Historical Review of Combined Experimental and Computational Approaches for Investigating Annulus Fibrosus Mechanics

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ABSTRACT

Intervertebral disc research has sought to develop a deeper understanding of spine biomechanics, the complex relationship between disc health and back pain, and the mechanisms of spinal injury and repair. To do so, many researchers have focused on characterizing tissue-level properties of the disc, where the roles of tissue subcomponents can be more systematically investigated. Unfortunately, experimental challenges often limit the ability to measure important disc tissue- and subtissue-level behaviors, including fiber-matrix interactions, transient nutrient and electrolyte transport, and damage propagation.

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Numerous theoretical and numerical modeling frameworks have been introduced to explain, complement, guide, and optimize experimental research efforts. The synergy of experimental and computational work has significantly advanced the field, and these two aspects have continued to develop independently and jointly. Meanwhile, the relationship between experimental and computational work has become increasingly complex and interdependent. This has made it difficult to interpret and compare results between experimental and computational studies, as well as between solely computational studies. This paper seeks to explore issues of model translatability, robustness, and efficient study design, and to propose and motivate potential future directions for experimental, computational, and combined tissue-level investigations of the intervertebral disc.

INTRODUCTION

The intervertebral disc is a fibrocartilaginous joint located between adjacent vertebrae of the spine. The disc is a complex, highly organized structure comprised of a tough, fiber-reinforced ring (annulus fibrosus, AF) surrounding a softer center (nucleus pulposus). The AF is an angle-ply laminate composite, with layers of unidirectional collagen fiber bundles embedded in a hydrated glycosaminoglycan-rich matrix. The nucleus pulposus is a less organized structure with a higher glycosaminoglycan-to-collagen ratio and greater water content than the AF [1]. The disc experiences large bending and compressive forces during physiological loading, hydrostatically pressurizing the nucleus pulposus and inducing circumferential tensile stresses in the AF [2]. Thus, the healthy disc supports large stresses, dissipates energy, and facilitates complex motions of the spine.

Degeneration, disease, and injury alter disc biochemical composition and have been shown to adversely impact mechanical and rheological performance [1, 3]. Unfortunately, the disc's avascularity results in minimal self-healing capabilities. As such, accumulated damage, such as annular tears or endplate disruption, tends to catalyze a cascade of degenerative remodeling [4]. Damage to the AF may lead to disc herniation, where extrusion of nucleus pulposus material may compress nearby nerve roots, causing debilitating pain [5].

Researchers have sought to better understand the mechanisms of disc injury for nearly 100 years. Unfortunately, inducing joint-level disc failures *in vitro* that mimic *in vivo* herniation morphologies is challenging, requiring multiple simultaneous loading

modalities and hyper-physiological loads to be applied [6-13]. Additionally, the relationships between pain, injury, and degeneration are complex and highly interdependent [5]. Therefore, researchers have focused on better understanding tissue-level mechanics, where the role of tissue subcomponents can be more systematically investigated. Results from such studies can be used to better elucidate intrinsic disc properties and as design targets for biological repair strategies [14].

Unfortunately, experimental challenges have historically limited the measurement of many important AF mechanical and rheological behaviors, including the independent and combined contributions of collagen fibers and the extrafibrillar matrix. Thus, theoretical and numerical frameworks were introduced to explain and complement experimental research efforts. The merger of experimental and computational work over the last several decades has significantly advanced the field, and these two aspects have developed independently, jointly, and reciprocally. In recent years, this relationship has continued to evolve as computational work additionally serves to guide and optimize experimental protocols and study designs, even inspiring the development of novel cutting-edge experimental techniques to explore previously untestable modeling results.

Rapid and complex development of experimental and computational work has led to improved understanding of fundamental AF tissue properties and behaviors, which, in turn, has led to improved clinical understanding of AF failure and repair strategy design [14, 15]. This rapid growth has resulted in a diverse set of experimental techniques and computational frameworks. Accordingly, the relationship between

experimental and computational work has become increasingly complex and interdependent. These factors have made it difficult to interpret and compare results between studies. The objective of this review is to explore these issues of translatability, as well as the issues of model robustness and combined experimental-computational study design, and to propose and motivate potential future directions for experimental, computational, and combined studies of the AF.

PROGRESSION OF TISSUE-LEVEL EXPERIMENTAL TESTING

Over the last 100 years, intervertebral disc research has sought to develop a deeper understanding of spine biomechanics, the complex relationship between disc health and back pain, and the mechanisms of spinal injury and repair. While many of the fundamental clinical questions remain the same, the experimental approaches utilized to answer them have developed significantly. This progression can be described by two trends: experimentation on smaller length scales due to technological advancements, and an increased emphasis on fundamental, material-level tissue mechanics. As such, experimental research on disc tissues has proceeded cyclically over the years. Important recurring themes include the relationships between age or degeneration and tissue structure, 'structure-function' relationships linking tissue structure and composition with rheology and mechanics, and multiscale relationships between the hierarchical levels of the disc.

Modern study of the disc began in the early 1930s with work that addressed, in some capacity, nearly all of these themes [16, 17]. As whole-disc mechanics became better understood through the late 1950s, increased interest developed in tissue-level

testing to better understand constituent contributions to whole-disc mechanics (Table 1, Figure 1) [18-20]. It was also around this time that mathematical models were adopted to describe the complex nonlinear mechanical and rheological behavior of other collagenous tissues [21-24]. The aim, in part, of developing these mathematical frameworks was to better elucidate the underlying contributions of tissue subcomponents to tissue- and disc-level mechanics, and to identify changes in subtissue behavior that were not quantifiable through bulk tissue mechanics, such as elastic modulus. However, experimental work remained guided almost exclusively by previous clinical and experimental observations published in the literature (Figure 2 - Arrow 1).

Over the subsequent decades, numerous influential studies contributed to an improved understanding of tissue-level rheological structure-function relations, morphological micro-architecture, and tissue permeability (Table 1, Figure 1) [25-33]. Improved experimental techniques over the past 20 years have brought about a new era of multiscale mechanics with reliable characterization of single lamellar mechanics, fibrillar mechanics, and micron-scale damage accumulation (Table 1, Figure 1) [9, 10, 34-39]. Recent studies have also continued to elucidate tissue-level mechanical structure-function relationships. These studies have shown that water content, collagen content, and collagen crosslinking all affect sub-failure and failure properties, and that these effects are dependent on the applied loading conditions [40-42]. Despite these advancements, experimental characterization of tissue mechanics is still limited. For example, there remains a limited supply of healthy human disc tissue that has not experienced degeneration or trauma [43, 44]. Additionally, complex and variable

physiological loads and boundary conditions experienced by the disc *in vivo* are difficult to recapitulate during *in vitro* testing. For this reason, many researchers default to quasi-static mechanical testing in room-temperature physiological saline solutions [40, 45-49].

While much of the tissue-level experimental work is focused on uniaxial tensile testing, relatively few researchers have studied the AF in compression, shear, or planar biaxial tension [26, 27, 50-55]. To robustly describe the three-dimensional mechanical response of highly anisotropic tissues with a single computational framework, mechanical characterization under a variety of boundary conditions is needed [56, 57]. Recent work in cardiovascular tissues addressed this issue by using a novel and comprehensive approach that combined experiments and inverse modeling to determine a minimal, but complete, dataset for modeling 3D tissue behavior [56, 58].

PROGRESSION OF TISSUE-LEVEL MODELING

Challenges in experimentation preclude the direct, simultaneous measurements of subtissue structure-function relationships, including fiber-matrix interactions, transient nutrient and electrolyte transport, and damage propagation, highlighting the need for complementary theoretical frameworks [59]. Since the 1970s, there have been tremendous advances in disc tissue modeling by applying mathematics- and physics-based frameworks developed for biological and synthetic materials. Concurrently, finite element models (FEMs) have been used to incorporate one or more constitutive frameworks to evaluate three-dimensional tissue mechanics. Since then, numerical

studies have provided significant insights into disc tissue elastostatic mechanics, multiphasic transient behaviors, and failure mechanisms.

The theory of hyperelasticity was originally developed for polymers and has been widely applied to mathematical modeling of biological tissues to account for large nonlinear deformations (Table 2) [60-64]. This framework was capable of properly describing the mechanical behavior of the nucleus pulposus, which is often described as an incompressible fluid or as a homogeneous isotropic material [65-68]. Work by Spencer et al. allowed for constitutive modeling of anisotropic AF tissue (Table 2) [69, 70]. Utilizing directional tensors and invariant mathematics, the constitutive theory for strongly anisotropic solids became one of the theoretical foundations employed for describing AF tensile mechanics.

Since the 1970s, constitutive relationships from Spencer's theory have been applied to investigate AF mechanics, including bulk-level mechanics, structure-function relationships, and structural contributions of tissue subcomponents and their interactions (Table 1) [41, 49, 55, 69-78]. Simplifying the native tissue architecture, these models used fiber-reinforced strain energy functions to describe AF microstructure as a homogeneous continuum, where the fibers are described using directional unit tensors [69, 70]. In these studies, although individual constitutive relationships vary, the underlying data-fitting approach was consistent. Typically, fiber-reinforced strain energy functions were determined a priori and included one or more invariant terms with their coefficients to represent structural contributions of subcomponents (i.e. fibers or matrix) or interactions between subcomponents (e.g.

fiber-matrix interactions, crosslinks, etc.). Model coefficients were determined by curvefitting the pre-determined strain energy model to experimental data. Then, the resulting model parameters were used to determine structural contribution of tissue subcomponents and their interactions to tissue level mechanics with respect to degeneration, disease, or loading condition.

While providing significant insights into AF subtissue mechanics, this curvefitting approach has several drawbacks. First, some of the commonly applied constitutive relationships, such as the Mooney-Rivlin material description, were originally developed for polymers, which typically have a more concave stress-strain response than fiber-reinforced biological tissues, creating unnecessary challenges during the curvefitting process. Second, since most of these strain energy models are phenomenological, the coefficients of the invariant terms do not usually have a physical interpretation [79]. Early work often relied on nonphysical model parameters reported in the literature to both calibrate and validate their models, compromising model robustness and complicating issues of translatability (Figure 2 - Arrow 2). Additionally, using strain energy functions that are determined a priori based on an investigator's hypothesized structure-function relationships may lead to overparameterization and limit translatability between studies [80].

Furthermore, these constitutive models are single-phasic and thus incapable of describing transient rheology and phase interactions [81, 82]. A framework attempting to describe cartilage viscoelasticity using mixture theory was developed in the 1980s and has since been widely applied to disc tissues (Table 2) [83-85]. To account for

osmotic fluid flow, the initial biphasic mixture theory was further extended by including additional phases for freely movable ion pairs (i.e. triphasic and multiphasic frameworks) or by assuming an instantaneous chemical equilibrium throughout the tissue (Table 2) [86-97]. In the latter approach, a constitutively calculated osmotic pressure was added to the hydrostatic pressure to account for osmotic swelling, and the solid matrix deformed by the volume-free and negatively charged ions (i.e. bicomponent mixture or biphasic-swelling framework). Both frameworks have been adopted and validated to describe transient electro-chemomechanically driven tissue swelling [98].

With development of theoretical frameworks, improved computing platforms, and multiscale tissue measurements, the finite element method has been a powerful tool for studying intervertebral disc mechanics since the 1970s. In the 1990s, Spencer's anisotropic theory was incorporated into existing structural finite element models that used trusses or cables to describe tissue anisotropy. This approach addressed issues caused by the grid dependency of the alignment of the spring fiber elements while providing an improved description for AF anisotropy and nonlinearity [66, 68, 99-102]. Tissue-level AF finite element models initially only served as a component of joint-level models but have since become an effective tool for experimental protocol design, improving the efficiency and quality of experimental work [45, 103, 104]. Since the 2000s, mixture theory-based models have been applied to finite element simulations, greatly complementing experimental studies that showed multiphasic transient responses in the disc, including fluid flow and nutrient transport. Thus, there has been a

divergence in the numbers and types of models available to describe disc tissue mechanics, each with their own strengths and limitations.

As experimental techniques progressed to evaluate microscale damage in real time, modeling frameworks have increasingly applied computational damage descriptions [36, 37]. After multiple iterations of refinement during the 1980s, continuum damage mechanics enabled models to describe the failure behavior of biological tissues [105-109]. More recently, damage models have been developed to account for variations in tissue structure and biochemistry due to degeneration, injury, and disease. This has been accomplished by reformulating classical continuum damage frameworks [110, 111]. Alternatively, tissue damage can be described by combining damage mechanics with composite lamination theory or smoothed-particle hydrodynamics [35, 112, 113]. A better understanding of damage accumulation in healthy and degenerated tissues has the potential to elucidate the fundamental mechanisms of tissue injury and the degenerative cascade [111]. Moreover, a better understanding of damage mechanisms and failure prevention in biological tissues can be used to create strong, bioinspired synthetic materials with broader applications [114]. Therefore, significant contemporary research efforts have focused on developing more complete tissue damage descriptions based on recently available experimental data.

RELATIONSHIP BETWEEN EXPERIMENTAL AND COMPUTATIONAL RESEARCH

The relationship between experimental and computational work has developed reciprocally over the years. At the tissue scale, early experimental work looked to computational models to quantify subtissue properties that were difficult or impossible

to measure due to limitations in experimental techniques (Figure 2 - Arrow 3). Changes in model parameters with physical meaning provided meaningful interpretations of subcomponent contributions and stress distributions between subcomponents [49, 55, 75, 77]. However, alterations in nonphysical model parameters have also been attributed to altered physical and biochemical properties, such as collagen crosslinking or fiber-matrix interactions [41, 55, 71]. Meanwhile, recent work on airway tissues showed limited relationships between model parameters and relevant biochemical properties (*e.g.* fiber parameters and collagen content), even when limiting the model description to include only terms for the fibers and matrix (*i.e.* no interaction terms) [80]. Together, these findings highlight the need for more physical model frameworks that provide a direct relationship between tissue structure and mechanics.

Ideally, computational models should be accurate, robust, and translatable. By accurate, we mean that model predictions should closely match experimentally measured physical or chemical properties that use similar boundary and loading conditions. By robust, we mean that a validated model can predict tissue behavior under a variety of boundary conditions and loading modalities. In general, separate datasets should be used for model parameter calibration and model validation. Strain energy functions obtained by constitutive curve fitting typically perform poorly in predicting tissue mechanics under alternate deformation states that were not included during model calibration [50, 55, 57, 115, 116]. For example, previous work showed that constitutive models calibrated to uniaxial tension data were not able to accurately predict biaxial tensile behavior [50, 55]. Calibrating model parameters with more

complex loading modalities, such as planar biaxial tension improved model predictions of uniaxial behavior, but still had limited capacity to describe shear mechanics [55, 57]. Attempts to improve model robustness by simultaneous curvefitting to uniaxial and biaxial tension data have also proved challenging, often resulting in relatively poor model fits [41, 72].

Recent work by Avazmohammadi *et al.* re-organized the experimental-modeling workflow to determine the optimal experimental dataset needed to provide robust model predictions for myocardium [56]. This work provided a methodology using optimization and inverse modeling to determine a combination of stress-stretch data required for robust model development. Results suggested that a combination of pure and simple shear optimized the experimental dataset needed for myocardium model development. It is likely that this approach can be applied to other fiber-reinforced laminate composites, such as the AF. However, there is limited experimental AF shear data in the literature due to difficulties in ensuring fiber engagement during testing [53, 54].

Computational models have proved invaluable for efficiently directing resource-intensive experimental studies (Figure 3 - blue arrow). Examples of this trend range from design of appropriate soft-tissue gripping techniques to optimization of growth conditions for tissue-engineered constructs [45, 103, 104, 111]. Computational parametric studies are also powerful tools for optimizing experimental design by predicting which test groups are needed to observe statistical differences [45, 117].

Finite element models could similarly be applied to evaluate fiber engagement during testing, which may help address challenges in AF shear testing.

Computational models yield a variety of physical and non-physical parameters that can be difficult to relate to one another. Recently, there has been growing interest in developing robust multiscale models that are developed at one length scale and validated at a higher or lower length scale. This modeling approach may serve to improve model accuracy, robustness, and translatability. We recently developed a multiscale, structure-based AF model with fibers occupying a separate volume from the extrafibrillar matrix (Figure 4 - 'SEP' model) [117]. This approach differs from models that use homogenization theory, where every volume element is described as a homogeneous combination of tissue subcomponents (*e.g.* fibers and matrix), which does not represent the native tissue architecture (Figure 4 - 'HOM' model). For both model types, material parameters were first calibrated to single lamellar experimental data of fiber-only or matrix-only experiments. Then, model validation was performed by comparing model predictions for multi-lamellar stress-stretch response to data reported in the literature for uniaxial, biaxial, and simple shear, resulting in a more rigorous validation process (13 test cases from 9 different studies). With the robust model validation approach used, the multiscale SEP model was able to closely predict 12/13 multi-lamellar tissue test cases, as opposed to the more traditional HOM model that only predicted 1/13 testing cases [117]. Despite being computationally more expensive, the multiscale, structure-based modeling approach enables studies that simultaneously

investigate tissue- and subtissue-scale mechanics, which is important for a deeper understanding of tissue injury, degeneration, and disease.

FUTURE DIRECTIONS

Many of the significant advances in AF tissue-level experimental testing were facilitated by newly developed or translated methods, while other advances arose from progressive development of existing techniques. Additionally, simulation-assisted experimental study design has greatly assisted in streamlining these developments. Experimental design over the last several decades has produced a variety of robust and repeatable methods yielding more complete and reliable datasets, yet little has been done to develop a consensus across the field regarding standardizing testing procedures [45, 56, 103, 104].

Numerous factors suggest the benefit of developing and implementing standardized protocols for tissue-level mechanical and rheological testing. The most fundamental is the need to interpret and compare results across the field. The long-observed dependence of measured mechanical and rheological properties on the details of specimen treatment, geometry, hydration state, and loading conditions severely hinders translation of experimental results. Standardizing test protocols that minimize variations due to experimental boundary conditions will yield more translatable, higher-impact studies, and more cohesive datasets. This is precisely the basis for numerous organizations working to standardize testing protocols for traditional engineering materials, such as the American Society for Testing and Materials (ASTM) or the International Organization for Standardization (ISO). Given that the effect of

experimental conditions can be large for biological tissues when compared to traditional engineering materials, this is a particularly salient issue for the field.

Computational studies often develop and calibrate their models based on data from the literature. Standardizing the techniques used for experimentation will thus also result in more consistent results serving as inputs for computational studies (Figure 3 - blue arrow). For example, by the early 2000s, numerous theoretical frameworks for multiscale AF mechanics had been developed without agreement on a single, reliable, subtissue-level dataset, and these joint-level studies repeatedly called for well-characterized single lamellar mechanics [66, 118]. In 2005, Holzapfel *et al.* published a study providing a comprehensive dataset of single lamellar mechanics with respect to AF region [34]. This dataset is now widely used in computational studies, which not only provides valuable subtissue-level data for model development, but also helps compare results between computational studies that use this dataset (Figure 3 - blue arrow). Additionally, publishing raw data would greatly facilitate comparison of experimental results, and provide accurate and accessible resources for groups using experimental data from the literature for model calibration or validation.

With reliable multiscale experimental datasets, the research focus of computational studies has shifted toward subtissue-level mechanics, and such studies require models with improved accuracy and robustness. In constitutive modeling-based studies, these demands can be addressed by applying an integrated computational-experimental methodology to determine an optimal experimental dataset to improve predictive power and robustness of the obtained constitutive model. In finite element

modeling-based studies, improved model accuracy and robustness can be accomplished by applying multiphasic and multiscale modeling frameworks. Ubiquitous single-phasic hyperelastic models developed based on bulk tissue mechanics describe elastostatic mechanics well but fail to describe changes in tissue mechanics due to swelling and loading rate [42, 46, 52, 119]. Including multiphasic descriptions accounts for variations in tissue hydration and transient behavior under both mechanical and biochemical boundary conditions, which is essential for elucidating tissue injury mechanisms [42, 120-123]. Multiscale models that are developed based on native tissue architecture and that are calibrated and validated at different scales have demonstrated improved accuracy and robustness [117]. Therefore, combining multiphasic and multiscale frameworks provides an approach capable of investigating multiaxial mechanics, swelling, and transport behaviors by accurately and simultaneously predicting the time-dependent tissue response.

However, caution should be exercised to avoid overcomplicated models that will be increasingly more difficult to validate. Thus, model complexity will still need to scale based on the scope of the research questions being addressed. Despite their increased complexity, multiscale models often reduce the number of model parameters needed [66]. Additionally, the model parameters that are included may have more physically interpretable meaning, which improves model translatability [66, 117]. Differing experimental dataset input, constitutive models, and computational boundary conditions still vary widely based on a particular study's focus, providing additional challenges to inter-study translatability. To address this issue, a consensus is needed

regarding protocols for model development in similar simulations. Additionally, the field may benefit from the development of a framework for translating results between different models, which may be achieved by standardizing model outputs (*e.g.* peak strains, strain energy densities, etc.).

CONCLUSIONS

Experimental and computational branches of AF research have developed independently and jointly over the last 50 years, significantly advancing the field. In particular, there is an improved understanding of fundamental tissue properties that has in turn led to improved clinical understanding of disc injury and repair strategy design. While the rapid and complex development of this relationship has advanced the field, it has also resulted in a wide variety of frameworks with limited translatability. A consensus on experimentation would improve translatability of experimental data published in the literature, while a concerted effort towards using models with parameters that have physical meaning would help improve translatability between models and experiments. There remains a continued need for multiscale development of combined experimental-computational approaches to improve our understanding of AF structure-function relationships and designs for biological repair strategies.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

Figure Captions List

Fig. 1 Outline of experimental, computational, and combined studies applicable to the progression of AF research [10, 18, 19, 22, 25-29, 33, 34, 36, 37, 39, 41, 45, 49, 55, 56, 62, 63, 66, 68, 70, 72, 76-78, 85, 92, 94, 95, 103, 104, 109, 124, 125]. Italicized study names did not specifically use or model AF tissue.

Fig. 2 'Traditional' workflows for AF experimental (EXP) and computational (COM) research, and their relation to the literature (LIT)

Fig. 3 Integrated approach for combining experimental (EXP) and computational (COM) with existing AF literature (LIT)

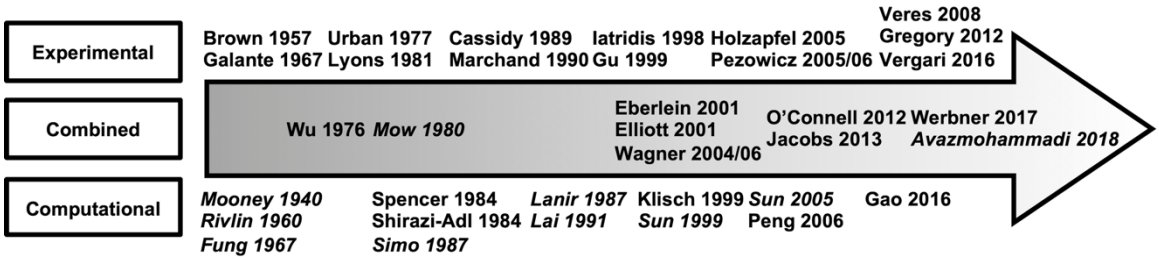
Fig. 4 Overview of multiscale model development, calibration, and validation with representative validation results. Typically, tissue- and joint-level models are developed using homogenization theory (HOM), where every element contains a summation of each described subcomponent. A separate (SEP) model was developed where fibers occupied a separate volume from the extrafibrillar matrix to better represent the native AF architecture (left column). Model calibration for both model types (HOM and SEP) was performed using single lamellar experimental data from Holzapfel *et al.* (middle column) [34]. Model validation was performed by developing multi-lamellar models and predicting uniaxial tension, biaxial tension, and shear behavior and comparing model predicted moduli with

experimental data (EXP). Figure adapted from [117].

Table Caption List

Table 1 Progression of experimental (EXP), computational (COM), and combined studies applicable to the development of AF research [10, 18, 19, 25-29, 32-41, 45, 49, 55, 56, 66, 68, 71, 72, 75-78, 95, 100, 104, 117, 124-126]. Italicized study names did not specifically use or model AF tissue.

Table 2 Progression of theoretical frameworks applicable to AF computational model development [62, 69, 85, 92, 94, 97, 109]



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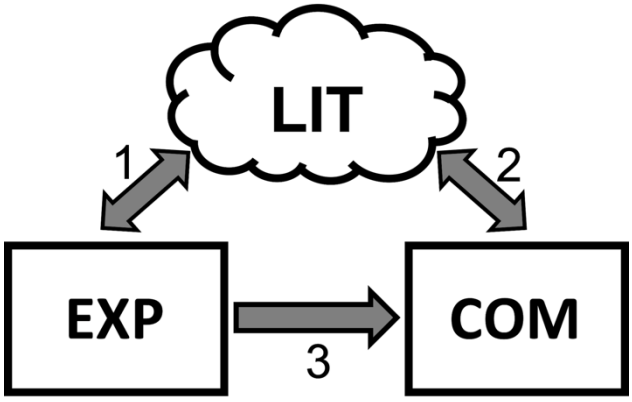

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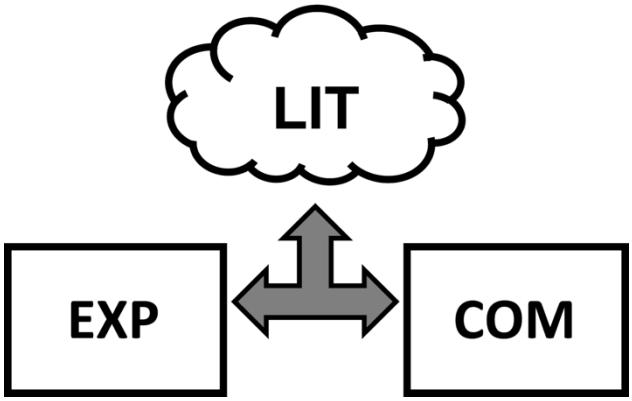

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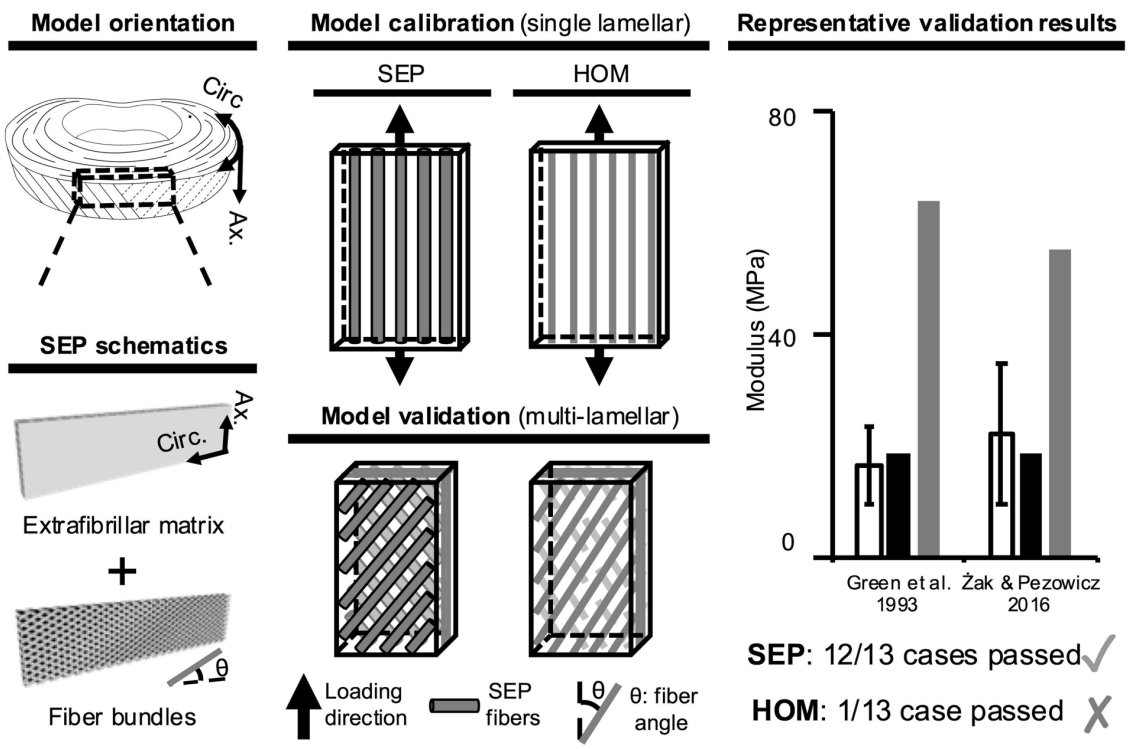

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	Type		Scale			Comments
	EXP	COM	Tissue	Subtissue	Fibrillar	
Brown 1957	x		x			Tissue-level tensile tests
Galante 1967	x		x			Comprehensive tissue-level study of mechanics and rheology
Wu 1976	x	x	x	x		Combined subtissue-scale study using a curvefitting approach
Urban 1977	x		x	x		Disc fluid and solute transport
Lyons 1981	x		x	x		Degradation of proteoglycans with degeneration
Shirazi-Adl 1984		x	x			Structural disc FEM with explicitly modeled AF and NP
Urban 1985	x		x	x		Disc rheological structure-function relations
Cassidy 1989	x			x	x	Lamellar and fibrillar micro-architecture
Marchand 1990	x			x	x	Lamellar micro-architecture
Skaggs 1994	x			x		Single lamellar mechanics and rheology
Goel 1995		x	x	x		Disc structural FEM with composite AF description
Lanir 1996		x	x			Study-design optimization for biaxial mechanics
Iatridis 1998	x		x	x		Anisotropic compressive properties and permeability
Gu 1999	x		x	x		Anisotropic permeability
Klisch 1999		x	x	x		Combined study simultaneously curvefitting tensile and compressive mechanics
Sun 1999		x	x	x		Triphasic tissue-level FEMs
Elliott 2000	x	x	x	x		Combined study of subtissue scale mechanics
Eberlein 2001	x	x	x	x		Disc FEM using Spencer's constitutive framework for AF description
Iatridis 2004	x	x	x	x	x	Multiscale combined damage behavior
Holzapfel 2005	x			x		Comprehensive single-lamella mechanics
Pezowicz 2005/06	x			x	x	Intra/inter-lamellar morphology
Sun 2005		x	x			Simulation-guided experimental protocol for testing fiber-reinforced soft tissue
Guerin 2006	x	x	x	x		Combined study investigating subtissue scale mechanics
Peng 2006		x	x	x		Constitutive modeling extended from Spencer's theory
Wagner 2004/06	x	x	x	x	x	Combined study simultaneously curvefitting uniaxial and biaxial mechanics
Veres 2008	x		x	x	x	Multiscale disc herniation morphology
O'Connell 2009/12	x	x	x	x		Combined study investigating uniaxial and biaxial mechanics
Gregory 2012	x			x		Mechanics of lamellar delamination
Isaacs 2014	x		x	x		Controlled biochemical-failure structure-function relations
Gao 2016	x		x	x		Multiphasic disc FEM predicting mechanics and electrochemistry
Vergari 2016	x		x	x	x	Interfibrillar strain analysis
Werbner 2017	x	x	x			Simulation-guided protocol design and validation for repeatable tensile failure
Avazmohammadi 2018	x	x	x	x		Study-design optimization for 3D characterization of myocardium
Zhou 2019		x	x	x	x	Multiscale, structure-based multiphasic tissue-level FEM

Table 2: Progression of theoretical frameworks applicable to AF computational model development [62, 69, 85, 92, 94, 97, 109]

	Comments
Mooney 1940	Theory of hyperelasticity
Spencer 1972	Constitutive theory for highly anisotropic solids
Mow 1980	Biphasic mixture theory
Lanir 1987	Bicomponent/Biphasic-swelling theory
Simo 1987	Advancement of continuum damage mechanics
Lai 1991	Triphasic mixture theory
Gu 1998	Multiphasic mixture theory

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