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Biomechanics and mechanobiology in functional tissue engineering

Farshid Guilak[1], **David L. Butler**[2], **Steven A. Goldstein**[3], and **Frank P.T. Baaijens**[4]

[1]Departments of Orthopaedic Surgery and Biomedical Engineering, Duke University Medical Center, Durham, North Carolina USA [2]Department of Biomedical, Chemical and Environmental Engineering, University of Cincinnati, Cincinnati, Ohio USA [3]Department of Orthopaedic Surgery, University of Michigan, Ann Arbor, Michigan USA [4]Institute for Complex Molecular Systems, Eindhoven University of Technology, Eindhoven, The Netherlands

Abstract

The field of tissue engineering continues to expand and mature, and several products are now in clinical use, with numerous other preclinical and clinical studies underway. However, specific challenges still remain in the repair or regeneration of tissues that serve a predominantly biomechanical function. Furthermore, it is now clear that mechanobiological interactions between cells and scaffolds can critically influence cell behavior, even in tissues and organs that do not serve an overt biomechanical role. Over the past decade, the field of "functional tissue engineering" has grown as a subfield of tissue engineering to address the challenges and questions on the role of biomechanics and mechanobiology in tissue engineering. Originally posed as a set of principles and guidelines for engineering of load-bearing tissues, functional tissue engineering has grown to encompass several related areas that have proven to have important implications for tissue repair and regeneration. These topics include measurement and modeling of the *in vivo* biomechanical environment; quantitative analysis of the mechanical properties of native tissues, scaffolds, and repair tissues; development of rationale criteria for the design and assessment of engineered tissues; investigation of the effects biomechanical factors on native and repair tissues, *in vivo* and *in vitro*; and development and application of computational models of tissue growth and remodeling. Here we further expand this paradigm and provide examples of the numerous advances in the field over the past decade. Consideration of these principles in the design process will hopefully improve the safety, efficacy, and overall success of engineered tissue replacements.

Correspondence address: Farshid Guilak, Ph.D., Duke University Medical Center, 375 MSRB, Box 3093, Durham, NC 27710 USA, Phone (919) 684-2521, Fax (919) 681-8490, guilak@duke.edu.

Conflict of Interest

Dr. Guilak is a founder of Cytex Therapeutics, Inc.

Keywords

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Introduction

Tissue engineering seeks to enable the repair or regeneration of tissues and organs through combinations of cells, biomaterial scaffolds, regulatory factors and environmental cues. This rapidly growing field primarily draws on various aspects of engineering, biomaterials, biology, and medicine, but has expanded to encompass a wide array of scientific disciplines needed to address the many challenges of the field. Despite many early advances (Langer and Vacanti, 1993), the field of tissue engineering encountered setbacks and delays in the translation of products to the clinic, with few commercial successes in early years of the field (Lysaght et al., 2008). However, the past decade has seen a significant expansion and maturation of the field, and there are now several tissue-engineered and cell-based products in clinical use as well as numerous preclinical studies and clinical trials underway.

In this regard, it is now clear that specific challenges still remain in the repair or regeneration of tissues that predominantly serve a biomechanical function. Furthermore, it is also becoming apparent that mechanobiological interactions between cells and scaffolds can have a critical influence on cell behavior, even in tissues and organs that do not serve an overt biomechanical role in the body. To highlight and address these issues and challenges, the United States National Committee on Biomechanics (USNCB) spearheaded an initiative on “functional tissue engineering”, which was originally posed as a set of principles and guidelines for tissue-engineering of load-bearing structures (Butler et al., 2000). The goals of the USNCB were primarily focused on: 1) increasing awareness among tissue engineers about the importance of biomechanical function when engineering tissues that serve biomechanical roles in the body; 2) identifying the structural and mechanical requirements needed for engineered tissues; and 3) encouraging tissue engineers to incorporate these functional criteria in the development and translation of tissue engineered products. This initiative was a catalyst for a session on “Functional Assessment of Engineered Tissues and Elements of Tissue Design” at the 2001 NIH BECON meeting on Reparative Medicine (Guilak, 2002; Guilak et al., 2002) and subsequently led to a workshop on this topic, funded in part by the National Science Foundation. This presentation and discussion from this workshop were summarized in a multi-chapter text that highlighted many different aspects of the field with a particular emphasis on the application of engineering principles to tissue engineering (Guilak et al., 2003).

Over the past decade, the field of functional tissue engineering has grown to encompass several related topics that have proven to have a critical influence on tissue repair and regeneration. The principles outlined previously for functional tissue engineering have also been advanced as well as recapitulated in more specific forms as they apply to particular tissues of the body (Baaijens et al., 2005; Butler et al., 2009; Butler et al., 2008; Guilak et al., 2001). Here we review and further expand these principles, and provide examples of some of the numerous advances that have occurred in the field over the past decade. As the

number of publications in this area has grown tremendously in the last decade, it is beyond the scope of this paper to review all of the outstanding studies in this area; rather, we have focused on several specific studies and review papers (with apologies to many authors whose studies were not included here). Consideration of these principles in the design process will hopefully improve the safety, efficacy, and overall success of engineered tissue replacements.

Principles of Functional Tissue Engineering

Many of the tissues of body – particularly in the musculoskeletal, cardiovascular, or pulmonary systems – have a primarily "biomechanical" function, such as load bearing, force generation or transmission, or fluid transport. In fact, the biomechanical properties of these tissues are critical to their normal *in vivo* behavior, and changes in tissue mechanical properties due to aging, injury or disease can result in significant tissue dysfunction.

In addition to the important role of biomechanics for these load-bearing (sometimes termed "structural") tissues, it is now apparent that biomechanical and mechanobiological factors are critical for regulating cell behavior in virtually all other tissues of the body (Ingber, 2003). In this regard, understanding the role of physical factors in regulating cell growth, differentiation, and metabolism in "non-structural" (e.g., metabolic) organs and tissues has also become an important focus of functional tissue engineering. Thus, a number of significant questions remain on the role of biomechanics in tissue engineering, and these questions are relevant to most tissues and organ systems in the body (Table 1). Here we describe principles of functional tissue engineering that can serve as guidelines for developing and improving engineered systems for restoring tissue function. While this list continues to expand, the proposed principles are not meant to be exhaustive and continue to serve as a roadmap for further development of this paradigm.

1. Measurement and modeling of *in vivo* biomechanical histories in native and repair tissues

In attempting to define design parameters for the biomechanical function of repair tissues, knowledge of the mechanical context in which normal and repair tissues will serve for different *in vivo* activities will be required to establish patterns of activity and the limits of expected usage. In this regard, a further understanding of the mechanical "thresholds" that normal tissues encounter for different *in vivo* activities are critical to developing appropriate design criteria for tissue repairs/replacements that can meet functional demands. For many tissues, these measurements are difficult to make, but they establish the history and boundaries of expected usage and will help develop "safety factors" for tissue-engineered implants (Juncosa et al., 2003).

Over the past decade, significant advances have been made in such *in vivo* measurements for a number of tissues and organs, particularly in studies that have combined novel imaging methods with theoretical modeling. For example, in the musculoskeletal system, we now have a much better understanding of the range and history of stresses and strains placed on tissues such as tendons/ligaments (Juncosa et al., 2003; Taylor et al., 2013), articular cartilage (Adouni et al., 2012; Coleman et al., 2013), and bone (Al Nazer et al., 2012; Fritton

et al., 2000). Similarly, in the cardiovascular system, a number of studies have combined novel imaging methods with computational models to extend our knowledge of the flow- and pressure-induced stresses in blood vessels and heart valves (De Hart et al., 2003; Loerakker et al., 2013; Marom et al., 2013).

Furthermore, these studies have been extended to the study of repair tissues as well, which likely experience an altered mechanical environment due to differences in activity or physiology (i.e., changes in gait, blood pressure), or due to differences in the mechanical properties of the implant as compared to those of the native tissues [e.g., (Awad et al., 2003; Butler et al., 2008; Defrate et al., 2006; Juncosa-Melvin et al., 2007; Van Canneyt et al., 2013)]. These studies have greatly extended the previous knowledge of the necessary requirements for tissue replacements that would be expected to withstand physiologic, or in many cases, pathologic loading conditions, and will hopefully provide important insights into future design criteria for implants (Nerurkar et al., 2010). However, it is important to note that most current models are designed to simulate “normal” tissues, and the major structural or compositional changes that occur in advanced stages of disease or degeneration may require more complex geometric or constitutive models that may not be appropriately simulated by current continuum models.

2. Understanding the biomechanical properties of native and repair tissues across all geometric scales

Within the context of understanding the functional demands of different tissues, it will be important to have a thorough understanding of the sub-failure and failure properties of native tissues – through the processes of development, injury, disease, repair, and aging (Butler et al., 2008). This information will guide the design and engineering of repair tissues that provide the appropriate functional properties. While the mechanical properties of native tissues have been studied extensively, there has continued to be major advances in our understanding of cell and tissue biomechanics over the past decade. These measurements have included both “structural” and “material” (i.e., “intrinsic”) properties. Structural properties reflect the overall functional requirements of a tissue or organ and include the influence of morphological parameters, such as tissue geometry. “Material” properties, which should reflect tissue properties independent of geometry or loading conditions, are of particular value for predictive theoretical models to allow description of the mechanical response of a tissue/organ to different loading conditions, potentially *in vivo*.

Due to their hierarchical structure and composition, most biological tissues have highly complex material properties (Table 2). The fundamental basis for these behaviors is an important area of study, particularly with the implicit goal of recreating tissue function from independent components (i.e., cells and biomaterials). Importantly, it remains to be determined which attributes of these material properties are essential for the normal, healthy function of different tissues, as well as for successful tissue-engineered replacements. Nonetheless, great strides have been made in the past decade in our understanding of the more complex constitutive behaviors of tissue that involve anisotropic (Groves et al., 2013; Isenberg et al., 2012; Nagel and Kelly, 2012; Sommer et al., 2013; Teng et al., 2012),

multiphasic (Azeloglu et al., 2008), viscoelastic (Shirakawa et al., 2013), nonlinear (Buckley et al., 2013), and transport (Motaghinasab et al., 2012) properties.

Another important area has been the adoption of several novel techniques that have allowed measurement of functional mechanical properties at the nano- and micro-scales. Not only do such techniques provide insight into the fundamental structure-function relationships of developing (Buskohl et al., 2012; Marturano et al., 2013) and mature (Beenakker et al., 2012; McLeod et al., 2013) native tissues, they now allow testing of scaffolds and engineered tissues across a broad range of geometries and scales that were not possible using standard macroscopic methods (Diekman et al., 2012; Gilchrist et al., 2011; Hammond and Kamm, 2013).

The combinations of the various mechanical testing methods that are now available have provided an unprecedented level of quantitative assessment of native and engineered tissues. Importantly, these findings further reveal the highly complex and unique structure function relationships present in most tissues, and emphasize the challenges inherent to replicating these characteristic in engineered tissues. For example, hydrated collagenous tissues possess anisotropic and nonlinear mechanical and transport properties that vary significantly with site (Elliott and Setton, 2001; Huang et al., 2005; Martufi and Gasser, 2011). Not only are these properties critical to the overall function of the tissue, but the interactions among the different phases can result in complex stress-strain and pressure fields that can only be predicted using inhomogeneous or fiber-reinforced models (Shirazi-Adl, 1989), particularly at the cellular level (Baer et al., 2003; Korhonen et al., 2008; Likhitpanichkul et al., 2005). Furthermore, the development of engineered tissue replacements that replicate this mechanical environment will likely require structures that mimic certain aspects of the native tissue architecture (Moutos et al., 2007; Nerurkar et al., 2008).

3. Prioritization of specific mechanical properties as design parameters for biomaterial scaffolds and engineered tissues

Despite the growing database of mechanical properties, structure, and composition of native tissue, the relative importance of the different properties in influencing the success of an engineered repair tissue is not fully understood. Given the difficulties in matching all of the complex behaviors and architecture of native tissues, a key issue in the development of engineered repairs will be the prioritization of various biomechanical properties as design parameters, as it will be difficult if not impossible to completely match all of the material properties of native tissues (Table 2). Nonetheless, it may not be necessary to match all of the material properties of native tissue *a priori* in view of the remodeling potential of the implanted tissue *in vivo* (Schmidt et al., 2010). Priority has often been placed on a single parameter such as the compressive or tensile modulus of a tissue (Butler et al., 2008; Xiao et al., 2013), yet the relative importance of all of the different properties of a tissue or its constituents is unknown. To better understand and refine these design criteria, it will be necessary to understand the trade-offs and interactions of different functional characteristics and the overall success criteria of the implant. Of course this is not a simple task due to the large combination of biomechanical properties and functional demands (Table 2), coupled with equally complex or undefined success criteria.

4. Development of biomaterials and scaffolds with prescribed biomechanical properties

Novel biomaterials and biomaterial structures can provide control of functional biomechanical and other physical properties at the macro-, micro-, and nano- levels. These biomechanical and biological interactions between cells and scaffolds can have a significant influence on cell behavior (Guilak et al., 2009), and thus, the potential for long-term success of engineered tissues. Major advances in the past decade has been in the improved understanding of these interactions, coupled with breakthroughs in the development of scaffolds with highly controlled mechanical properties at multiple scales (Boffito et al., 2014; Courtney et al., 2006; Fan et al., 2013; Pennella et al., 2013; Soliman et al., 2010).

For example, the adoption of rapid-prototyping techniques such as microfabrication, 3D printing, or stereolithography has allowed the fabrication of a variety of scaffolds with controlled architecture and mechanical properties (Butscher et al., 2011; Engelmayr et al., 2008; Hollister, 2005; Hoque et al., 2005; Mironov et al., 2009; Paten et al., 2013). Additionally, a range of advanced textile processes including 2D or 3D weaving, knitting, and braiding have been applied to the development of scaffolds and constructs with highly biomimetic properties, as well as the ability to provide cell-instructive signals (Almeida et al., 2013; Brunger et al., 2014; Freeman et al., 2011; Liberski et al., 2011; Moutos et al., 2007; van Lieshout et al., 2006). Other non-woven techniques such as spun-bond or melt-extrusion have been shown to be highly versatile in the formation of different fiber architectures and to readily allow for scale-up and manufacturing (Tuin et al., 2013; Zeugolis et al., 2009). Probably the most rapid and broad adoption of materials processing methods for tissue engineering has been the use of hydrodynamic processing methods such as electrospinning, which provides a versatile method of controlling fiber architecture and properties at the nano- and micro-scales (Boland et al., 2004; Chew et al., 2006; Courtney et al., 2006; Mauck et al., 2009; Vaz et al., 2005). Importantly, recent studies suggest that the geometrical and biomechanical properties of electrospun scaffolds can also modulate the immune response to the scaffold (Ballotta et al., 2014; Garg et al., 2013).

New advances in the area of hydrogels have led to the development of biomaterials with tunable properties at the bulk or the cellular level (Stahl et al., 2010; Tseng et al., 2013; Wang et al., 2010). Biomaterials that undergo phase transition from liquid to solid through exposure to light, temperature changes, or chemical crosslinking/degradation can provide versatile environments for controlling cell behavior while defining the mechanical environment and functional properties of the scaffold (Betre et al., 2006; Chao et al., 2010; Cuchiara et al., 2012; Dankers et al., 2005; Sharma et al., 2013). Furthermore, chemical functionalization of such materials with proteins or gene delivery systems has been shown to provide an additional level of design capability for scaffold function (DeLong et al., 2005; Francisco et al., 2014; Glass et al., 2014; Hume et al., 2011; Kisiel et al., 2013; Salimath and Garcia, 2014).

Finally, the combinations of different biomaterials into “composite” scaffolds may in fact provide unique systems for controlling the spatio-temporal mechanical properties that are characteristic of native tissues (Table 2). For example, combinations of fiber-gel systems can be created to reproduce the nonlinear, anisotropic, and viscoelastic behavior of different tissues (Ekaputra et al., 2008; Freeman et al., 2011; Hong et al., 2011; Moutos et al., 2010),

whereas combinations of different hydrogels to form interpenetrating networks (IPNs) can provide toughness and fracture resistance that is not possible from single network gels (Daniele et al., 2014; Liao et al., 2013; Rennerfeldt et al., 2013; Suri and Schmidt, 2009). It may also be important to consider temporal factors in the design criteria of bioscaffolds. Whether a tissue engineered scaffold should recapitulate the properties of the native tissue to be repaired or the properties of the tissue during earlier stages of development or repair has yet to be determined and certainly may vary with tissue type.

5. Development of success criteria based on appropriate outcome measures

A critical step in achieving success in tissue-engineered repair and regenerative medicine will be the development of appropriate standards of clinical success and the completion of prospective outcomes studies to compare the safety and efficacy of different procedures. These criteria will of course need to be specific for each tissue or organ. Inherent in this process will be the further development of minimally invasive methods (e.g., imaging, biomarkers) that can be used for the assessment of tissue function *in vitro* as well as *in vivo* (Acosta Santamaria et al., 2013; Boerckel et al., 2012; Dejaco et al., 2012; Delaine-Smith et al., 2014; Hagenmuller et al., 2010; Kotecha et al., 2013; Marcos-Campos et al., 2012; Mariappan et al., 2010; Marturano et al., 2014; Vogl et al., 2010).

6. Investigation of the effects of mechanical factors on tissue repair *in vivo*

Once implanted, tissue-engineered constructs will be subjected to significant loads and deformations *in vivo*. Depending on the type of tissue/organ, the stress/strain environment may vary widely within the body. In this regard, both the mechanical and biological consequences of *in vivo* loading must be understood to improve the success of engineered repairs and to develop appropriate rehabilitation protocols following surgery to correct acute or chronic injuries (Boerckel et al., 2012; Juncosa et al., 2003; Willie et al., 2010).

From a mechanical standpoint, implanted tissue will need to eventually perform their prescribed function, presumably in a manner that restores native tissue function (although an exact replication of native tissues is likely to be difficult to achieve and may not be necessary assuming consideration of appropriate safety factors above functional load limits). Thus, the development of minimally invasive measures of tissue/organ function, and their application to engineered implants, will be vital to the understanding of the *in vivo* function of engineered tissues (summarized in the previous section).

From a biological, or “mechanobiological” standpoint, cells within implanted constructs will be similarly subjected to a complex biomechanical environment, that may consist of time- and spatially-varying stresses, strains, fluid pressure, fluid flow, and other biophysical parameters (Mow et al., 1994). It is now clear that such physical signals may significantly influence cellular growth, differentiation, and metabolism, and thus could play an important role in the long-term outcome of engineered tissues. Not only is a better understanding of the *in vivo* mechanical environment required, but additional data are needed on the response of cells to these signals and how they influence cell growth and differentiation.

7. The use of physical factors to enhance tissue regeneration *in vitro*

Mechanical factors play an important role in regulating cell physiology, and a wealth of evidence now shows that physical factors may be used to improve or accelerate tissue regeneration *in vitro*. The development and study of "bioreactors" for physical stimulation of engineered constructs has expanded massively over the past decade, with a variety of techniques showing tremendous promise in controlling cell growth, differentiation, and biological activity (Butler et al., 2009; Cimetta et al., 2013; Darling and Athanasiou, 2003; Hansmann et al., 2013; Rouwkema et al., 2011; Yeatts et al., 2013).

Early studies have shown that various mechanical stimuli, whether it be stretch, compression, pressure, or enhanced perfusion/transport could greatly enhance matrix formation in the context of tissue engineering [reviewed previously in (Butler et al., 2000)]. From these seminal studies, investigators have examined other types of physical stimuli such as combinations of different mechanical or physicochemical loading regimens that could even further improve construct qualities (Huang et al., 2012; Huey and Athanasiou, 2011; Jungreuthmayer et al., 2009; Meinel et al., 2004; Sampat et al., 2013; Schatti et al., 2011; Zhang et al., 2009). With further understanding of the role of the biomechanical microenvironment on cell behavior (Guilak et al., 2009; Reilly and Engler, 2010), other studies have examined the role of factors such as extracellular matrix topography or modulus within scaffolds as means of influencing local cellular responses (Dellatore et al., 2008; Gauvin et al., 2012; Guex et al., 2013; Kolambkar et al., 2014; Lim et al., 2011; Nii et al., 2013).

As the field has progressed, new studies have focused on determining the mechanisms of physical signal transduction (Liu and Lee, 2014; Mammoto et al., 2012; Pioletti, 2013). One goal of this approach has been to take advantage of chemical means to circumvent the standard bioreactor loading systems to directly stimulate cellular responses (O'Conor et al., 2014). With increased knowledge of the mechanotransduction cascades in primary and stem/progenitor cells, these approaches may serve as a means of controlling cell fate through physical means, as well accelerating tissue growth with or without other exogenous growth factors or gene delivery (Neumann et al., 2013; O'Conor et al., 2013; Shah et al., 2014; Song et al., 2013; Wang and Chen, 2013). In particular, few studies have used model systems to investigate the mechanobiology of repair tissues within environments that simulate important physiologic characteristics that may inhibit repair, such as aging, overloading or systemic diseases (i.e., inflammation, infection, obesity/diabetes, etc.) (Choe et al., 2006; Lima et al., 2009; Liu and Agarwal, 2010; Ousema et al., 2012).

8. Development and validation of computational models of tissue growth and remodeling

One of the key discriminating features of a living tissue replacement compared to synthetic substitutes is the ability to grow, and mechanical stress is believed to be an important regulator of this process. Experiments provide evidence for the ability of engineered tissues to grow *in vitro*, but the underlying mechanisms are poorly understood. Similarly, *in vivo*, the mechanical properties and architecture of engineered tissues will evolve in response to the biomechanical and biochemical environment. A thorough understanding of the remodeling mechanisms will enable definition of the required initial conditions of the

substitute to further mature to a healthy, functional tissue and to avoid adverse remodeling or degeneration.

In the past decade, the field of tissue engineering has seen tremendous advances in this area, particularly in the development of theoretical models of growth and remodeling that allow simulation of a subset of the numerous parameters that are potentially involved in tissue repair or regeneration (Hwang et al., 2013). The ability to simulate tissue responses to factors such as scaffold/hydrogel properties, transport (e.g., nutrients, waste products, oxygen, biomarkers, drugs, etc.), matrix accumulation, or mechanical stimuli could greatly decrease the number of *in vitro* and *in vivo* experiments that need to be run to most rapidly improve the properties of engineered constructs and grafts (Ateshian et al., 2014; Bovendeerd, 2012; Buskohl et al., 2012; Haider et al., 2011; Klisch et al., 2008; Loerakker et al., 2013; Niklason et al., 2010) and could potentially identify *in vitro* predictors of *in vivo* outcome (Butler et al., 2008).

Future Directions

The field of functional tissue engineering has experienced phenomenal growth over the past decade, with revolutionary advances in many of the areas outlined above. The rapid evolution of new technologies in fields such as cell and molecular biology, biomaterials, gene therapy, and nanotechnology, coupled with tremendous advances in computational methods and hardware, will undoubtedly have a significant impact on functional tissue engineering over the next decade. Many challenges still remain, of course, in the testing, scale-up, and manufacturing processes that will be required before these technologies can be translated to the clinic. Furthermore, packaging, storage and handling properties will also be critical parameters to include the design of engineered constructs. Nonetheless, the field of functional tissue engineering has come into its own and on its current path is likely to have a very promising future.

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Table 1

Questions on the role of biomechanics in tissue engineering

- What are the ranges of stress and strain that native or repair tissues experience *in vivo* under physiologic or pathologic conditions?
- What are the mechanical properties of native, diseased, or repair tissues at multiple scales?
- Which of these properties should be used as design parameters in the development of engineered tissues?
- What are the mechanical properties of biomaterials, scaffolds, and engineered tissues (at multiple scales) and how can we control these properties as design parameters?
- When evaluating the biomechanical function of tissue-engineered repairs, how do we define success?
- Can mechanical stimulation (i.e., in bioreactors) improve implant properties before implantation?
- How do physical factors influence the behavior of cells and engineered constructs once they are implanted *in vivo*?
- How do physical interactions with the microenvironment regulate the growth, differentiation, and metabolism of either primary or stem/progenitor cells?
- How do biomechanical factors influence growth and remodeling of native or repair tissues?
- What parameters and constitutive models can be used to predict the growth and remodeling of engineered tissues?
- How do other genetic and environmental factors (e.g., co-morbidities, inflammation, etc.) interact with biomechanical factors to modulate tissue-engineered repair?

Table 2

Functional Properties of Natural And Engineered Tissues [adapted from (Butler et al., 2000), with permission]

Anisotropy (Properties vary with direction)
Tensile, compressive, shear moduli
Hydraulic permeability
Diffusion and other transport properties
Friction and wear
Failure stress and strain
Fatigue life
Inhomogeneity (Properties vary with site)
Potentially all properties
Morphology
Congruence
Microstructure
Nanotopography
Nonlinearity
Material nonlinearity
Tension-compression nonlinearity
Nonlinear permeability
Nonlinear diffusivity and deformation-diffusion coupling
Nonlinear viscoelasticity
Coupling of normal and shear stresses
Friction and wear
Physicochemical-mechanical coupling
Electrokinetic effects
Mechano-osmotic coupling
Mechano-electric coupling (e.g., piezoelectricity)
Residual stresses
Swelling
Tribological Properties
Frictional coefficient
Wear properties
Adhesive properties
Hardness
Viscoelasticity
Multiphasic or poroelastic
Energy dissipation
Intrinsic material viscoelasticity
Fluid viscosity