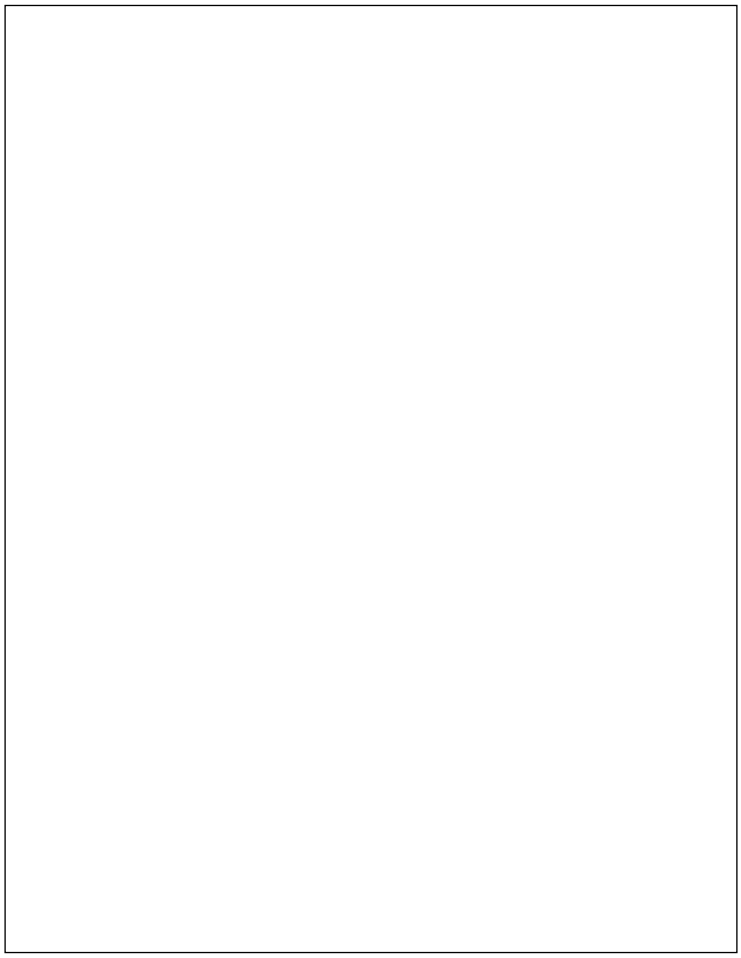

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Advances toward multiscale computational models of cartilage mechanics and mechanobiology

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Abstract

Across spatial scales, biological systems exhibit exquisite hierarchy in architecture and function, leading to complex, observable phenomena. In the articular cartilage of our joints, the organization of molecule- to tissue-level structures governs the interplay of macromolecules and determines the biological activity of embedded cells (chondrocytes), motivating the development of new computational models to provide insight and understanding. We review recent work on multiscale modeling of cartilage, with an emphasis on finite element based methods, and emerging experimental approaches that enable calibration and validation. Through new nested modeling approaches, we are now able to dissect interactions of constituent macromolecules, and we envision the ability to soon define the mechanical microenvironment experienced by and within single cells that guide biological activity.

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Multiscale, Modeling, Molecular, Cellular, Cartilage, Joint.

Introduction

Articular cartilage and osteoarthritis

Structural heterogeneity, a hallmark of biological systems, spans from tissue to molecular scales and is integral to the function of cartilage. Articular cartilage has a layered architecture arising from the heterogeneous organization of its constituents, which include heterogeneously distributed fluid and electrolytes, collagen fibers, proteoglycans, and chondrocytes [1]. The remarkable macromechanics of cartilage derive from this heterogeneity among layers and from the complex micromechanics of interacting constituents within each layer [2,3].

Mechanical stimuli elicit responses in cartilage across length scales. The heterogeneous solid phase encompasses a polar proteoglycan mesh and a collagen fiber network (extracellular matrix or ECM), which form distinct macroscopic layers (superficial, middle, and deep) and which contribute to mechanical stiffness and permeation of fluid. Cartilage cells (chondrocytes) occupy location-dependent subpopulations with distinct morphologies, gene-expression profiles, and subcellular components, all subject to significant deformation (strain). Strain and stress, hallmark biophysical parameters in mechanobiology, influence biochemical pathways at multiple scales—ECM, cell, and nucleus—through a cascade of mechanotransduction mechanisms [4].

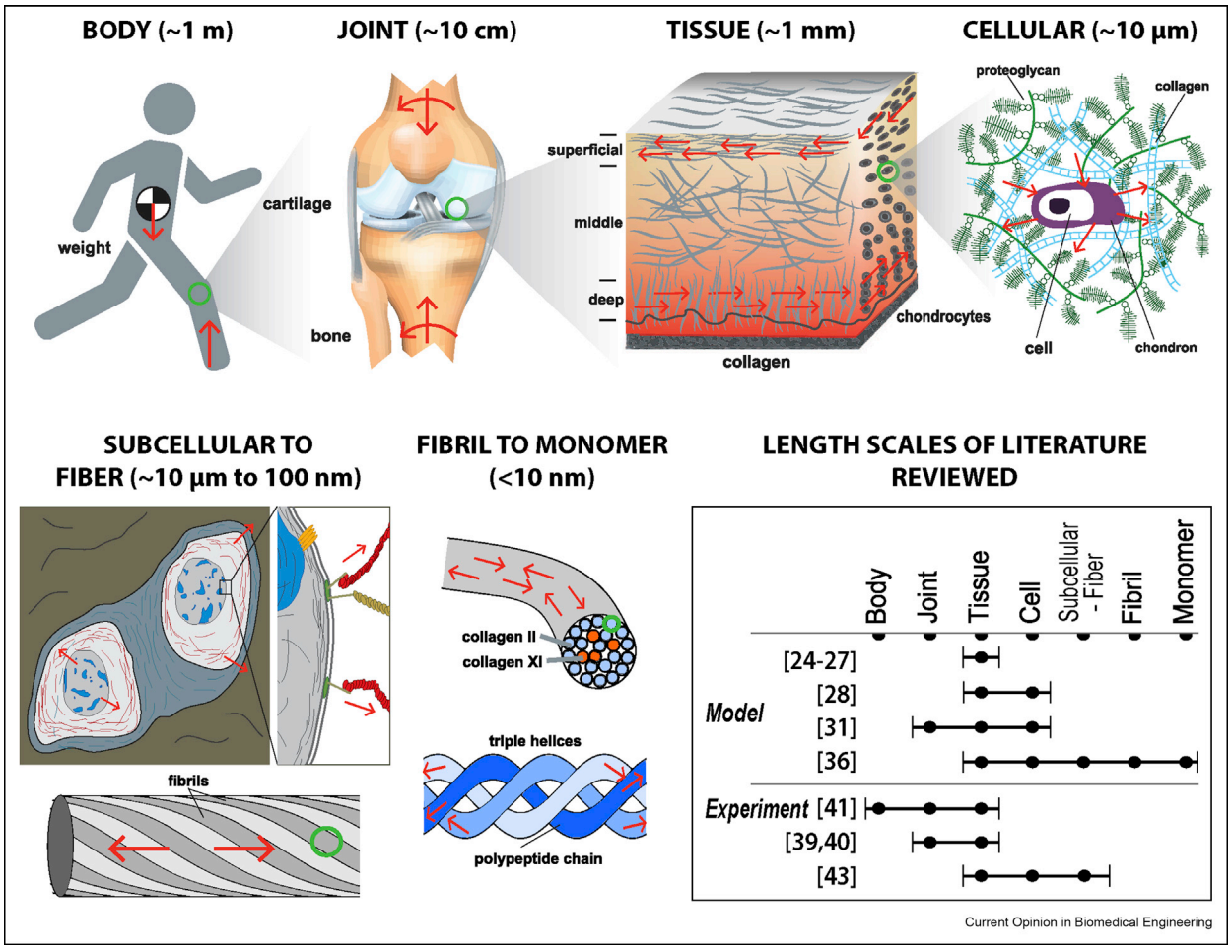
Mechanical stimuli also contribute to osteoarthritis (OA), a complex disease with a multifactorial etiology [5–9] that poses severe socioeconomic burden [6,10]. One hallmark of the disease is the decline of the mechanical integrity of cartilage that ultimately leads to pain, disability, and total joint arthroplasty. A full mechanistic understanding of OA requires clarifying all pathological changes across all scales [11], and every advance in our understanding promises potential targets for new treatments and therapies.

Structural heterogeneity motivates biomechanical modeling across scales

Multiscale models naturally mirror the architecture of cartilage tissue, properties of which derive from hierarchical interactions within embedded microstructures. Here, we apply the term “multiscale” to physiological models including more than one biological scale; multiscale models of cartilage, for example, link organism, organ/joint, cartilage, cell/chondrocyte, molecule, and even gene (Figure 1). Typically, finite-element (FE) analysis applies at the macroscale (tissue) and couples with microscale models (fiber networks) that serve as material models [12–16].

The advance of multiscale biomechanical models requires novel experimental data to inform tissue properties and to enable new constitutive formulations and means of calibration. Indeed, multiscale experiments can quantify mechanical and biological properties of

Figure 1



Computational models and experiments provide complementary information that characterize the mechanics of biological systems at multiple length scales. Within the musculoskeletal system of the knee, body forces load the joints, which distribute forces according to their geometries and properties of tissues. Tissue forces transfer to chondrocytes, the cells in cartilage, via a complex interplay of fluid, electrolytes, and macromolecules like collagen fibers and proteoglycans within three subtissue zones. Within the extracellular matrix, for example, collagen fibers sustain tensile forces that transfer to fibrils and monomers (elements adapted from Ref. [49]).

tissues, and, for example, imaging methods can estimate tissue structure and even strains. Using these data to inform computational models, however, enables testing and/or prediction otherwise difficult or impossible via experimental methods (e.g. intratissue stresses in human joints during daily activities).

Multiscale modeling is suited to capture heterogeneity of not only length scales but also temporal scales, for example, from equilibrium and injury to growth and aging. The ability to model the interplay of different spatiotemporal scales allows researchers to clarify distinct mechanisms of signaling (e.g. strain transfer to subcellular domains). Most multiscale mathematical models begin with relatively simple models that preserve enough biology to be meaningful, without introducing unnecessary or burdensome complexity. The principles of such models can apply to many biological systems, making multiscale modeling a conducive, powerful, and broadly applicable tool [17].

Need for multiscale models of articular cartilage

Computational simulations provide tools to identify multiscale interactions that advance understanding of cartilage function in health and disease, with potential for individual patient specificity [18]. The interdependency of mechanobiological responses across scales and variability among individuals increase the complexity and challenge of establishing the clear, mechanistic understanding needed to drive clinical interventions. Integrative multiscale modeling offers the descriptive and predictive potential to meet these challenges [19].

Benefits notwithstanding, the literature is rich with examples of the limitations of applying continuum

mechanics to tissues [20]. An obvious constraint is our current understanding of function within each length scale of interest. As our knowledge of biomechanics of cartilage at individual scales advances, so will our capacity to adapt multiscale modeling strategies from traditional disciplines.

Emerging computational models of cartilage that span length scales can overcome limitations inherent to experiment and observation, offering enormous potential to generate knowledge otherwise beyond reach. Multiscale models can test hypotheses in poorly understood or unknown systems, for instance, or enable *in silico* experiments where *in vitro* or *in vivo* experiments are impossible or insufficient [17]. Despite the benefits and potential of such approaches, very few studies propose, develop, or apply multiscale computational models of cartilage.

Recent computational models and experimental methods relevant to cartilage

Computational models of cartilage

The complex properties of cartilage that determine function also complicate computational models of the tissue. Cartilage is not only mechanically nonlinear but also multiphasic, anisotropic, viscoelastic, and spatially heterogeneous [21–23]. To capture these effects, we and others proposed image-driven constitutive modeling to exploit image-derived data and improve predictions of the intratissue responses of cartilage [24–26]. Some of the embedded assumptions, for example, isotropic ECM and fiber-based permeability, may be reasonable even at smaller scales, but a coupled microscale model of the collagen network would enable predictions of more phenomena. A recently proposed constitutive model for engineered cartilage assumes a linear biphasic mixture, among other classical assumptions, to link solute transport and uptake, cell proliferation, ECM synthesis, and remodeling of mechanical properties resulting from mechanical loading [27]. To simulate conditions *in vivo* more generally, the model would benefit from extension to finite-strain theory.

The macroscale mechanics of cartilage affect model predictions at the single-cell level. Cell-level responses of single and anatomically based 11-cell biphasic FE models embedded in an ECM highlight significant differences in volume-averaged cell mechanics at peak response during a stress relaxation test modeled with finite-strain theory [28]. The differences between single and 11-cell representations, while negligible at equilibrium, stem from heterogeneous distributions in the displacement and fluid pressure within the ECM [28]. Such interscale relationships demonstrate the significance of multiscale modeling.

Multiscale models of soft tissues including cartilage

With so little published in the last 5 years on multiscale modeling of cartilage, we include multiscale models and studies of soft tissues with relevance to cartilage. Three reviews of multiscale computational biomechanics reveal distinct trends, and several studies indicate potential directions of advance for cartilage modeling.

The first review bins models according to order of intent, starting with causal confirmation (CC), then predictive accuracy (PA), and at the highest order of intent, determination of effect (DoE models predict propagation of effects across radically different scales). Overwhelmingly, most musculoskeletal and cardiovascular models fall under CC, and the review opines that to approach higher-level intent, advances should address open problems with stricter demands on model validation [29]. Indeed, multiscale modeling is a huge concept, and intent-based categorization provides a constructive lens to compare relative and contributive value. Models with CC intent—the vast majority—identify what might be important to research. To move this field forward, we must clarify questions of how and why effects propagate across scales with higher-level PA and DoE models, respectively.

The second review curates models of tendon mechanics across scales, with obvious application to cartilage, given reasonably analogous networks of collagen support mechanical load in both types of tissue [30]. Mechanical models of tendon tissue, fibers, or fibrils are generally phenomenological (contain parameters that lack clear physical interpretation) or microstructural (combine behaviors of different components) and can examine mechanical responses across scales. Very few studies, however, focus on multiscale load transfer, which remains one of the biggest challenges in multiscale modeling generally [30]. To systematically bridge scales would provide invaluable data to develop multiscale models, and considering the proliferation of well-developed, coupled two-scale studies, this aim seems imminent.

The third review highlights multiscale models based on Mixture Theory, the multiphase properties of which are ideal for cartilage [17]. Listing several theoretical approaches and examples, the authors note that all face challenges in light of the complexity of biological systems. Nonetheless, multiscale approaches based on Mixture Theory present strong opportunities to bridge spatial and temporal scales in modeling soft tissues and may enable more predictive (PA) models.

The complexity of biological systems and concomitant peril of computational expense make simplifying multiscale models without loss of biological or mechanical fidelity paramount. Recent studies demonstrate the efficacy of two such approaches. The first, investigating how chondrocytes regulate bone formation on the basis of load, simplifies the microstructure, and assumes chondrocytes attach to surrounding matrix continuously for the multiscale FE model [31]. The results identified a correlation between hydrostatic stress at the cellular level in growth-plate cartilage, and zonal chondrocyte morphology, and function over time. Although simplified, the model captures the depth-dependent heterogeneity crucial for modeling cartilage. Similarly, to simulate molecular processes within cellular environments, the second validated a simplifying technique that incorporates macromolecules on the basis of coarse-grained representation within an aqueous solvent (mesoscopic description), as well as mutual exchange of forces [32]. This technique could also apply to models of chondrocytes and increase efficiency of cartilage models.

Recent models of biological tissues provide other modeling concepts applicable to cartilage. A study of soft and hard tissues (cortical veins and bones, respectively) applied asymptotic homogenization techniques on the basis of microscale representative volume elements [33], demonstrating the efficacy of linking local constituents to macroscopic behaviors and the power of multiscale models to clarify mechanical—biological couplings. Degeneration of cartilage in OA and rupture of collagen fibers during microcracking [34,35] represent two challenges with rich translational potential where multiscale models could synthesize experimental data toward new, clinically relevant knowledge. To realistically advance toward predicting long-term patient-specific evolutions, however, we must improve the accuracy of such models [33].

Another recent model demonstrates elegant use of necessary and sufficient assumptions. Using tendon as a representative soft collagenous tissue, the authors developed a multiscale model of localization of stress—strain at the microscale. Applying a multistep homogenization technique from nanoscale (intermolecular cross-links and mechanics), through the microscale (collagen fibers), to the macroscale (homogenized tissue), the model produces valid results, yet addresses only elastic mechanisms, neglecting contributions from inelastic phenomena and damage. The approach drives at a better understanding of multiscale mechanics of tissues, perhaps shedding light on aspects of mechanobiology of cells and organs [36]. Importantly, this work identifies what assumptions are necessary, and how many are reasonable. Simply modifying the model according to minor differences between fibers in tendon and those in cartilage would shed light on fiber performance and contribute significantly to models of cartilage.

Homogenization is ideally suited to bridge joint, tissue, and intratissue scales by coupling macro-micro boundary value problems. A direct, two-scale homogenization technique called FE^2 or multilevel FE (FE analyses augmented to derive material behaviors from a distribution of finer scale FE analyses) solves a range of classic problems in the transfer of information from microscales to macroscales [37]. Combining Theory of Porous Media with FE^2 produces a new modeling framework ideally suited to modeling cartilage. A preliminary (2-D) simulation employed this new framework to compare compression tests of two tissues, each with a different microstructure. The tissue-scale results were nearly identical, while microscale results differed significantly, underscoring the need to incorporate microstructures [38]. This extended FE^2 method is inherently multiphase and can naturally represent the anisotropic microstructure and through-thickness heterogeneity of cartilage. We see great promise for this framework to couple diverse length scales in multiphysics models of cartilage.

Recent experiments to drive the development and calibration of multiscale cartilage models

The complexity of cartilage structure and behavior drives the need for elegant experimental methods that can aide in the calibration and validation of new computational models. One recent approach involved the combination of multiple data types, including joint anatomy (via magnetic resonance imaging), joint kinematics (via robot-assisted testing), tissue mechanics (via compression testing), and microstructural morphology (via histology), all from the same specimens [39]. Multiscale biomechanical and structural data therefore provide means to bridge the joint to cell scales from the same individual.

Advanced experimental approaches involve the use of image data, which enables noninvasive acquisition of local tissue architecture and function. A recent study describes using high-speed microscopy to quantify bulk and local strain fields to predict the fissure formation characteristic of cartilage damage [40]. An important finding was that while bulk mechanics predict fissures at the population level, only local strains predict damage in individual samples. Concurrent developments in magnetic resonance imaging provide the ability to measure local mechanics in the cartilage of human subjects *in vivo*. Early results emphasize the dominant role of shear strain in the knee *in vivo*, a finding impossible to measure via any other conventional medical imaging modality [41]. Only now are we positioned to link local mechanics measured in individuals to the progression of damage [42].

Emerging methods now enable extraction of full-field biomechanical data at cellular and subcellular scales.

Using deformation microscopy, which couples image data to computational models, we can now map matrix to subnuclear level strain data [43]. This method enables us to quantify strain transfer from the extracellular or pericellular domains to intracellular and intranuclear regions, document amplified strains in chromatin domains [44], and clarify the role of specific nuclear membrane proteins that regulate the transfer of strain to the nuclear interior [43]. As computational models move to increasingly small scales, microscopy data will likely guide their calibration and validation.

Discussion and outlook

The goal of computational modeling is to quantify and predict phenomena that would otherwise be difficult or impossible to compute using available experimental methods. While existing models provide insight into mechanical quantities such as stress and strain, the leading edge of the field has yet to connect these data to known architectures of matrix molecules like collagen subtypes, proteoglycans, and glycoproteins and to regional variations in water content. Multiscale models of cartilage could allow researchers to understand how complex interactions at the molecular scale—for example, between the network of collagen and the densely packed proteoglycans—generate the remarkable macromechanics of cartilage. Many open questions remain. What role do local variations in minor collagen types, lubricating proteins, and molecular cross-linkers play in the stiffness and damage resistance of cartilage? How does damage or progression of OA affect these micromechanics? Do these evolving micromechanics present new treatment targets?

Distinctly few conventional models connect mechanical and biological/biochemical factors, let alone on varying spatial and temporal scales. Macroscale computational models may estimate stiffness in the bulk tissue matrix, and hierarchical models may refine our understanding of the local (substrate) stiffness experienced by individual cells; however, stiffness is only one parameter driving cellular expression. Activity of ion channels [45], cell–cell connectivity [46] and signaling [47], and intracellular cytoskeletal networks [43] require more advanced models that predict distinct mechanotransduction and biochemical pathways. Emerging knowledge of chondrocyte biological activity in health and through the progression of disease [48] may in part drive this need. Alternatively, new computational formulations that incorporate growth and development may predict new biological activity not previously envisioned.

Predictive multiscale modeling of the mechanics and evolution of cartilage is a difficult task because much of the required knowledge (experiments, theories, and numerics) remain poorly understood or disjointed (Figure 1). Additionally, no multiphase, multiscale models relevant to cartilage mechanics and mechanobiology currently exist—a paucity that offers enormous opportunity for future models that link patient-specific large-strain mechanics, biology, and biochemistry in 3-D, and drive patient-oriented treatments and soft-tissue replacements in tissue engineering.

Author contributions

All authors contributed to the conception, design, and writing of the manuscript.

Conflict of interest statement

Nothing declared.

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- • of special interest
- •• of outstanding interest

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