaluate and calibrate models when critical length-scales, timescales, and interfaces are hidden from view, and highlights how the challenges discussed here with characterizing musculoskeletal tissues are in fact representative of challenges across tissue characterization in general.

Design of biomaterial scaffolds

The engineering of biological tissues typically begins with the design and construction of a scaffold material that provides cells with appropriate mechanical, steric, biochemical, and electrical cues. The most prevalent building block in tissue ECM is the structural protein collagen, along with a series of non-collagenous proteins including elastin and with, in the case of bone, hydroxylapatite mineral. Understanding and replicating the properties of these tissues is the focus of this section. The section begins with the work of the Zhang group on how collagen matrices behave mechanically,[11] and work from Lee and co-workers on how collagen matrices in the cornea of the eye self-assemble into a well-organized and transparent tissue.[12] The question of how non-collagenous proteins that comprise a critical component of collagenous tissues are structured and self-assemble is a key tool needed for biomaterials design, and the work of the Weiss group on controlling tropoelastin structure and assembly represents the current state of the art in this field.[13] Even the simplest aspects of multi-body interactions such as frictional sliding are challenging to understand and quantify if they occur over hierarchies, as described by the Pugno group.[14] Understanding what happens when mineral interacts with collagen is further challenging because of difficulties in simultaneous imaging of mineral and protein phases. The Fratzl group reports a new and highly promising set of tools for characterizing these interactions under well-defined conditions of mechanical load.[15]

While these efforts to understand fundamental mechanisms of deformation and failure progress, advances in scaffold design are emerging rapidly based upon this progress. Although the full hierarchical set of interactions that govern the behavior of collagenous tissues has not been fully elucidated, the basic collagenous units are known, and the Fu group has recently developed a modular collagen-tube system for modular tissue engineering that replicates many of these key aspects of collagenous tissues.[16] The ability of the Chao group to provide nanofibrous scaffolds whose crimped character replicates that of collagenous tissues represents a mechanics-based approach to providing cells with physiological strain transfer mechanisms.[17] The aforementioned work of the Weiss group similarly presents a remarkable toolkit for tropoelastin design.[13]

The range of biomaterials available for providing cells with appropriate microenvironmental cues or appropriate structural support is enormous, as is the range of techniques available to

synthesize these materials and the associated scaffolds. Our focus here is a handful of methods for which accurate and integrated multiscale quantification and design can be made. The shining example of this is the silk-based and silk-elastic-like polymeric system of the Kaplan and Buehler groups.[18,19] These material systems have simple repeating units that can be synthesized with remarkable precision and whose interactions, self-assembly, and subsequent scaffold-level mechanics can be predicted. The material systems are highly versatile, and can be modified to express a range of multiphysical, cross-scale properties, such as the photocatalytic system developed by the Xu group and reported in this issue.[20] The ability to predict the bounded properties of layered elastomeric fibrous scaffolds, as described by the Sacks group, makes electrospun systems appealing for structural tissue engineering applications such as aortic valve replacements.[21] The Mofrad group's model of calcified aortic valve disease progression[22] provides interesting opportunities for designing disease resistant aortic valve replacements. More broadly, as described by the He group[23], these and related scaffolds are enabling a transformation in regenerative medicine.

Cell biophysics and the mechanobiology

How do cells make decisions, and how can these decisions be influenced? These are central questions to the field of engineering mechanobiology, and answering them necessarily requires integrated experiment and modeling of biological materials and systems. This is a field in which modeling is well ahead of our ability to test models experimentally. Spector and Grayson[24] encapsulate this wide-ranging field in an elegant review of modeling approaches to understanding stem cell fate decision making. The Mofrad group[25] describe how the molecular components involved with the associated mechanotransduction can be accessed and modeled using systems biomechanics. The Vernerey group presents a multiscale structural approach to understanding and predicting the responses of cells to mechanical loads.[26]

However, the basic physical phenomena that underlie cellular mechanobiology and biophysical function are still not fully known, with new mechanisms being revealed regularly. The previously unsuspected role of actin cytoskeleton-mediated constriction of membrane organelles is detailed here by Curchoe and Manor,[27] revealing a fascinating role of endoplasmic reticulum scaffolding. Articles in this issue reveal new physics underlying mechanosensitive lamellipodium dynamics from the Ji group,[28] new insights into neutrophil surface protrusion and tether extraction form the Shao group,[29] and the first multiscale insight into how cell mechanics relates to craniosynostosis from the Sniadecki group.[30] New insight is continuously emerging in well-studied fields such as exocytosis, including an article from the Gao group providing insight into how adhesive elastic escape lipid vesicles.[31]

Mechanics is not only a driving force in cellular function, but also an indicator of a cell's health and history. Harnessing this for diagnosis and environmental monitoring requires careful measurement combined with multiscale analysis. One of the most successful and promising areas in this regard is the use of cell cytometry to extract cell mechanical properties from the way that cells deform in a constricted microfluidic chamber. Although these measurements have been available for some time, it is only more recently that the

numerical simulation of these processes has enabled real-time analysis of these assays. Work published in this issue by the Guck group is a major step forward in this regard.[32] The ways that cells remember the history of their microenvironments presents a possible pathway towards decoding the history of an ecosystem via probing of mechanical properties. The Feng group has presented initial data suggesting that it might be possible to track the history of environmental pH in an ecosystem by through nano-indentation of cells of the fungus *Aspergillus niger* that have been harvested from that ecosystem.[33] Taken together, these contributions show a rise in the commercial and clinical importance of the fields of biomechanics and mechanobiology that is enabled through careful integration of modeling and experiment.

Mechanobiology of cell-microenvironment interactions

An important aspect of cellular mechanobiology is the ways that memory is stored both within cells and within their microenvironments affect subsequent cell and tissue function. The classic work of Engler, Discher and colleagues showing differential gene expression in mesenchymal stem cells based upon the stiffness of the substratum upon which they are cultured has spawned a wide-ranging set of research emphasizing how the fate and function of living cells is shaped by the mechanical, electrical, thermal, and electrical fields around them. Dissecting the multiscale features of the cell microenvironment that result in long-term memory of stored in cells or ECM is important to understanding a range of developmental and healing phenomena and a range of pathologies of remodeling. Understanding how cells manipulate their environment and are simultaneously controlled by it is similarly critical. Multiscale modeling integrated with experiment plays a central role in both pursuits.

A question that predates mechanobiology is how does the chemical microenvironment affect cell function? As highlighted in a paper from the Winkelstein group, this question is the foundation of the entire field of drug therapy and discovery. This field has proceeded almost entirely by experiment on living systems and numerical experiments simulating protein docking. However, the Winkelstein group is pioneering methods for identifying pathways to neuronal regulation through careful multiscale analysis, an approach that has much potential.[34]

The study of how cells interact with their environment is deeply connected to the development of hierarchical scaffolds and of textured, structures, and tailored substrata. A contribution from the Pathak group highlights this, showing how the nanoscale matrix topography of a substratum affects cell motility, a strong function of adhesion disposition, actin organization, and cell shape.[35] In addition, the temporal presentation of cellular cues appears to be highly important. A contribution from the Chun lab shows that fibroblast dynamics can be a strong function of the proteins decorating the substratum upon which they are cultured.[36]

A focus of this area is therefore how one can replicate a realistic three dimensional cell environment, and how one can manipulate this to represent or produce models of diseased states. As described in a contribution from the Morss Clyne group, an important component

of this environment can be neighboring cells.[37] A contribution from the Reinhart King group highlights the strong effect of matrix stiffness heterogeneity on endothelial cell response, and presents a novel protocol for achieving this heterogeneity.[38] In the case of artificial cardiac tissues, idealized systems developed to understand cell biophysics focus on roles of electrical and mechanical stimulation in producing an environment sufficient to cause cells, often derived from induced pluripotent stem cells, to develop an adult phenotype. Here, two levels of integrated modeling and experiment are required. At one level, matrix materials must present the opportunity for cells to connect to one another electrically to develop mature, synchronized beating patterns, as described by a contribution from the Du group.[39] At the next level, cell-cell interactions and percolation of cardiomyocytes is needed for effective contraction of an artificial cardiac tissue. As shown in a contribution from the Genin group on the effects of fibrotic remodeling analogous to fibrotic cardiomyopahty, the loss of tissue-level electrical percolation appears to be hastened by multiscale effects of myofibrobalsts on conduction.[40] An additional case where electrical propagation is vital is in the sensing of noxious events in the cell microenvironment. Physiologically, these are detected by ion channels on nociceptor cells that open in response to mechanical, electrical, and chemical factors. The understanding of how these coupled effects produce pain has arisen largely from integrated modeling and experiment, as described in an interesting contribution from the Xu group.[41]

Outlook and perspectives

The field of biomaterials modeling has, like the study of metals, arisen from models of interesting phenomena observed in phenomenological experimentation. Just as with metals in the last century, a tremendous effort is underway to develop a fundamental understanding and predictive capacity for biomaterials through integrated multiscale modeling and experiment. The ability to design from first principles is already available in a few biomaterials systems including silk scaffolds, but for most biomaterials systems and for manipulation of cells through mechanobiological cues, this capacity is still developing. A pressing need exists for design of integrated modeling and experimentation. Efforts such as the Interagency Modeling and Analysis Group are critical as the effort to put the design and manipulation of hierarchical biosystems on solid theoretical footings develops, and to harness emerging fields such as mechanobiology as engineering tools.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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