ABSTRACT

“Tissue engineering” uses implanted cells, scaffolds, DNA, protein and/or protein fragments to replace or repair injured or diseased tissues and organs. Despite its early success, tissue engineers have faced challenges in repairing or replacing tissues that serve a predominantly biomechanical function. An evolving discipline called “functional tissue engineering” (FTE) seeks to address these challenges. In this paper, the authors present principles of functional tissue engineering that should be addressed when engineering repairs and replacements for load-bearing structures. First in vivo stress/strain histories need to be measured for a variety of activities. This in vivo data provides mechanical thresholds that tissue repairs/replacements will likely encounter after surgery. Second, the mechanical properties of the native tissues must be established for sub-failure and failure conditions. This “baseline data” provides parameters within the expected thresholds for different in vivo activities and beyond these levels if safety factors are to be incorporated. Third, a subset of these mechanical properties must be selected and prioritized. This subset is important, given that the mechanical properties of the designs are not expected to completely duplicate the properties of the native tissues. Fourth, standards must be set when evaluating the repairs/replacements after surgery so as to determine, “how good is good enough”? Some aspects of the repair outcome may be inferior, but other mechanical characteristics of the repairs and replacements might be suitable. New and improved methods must also be developed for assessing the function of engineered tissues. Fifth, the effects of physical factors on cellular activity must be determined in engineered tissues. Knowing these signals may shorten the iterations required to successfully replace a tissue, and direct cellular activity and phenotype toward a desired end goal. Finally, to effect a better repair outcome, cell-matrix implants may benefit from being mechanically stimulated using in vitro “bioreactors” prior to implantation. Increasing evidence suggests that mechanical stress, as well as other physical factors, may significantly increase the biosynthetic activity of cells in bioartificial matrices. Incorporating each of these principles of functional tissue engineering should result in safer and more efficacious repairs and replacements for the surgeon and patient.
Introduction

The goal of “tissue engineering” is to repair or replace tissues and organs by delivering implanted cells, scaffolds, DNA, proteins, and/or protein fragments at surgery. Tissue engineering merges aspects of engineering and biology, and many rapid achievements in this field have arisen in part from significant advances in cell and molecular biology (e.g., the isolation and manipulation of cells, genes, and growth factors), biomaterials (new and innovative delivery vehicles), and the integration of biology and materials to deliver viable cells in compatible support structures.

Many of the tissues and organs to be replaced have an important biomechanical function. In fact, the biomechanical properties of these tissues are critical to their proper function in vivo. In order for tissue engineers to effectively repair or replace these load-bearing structures, they must address a number of significant questions. What are the thresholds of force, stress, and strain that normal tissues transmit or encounter? What are the mechanical properties of these tissues when subjected to expected in vivo stresses and strains, as well as under failure conditions? Which of these properties should a tissue engineer insist upon incorporating into the design? When evaluating the resulting tissue engineered repairs, how good is good enough (i.e., do tissue engineered repairs and replacements need to exactly duplicate the structure and function of the normal tissue or organ)? When developing these implants in culture, how do physical factors such as mechanical stress regulate cell behavior in bioreactors as compared to signals experienced in vivo? And finally, can tissue engineers mechanically stimulate these implants before surgery to produce a better repair outcome?

To address these questions and others, the United States National Committee on Biomechanics (USNCB) formed a subcommittee¹ in 1998. This committee adopted the concept of “Functional Tissue Engineering”, or FTE. The USNCB’s goals in advancing FTE were to: 1) increase awareness among tissue engineers about the importance of restoring “function” when engineering tissue constructs; 2) identify the critical structural and mechanical requirements needed for each tissue engineered construct; and 3) encourage tissue engineers to incorporate these functional criteria in the design, manufacturing, and optimization of tissue engineered constructs.

To address its first goal, the USNCB sponsored a panel session, “Functional Tissue Engineering- The Role of Biomechanics” at the recent 1999 Summer ASME Bioengineering Conference in Big Sky, Montana. Three speakers were invited to give their perspectives on FTE for the musculoskeletal system. Drs. Farshid Guilak, Steven Goldstein, and David Butler evaluated aspects of FTE related to articular cartilage, bone, and tendon/ligament, respectively.

For the purposes of this paper, common aspects of these presentations have been recast into “principles of functional tissue engineering” so as to emphasize commonalities in desired outcome. While the process used to successfully repair these tissue classes may differ, as do their expected mechanical environments in vivo, common features of all three deserve consideration.

Musculoskeletal as well as other tissue systems (e.g. cardiac muscle and blood vessel) can benefit from new and exciting developments in FTE. Obviously, the strategies employed to engineer these tissue products will be unique to the structure under consideration. What constitutes “success” will also vary among tissues. For example, tissues or systems that are designed to prolong life may tolerate a lower margin for error than those that are designed to improve the quality of life. The difficulty in performing a procedure, and the duration that a specific treatment lasts, may also factor into its perceived success. For example, therapies of replacement or regeneration of bone might be expected to last the lifetime of the individual, while replacement of cartilage may be considered successful if it delays total joint replacement for five to ten years. Some of these issues will be addressed in this paper.

Principles of Functional Tissue Engineering

What follows are principles of functional tissue engineering that can dramatically influence both the quality of the implants that tissue engineers design and the repair outcome after surgery. These principles are presented in an order that is designed to require fewer iterations to yield constructs that can effectively repair or replace diseased and injured structures. The principles are by no means complete, but are believed to be critically important to a successful outcome. The paper concludes with a brief description of opportunities that may be available for future research in functional tissue engineering.

1. In vivo stress and/or in vivo strain histories need to be measured in normal tissues for a variety of activities.

Knowing the mechanical “thresholds” that normal tissues encounter for different in vivo activities are critical to effectively designing tissue repairs/replacements that can meet functional demands after surgery. While these measurements can be difficult to make, they establish the patterns of activity and the bounds of expected usage.

Numerous investigators have measured in vivo forces and strains in ligaments and tendons. In vivo forces have been measured using buckle and E-type gages [1-4], implantable force transducers [5-11] and modified pressure transducers [e.g., 8,12]. Investigators have shown that while peak forces can vary both within and between activities, these forces increase with the speed of the activity [8,9]. Tendons typically develop forces earlier than joint ligaments, primarily because muscles must first transmit their developed force to an in-series tendon to effect large enough motions before ligaments can develop loads [12]. When forces are expressed as percentages of their failure capacity, tendons typically develop much larger forces than ligaments, reaching 30% to 40% of ultimate strength whereas ligaments develop forces than rarely exceed 10% to 12% of failure force [5,9,13]. These differences in percentage of failure force suggest that ligaments maintain a safety factor of 8 to 10 (except of course during trauma) whereas tendons have a factor of only 2.5 to 3. In situ loads measured in cadaveric knees support the small forces in the anterior cruciate ligament [14,15]. These forces can also vary within ligaments as evidenced by the large variations in both in situ forces and in vivo strains in the anterior cruciate ligament for different activities [14-17].

For other tissues, however, there is a lack of information on the normal in vivo mechanical environment. Peak stresses in articular cartilage loading against an endoprosthesis have been shown to exceed 18 MPa [18], but stresses in a normal joint have been more difficult to measure. Experiments using pressure-sensitive films have shown that normal stresses may range from 5 to 10 MPa in vivo [10], but may be significantly increased by the presence of an osteochondral defect on the joint surface [19]. Surprisingly little information has been reported on the deformation behavior of articular cartilage in vivo. One of the few reports of this nature utilized sequential planar radiographs to show that cartilage deforms no more than 15-20% under normal physiologic compression [20]. Because of the difficulties involved in measuring the in situ loads and deformations of cartilage under realistic in vivo conditions, many investigators have turned to theoretical models of the diarthrodial joint to predict these parameters [21]. This is an area that requires further study and will most likely benefit from both theoretical and experimental approaches.

Analogous to cartilage, experimental difficulties have limited the information available on the normal in vivo stresses and strains engendered in bone tissue. For more than 100 years it has been assumed that bone structure and morphology reflect the demands placed on it by normal physical activities. As a result, its organization and mechanical properties vary dramatically as a function of anatomic location and physiologic condition (i.e., age, gender, disease state) [22,23]. On the other hand, the observed highly regulated structure/function properties suggest that its inherent capacity for adaptation would result in a relatively narrow range of normal in vivo strains. Numerous studies designed to measure bone surface strains are supportive of this principle, with reported values ranging between approximately 400 and 3000 microstrain (tension or compression), across many animal species [22]. More recently, relatively similar measures have been documented in human subjects [24]. It is important to note that these studies are focused on cortical bone, since its location and
surface properties enable the use of strain
gauge devices. The trabecular bone
compartment presents substantial
experimental challenges, due to its
anisotropic, macroscopically porous
architecture. In vivo strains can only be
estimated by analytical or computational
methods. Most investigators have approached
this challenge by developing finite element
models of the bone region of interest.
Boundary conditions are typically determined
by measuring joint or muscle insertion loads
[i.e., 25] and applying them in computational
models that have mesh geometries that are
derived from high resolution images of the
trabecular bone structure of interest [see 26].
Interestingly, the range of predicted strains in
trabecular bone are similar to those measured
in cortical bone.

2. The mechanical properties of the
native tissues must be established
for sub-failure and failure
conditions.

To effectively design tissue-engineered
implants, it is important to understand the sub-
failure and failure properties of the native
tissue [27]. Sub-failure properties can be
measured within the bounds of expected
loading established above. Sub-failure
properties can be determined from viscoelastic
experiments such as static or cyclic creep or
stress relaxation testing. However, the native
tissue should also be tested up to failure,
especially if tissue engineered implants are to
be designed with safety factors like the native
tissue. Such failure testing provides both
structural and material properties of the tissue
to be replaced. “Structural” properties allow
comparison of tissues or constructs to a
baseline functional level, and incorporate the
role of important morphological parameters,
such as tissue geometry or joint congruence.
“Material” properties are valuable in that they
may be determined in simplified loading
configurations, in combination with
physiologically relevant theoretical models,
but may be used to describe the mechanical
response of a material to any loading history.

Due to their complex structure and
composition, most biological tissues can be
classified from a material standpoint as
inhomogeneous, viscoelastic, nonlinear, and
anisotropic materials (Table 1). The
fundamental basis for these behaviors is not
fully understood, and may differ among
different tissues. Importantly, it remains to be
determined which aspects of these mechanical
properties are essential for the normal, healthy
function of different tissues, as well as for
successful tissue-engineered replacements.

Articular cartilage, for example, normally
exhibits little or no wear with millions of
cycles of loading that may reach ten times
body weight. Its unique mechanical and
tribological properties, which are unparalleled
in man-made bearings, have been attributed to
the complex structure and composition of
extracellular tissue matrix [28]. In response to
an externally applied load, articular cartilage
is subjected to a complex state of tensile, shear
and compressive stresses. Because of the
large water content of the extracellular matrix
(75%-85%), mechanical loading also results in
pressure gradients in the interstitial fluid. As
the extracellular matrix is permeable to water
and possesses a significant amount of fixed
negative charge (due to the presence of
proteoglycans), pressure gradients cause
movement and redistribution of the interstitial
fluid. Fluid movement may also be
accompanied by electrokinetic effects such as
streaming potentials and currents as various
ions are moved through the charged matrix
[29,30]. It is now well accepted that the
primary mechanism of viscoelasticity in
cartilage results from frictional interactions
between the solid and fluid phases, although
there is evidence that the solid matrix exhibits
intrinsic viscoelasticity. Cartilage also
exhibits highly nonlinear mechanical
properties such as strain-dependent moduli
[31], strain-dependent hydraulic permeability
[32], and a difference of nearly two orders of
magnitude in tensile and compressive moduli
[33]. These properties are also anisotropic,
particularly in tension, and vary significantly
with distance from the tissue surface and with
site on the joint [34]. More complex but
equally important mechanical behaviors
include the presence of internal swelling
pressures that give rise to inhomogeneous
residual stresses within normal articular
cartilage [35]. Finally, cartilage possesses
important geometric and material
characteristics that endow it with unique
frictional properties. This low coefficient of
friction, coupled with fluid-dependent
mechanisms of load support, allow for
minimal tissue wear under a relatively harsh
mechanical environment [36].
Investigators have also characterized subfailure and failure properties in tendons and ligaments. Creep testing reveals a large initial elastic response followed by a small additional viscoelastic deformation over time [27]. Corresponding stress relaxation experiments demonstrate a rather substantial reduction in stress over time to about 40% to 60% of initial values [37-39]. A uniaxial failure test can then be performed to force/stress levels that originally compromised the tissue both as a structure and as a collagenous material [27,40-42]. The linear stiffness, maximum force and maximum deformation at failure, and the energies to maximum force and failure (areas under the curve) provide descriptions of the structural capacity of the tissue. Linear modulus, maximum stress and maximum strain, and strain energy densities to maximum stress and failure can also be computed to provide estimates of the quality of the tissue as a material. These parameters follow directly from the corresponding structural properties but factor out the size of the tissue by dividing forces by initial area and deformations by initial length. Typical values for these material properties can vary dramatically depending upon whether strains are measured in the midsubstance or between the tissue ends.

Bone mechanical properties can best be characterized as a function of hierarchical organization. At each level of hierarchy, a continuum mechanics approach to measuring bone properties reveals significant anisotropic (nearly orthotropic) behavior [43,44]. From a physiologic, functional point of view, the integrity of a bone region is dominated by its gross geometry and apparent density. Experimental data suggests that its pre-yield material properties are substantially dependent on its mineral (or mineral/matrix) content, and post-yield or failure behavior is more influenced by its glycoprotein matrix [43,44]. Since bone can adapt substantially to its physical demands, if given sufficient time and early protection from excessive loads, it may attain required properties through a self-regulating process. As a result, the most important design parameter for a tissue engineered bone construct may be the biophysical mechanisms that enable effective remodeling/adaptation to physical demand.

The abundance of data now available in the literature from biomechanical testing does not, however, answer one important question facing the tissue engineer. Which, if any, of these parameters should be used when designing an engineered repair or replacement? Realistically, it will be difficult if not impossible to match all of the material properties and structure of native tissues with tissue engineered constructs. Thus, it would be advantageous to prioritize the multitude of complex properties that are sought (Table 1). Should the tissue-engineered construct match the failure properties of the normal tissue? Should it mimic the viscoelastic behavior of normal tissue? Should its properties be identical to adjacent host tissues, even if they are potentially not “normal.” Or should the construct simply be designed with peak stresses and strains that are some fixed percentage of ultimate values? These issues may be equally applicable with respect to structural parameters as well as material properties. Should the regenerated tissue contain all of the load-bearing constituents of the normal, uninjured structure? Is proper organization required to replicate normal tissue function? Does the tissue in question require the same geometry, organization, and microstructure? How does integration between the graft and host tissue influence success? Clearly the choice of these parameters will depend on the tissue in question, but may involve similar themes or methodologies.

The answers to many of these questions cannot be answered without further fundamental information on the biomechanical and biological properties of native and engineered tissues. Few studies have reported quantitative measures of the material properties of tissue-engineered cartilage. Of the few that have, focus has been placed on the compressive moduli and hydraulic permeability of cartilage [45-48]. While these properties are likely the most logical starting points, the relative importance of recreating the tissue’s compressive properties in comparison to tensile properties, failure properties, or frictional properties, for example, are not yet known. On a structural basis, many questions remain regarding the relative importance of recreating the native tissue and joint architecture. For example, most attempts at articular cartilage regeneration have sought complete integration between host and repair tissues [49,50].

3. A subset of these mechanical properties must be selected and prioritized.
Complete graft integration has been used as a “gold standard” of cartilage repair, yet the long-term implications of either complete or incomplete tissue integration are not fully understood. Additional factors such as the congruence of opposing cartilage surfaces in a joint may have important implications on the stress environment within the joint [51]. At this point, however, few tissue-engineering approaches are able to precisely control the structure and geometry of newly formed cartilage. An important consideration in such studies may also be the choice of an animal model and how representative the native tissue structure and properties are compared to the human [52]. Since all of these complex issues are unlikely to be addressed at once, it becomes important to prioritize their relative influence on the overall success of a given procedure.

Choosing the most critical properties for a bone construct are somewhat different. From a long-term functional perspective, the most important property of the regenerating bone tissue will be its ability to remodel and adapt to habitual physical demands. Likely, the most rapid way of achieving this goal is to design a construct with a high macroscopic porosity and surface to volume ratio and chemical properties that would promote osteoblast attachment and osteoclast resorption of its surfaces. However, this path of optimization would occur at the loss of initial mechanical integrity. Since the construct could be augmented with many typical orthopaedic fracture fixation hardware devices, it provides designers an opportunity to select a balance between initial mechanical competence and rate of incorporation and replacement.

Similar arguments arise when trying to prioritize structural and material properties for tendon and ligament replacement. Since these tissues carry primarily tensile forces, and only up to 10% (ligament) to 40% of failure (tendon), it would seem logical to try and replicate only the “toe” and early linear regions of the loading curve. Thus toe limit stress and strain as well as tissue stiffness and modulus would seem to be the most important parameters to replicate in the tissue engineered replacement. However, these tissues are also repeatedly loaded under a combination of load and displacement control. Thus, cyclic creep and stress relaxation parameters are probably equally important characteristics to include in the tissue-engineered designs. The peak loads and displacements selected for these viscoelastic tests will change dramatically when new tissues are to be replaced.

4. **Fourth, standards must be set when evaluating the repairs/replacements after surgery so as to determine, “how good is good enough”**?

Assessment of the outcome of successful functional tissue engineering will require quantitative measures of graft properties, structure, and composition. Some aspects of the repair outcome may be inferior, but other mechanical factors of the repairs and replacements might be suitable.

With an emphasis on the material properties and structure of tissue-engineered grafts, it will be necessary to quantify and report outcome measures directly related to the functional behavior of the tissues. Given the biomechanical nature of many tissue-engineered products, there have been surprisingly few reports of the material or structural properties of engineered tissues. In articular cartilage, for example, several investigators have reported either mechanical properties of grafts prior to implantation [47] or at sacrifice [45,46,53]. In tendon, cell-based repairs using autogenous mesenchymal stem cells have resulted in 20 to 30% improvement in material properties when cells are not organized in culture [54]. When these cells are aligned in culture [55,56], the structural and material properties of these repairs have been found to be 100% better than natural repairs of unfilled defects [57]. However, those conditions that optimize the repair outcome for tendon or ligament repair are still not known.

An important direction for the field will be the development of new methodologies that will allow assessment of the material or structural properties of engineered tissues in a non-invasive or minimally invasive manner. For example, the use of biological markers of tissue metabolism [58], in vivo (arthroscopic) biomechanical probes [59], magnetic resonance imaging [60], CT, ultrasound, DEXA [61], and other techniques to assess tissue function may prove to be critical in longitudinal studies of tissue engineered repair, particularly in the clinical setting.

5. **What physical regulation do cells experience in vivo as they interact with an extracellular matrix?**
Once implanted in the body, engineered constructs of cells and/or matrices will be subjected to a complex biomechanical environment, potentially consisting of time-varying changes in stresses, strains, fluid pressure, fluid flow, and cellular deformation [29,30,62]. It is now well accepted that these various physical factors have the capability to influence the biological activity of normal tissues [reviewed in 63], and therefore, may play an important role in the eventual success or failure of engineered grafts. In this regard, it would be important to better characterize the diverse array of physical signals that engineered cells may experience in vivo, as well as their biological response to such potential stimuli. This information may provide important insights into the long-term capabilities of engineered constructs to maintain the proper cellular phenotype and may shorten the iterations required to successfully replace a tissue.

The cells used in the tissue-engineered construct or those that are recruited or migrate to the construct must be organized and stimulated to rapidly synthesize the desired extracellular matrix. The scaffold can play a significant role in influencing the behavior and ultimately the phenotype of the cells. Whether the cells are grown on the scaffold ex vivo [e.g. 54,57], or migrate to it, in vivo, their interaction with the scaffold material may be a critical factor in determining success. The chemical, mechanical and architectural properties of the scaffold will affect the number, phenotype, and adherence properties of the cells. As a result, the mechanical influence on the cells will be related to the mechanical properties of the scaffold, the boundary loading conditions acting on the surgically placed construct, and the number and quality of focal adhesion contacts of the cell to the scaffold. In addition, the shape and morphology of the cells will be related to the cell/scaffold interactions. All of these factors will contribute to the cell’s ability to respond to both mechanical and biologic signals, and subsequently to synthesize and express extracellular matrix. [64-67].

Mechanical stress is an important modulator of cell physiology, and there is significant evidence that physical factors may be used to improve or accelerate tissue regeneration and repair in vitro. For example, early studies showed that cyclic mechanical stretch of skeletal myofibers increased the alignment of myotubes that assembled into “organoids” in culture [68]. In other studies, mechanical stretch has been shown to increase cellular alignment, proliferation, and protein synthesis in many different cell types [69,70]. As the cells used in the tissue-engineered construct must be organized to rapidly synthesize the desired extracellular matrix, control of cellular alignment a priori may provide important advantages in controlling matrix deposition, and presumably, a more rapid development of functional biomechanical properties. More recently, mechanical “bioreactors” have been used to increase matrix deposition in tissue-engineered cartilage by exposing chondrocytes to fluid flow [71], simulated hypogravity [48], and cyclic compression [72,73]. Recent studies have shown improved success of tissue-engineered systems such as blood vessels by preconditioning grafts with pulsatile fluid flow and pressure [74].

Cells even align when cell-collagen composites are contracted onto suture exposed to a static load [55]. Mesenchymal stem cells align within about 24 hours in culture. The cells align more rapidly when cell density is increased, although a threshold of cell density exists above which no change in the rate or extent of alignment occurs. The nuclei of these cells also become more spindle-shaped with increasing cell density [55]. However, little is known about how cyclic loading affects cell shape and alignment and how mechanical loads influence cell proliferation, differentiation, and protein expression under these conditions.

**Future Directions**

Clearly, the field of tissue engineering needs to establish functional criteria that will help those who seek to design and manufacture these repairs and replacements. Conferences and workshops must be organized to bring together experts from academia, industry, and government to agree on functional (structural and mechanical) requirements for important load-bearing tissues. Expanded funding in this area will
also be needed to help basic and applied researchers establish these criteria so that new and more innovative tissue engineered repairs and replacements can be provided to the surgeon and patient.

Scale-up, packaging, storage and handling properties are also critical. The implants must be capable of retaining their mechanical, structural, and biological integrity during large-scale production, packaging, and storage. If the tissue-engineering construct is too fragile or difficult to handle in the operating room, surgeons will likely not use the devices in patients. Understanding those conditions that preserve the character of the implants will be essential for the success of tissue-engineered products.

With rapidly evolving new technologies being developed, the future of tissue engineering for tendon, ligament, cartilage and bone repair should be quite bright. Growth factors, introduced during fabrication or delivery of the constructs, offer the promise of further improving repair quality. However, these factors must be temporally and spatially delivered appropriately if tissue engineers expect to stimulate early cell proliferation and subsequent matrix synthesis. This matrix must also be deposited and rapidly organized if the repair is to be capable of resisting the large in vivo forces of daily activities. The organization and orientation of these matrices might also be further enhanced through strategic mechanical stimulation of the constructs during the in vitro fabrication process or early post-surgical periods. Providing either controlled strain or load signals to the constructs will likely be beneficial by instructing and organizing the cells in a way in which they synthesize an appropriately aligned matrix, just as loads applied to the suture passing through the construct aligned the MSCs suspended in a collagen gel [54,55]. However, the load (strain) levels that must be chosen and their frequencies must still be determined and are likely to be tissue and site specific. Novel matrices must also be identified with enough compliance so the cells can organize the construct but with enough stiffness to resist the expected in vivo loading regimes. These matrices may contain pre-formed organic or synthetic fibers that can initially sustain in vivo loading. These matrices should initially attract, anchor and protect the cells, but then degrade at controlled rates that prevent mechanical disruption of the repair and ensure biocompatibility. Many of these treatments are now being investigated and offer real promise for the repair of problematic soft and hard tissue injuries.

References


Table 1. Functional Properties Of Natural And Engineered Tissues

<table>
<thead>
<tr>
<th>Property Type</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anisotropy</td>
<td>Properties vary with direction</td>
</tr>
<tr>
<td></td>
<td>Tensile, compressive, shear moduli</td>
</tr>
<tr>
<td></td>
<td>Permeability</td>
</tr>
<tr>
<td></td>
<td>Failure stress and strain</td>
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<tr>
<td></td>
<td>Fatigue life</td>
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<tr>
<td>Geometry</td>
<td>Morphology</td>
</tr>
<tr>
<td></td>
<td>Microstructure</td>
</tr>
<tr>
<td></td>
<td>Congruence</td>
</tr>
<tr>
<td>Inhomogeneity</td>
<td>Properties vary with site</td>
</tr>
<tr>
<td></td>
<td>Potentially all properties</td>
</tr>
<tr>
<td>Nonlinearity</td>
<td>Stress-strain relationship is not linear</td>
</tr>
<tr>
<td></td>
<td>Tension-compression nonlinearity</td>
</tr>
<tr>
<td></td>
<td>Nonlinear permeability</td>
</tr>
<tr>
<td></td>
<td>Material nonlinearity</td>
</tr>
<tr>
<td></td>
<td>Nonlinear viscoelasticity</td>
</tr>
<tr>
<td></td>
<td>Coupling of normal and shear stress</td>
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<tr>
<td>Physicochemical-mechanical coupling</td>
<td>Residual stresses</td>
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<tr>
<td></td>
<td>Swelling</td>
</tr>
<tr>
<td></td>
<td>Electrokinetic effects</td>
</tr>
<tr>
<td>Tribological Properties</td>
<td>Frictional coefficient</td>
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<tr>
<td></td>
<td>Wear properties</td>
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<tr>
<td></td>
<td>Hardness</td>
</tr>
<tr>
<td>Viscoelasticity</td>
<td>Properties vary with time or rate of loading</td>
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<tr>
<td></td>
<td>Multiphase or poroelastic</td>
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<tr>
<td></td>
<td>Energy dissipation</td>
</tr>
<tr>
<td></td>
<td>Intrinsic viscoelasticity</td>
</tr>
<tr>
<td></td>
<td>Fluid viscosity</td>
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