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Shape, Loading, and Motion in the Bioengineering Design, Fabrication, and Testing of Personalized Synovial Joints

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Abstract

With continued development and improvement of tissue engineering therapies for small articular lesions, increased attention is being focused on the challenge of engineering partial or whole synovial joints. Joint-scale constructs could have applications in the treatment of large areas of articular damage or in biological arthroplasty of severely degenerate joints. This review considers the roles of shape, loading and motion in synovial joint mechanobiology and their incorporation into the design, fabrication, and testing of engineered partial or whole joints. Incidence of degeneration, degree of impairment, and efficacy of current treatments are critical factors in choosing a target for joint bioengineering. The form and function of native joints may guide the design of engineered joint-scale constructs with respect to size, shape, and maturity. Fabrication challenges for joint-scale engineering include controlling chemo-mechano-biological microenvironments to promote the development and growth of multiple tissues with integrated interfaces or lubricated surfaces into anatomical shapes, and joint-scale bioreactors which nurture and stimulate the tissue with loading and motion. Finally, evaluation of load-bearing and tribological properties can range from tissue to joint scale and can focus on biological structure at present or after adaptation.

Keywords

synovial joint; articular cartilage; tissue engineering; shape; motion

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#Equal Contribution

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1. INTRODUCTION

Healthy synovial joints facilitate efficient and pain-free skeletal articulation. Within synovial joints, articular cartilage covers the ends of long bones and acts as a low friction, wear resistant, bearing surface in the presence of a lubricious synovial fluid. Extrasynovial ligaments and, when present, intrasynovial ligaments and menisci provide stability and help define range of motion. However, the biomechanical functions of joint tissues can be compromised by trauma or disease such as osteoarthritis. Because the intrinsic regeneration of normal articular surfaces is limited and present medical therapies are palliative and not disease-modifying (Buckwalter and Mankin, 1998), surgery is often performed to treat pain and dysfunction.

The current surgical treatment paradigm for damaged articular surfaces depends on lesion size and severity (Fig. 1). Microfracture is commonly used for focal cartilage defects $<2\text{cm}^2$ to stimulate reparative mesenchymal stem cells from subchondral bone to form a fibrocartilage repair tissue (Buckwalter and Mankin, 1998, Steadman, et al., 2002). Osteochondral autograft transplantation or autologous chondrocyte implantation (ACI) are used for $2\text{--}3\text{cm}^2$ defects, and osteochondral allografts are used for large ($\sim 4\text{cm}^2$) or multiple lesions (Brittberg, 1999, Bugbee, 2004, Hangody, et al., 2001). For severe degeneration, joint resurfacing or replacement is typically prescribed.

While these treatments are evolving, limitations continue to spur the development of new therapies. Drawbacks include the quality and consistency of repair tissue with microfracture and ACI (Buckwalter and Mow, 1992, Minas, 2001), osteochondral graft availability and chondrocyte viability with allogenic grafts (Schachar, et al., 1999, Vangsness, et al., 2003), and wear and loosening of prostheses (Bauer and Schils, 1999, Revell, 2008). Tissue engineering therapies are attractive for their potential to restore the biological and mechanical functions of joints. As treatments for small articular defects improve, focus is shifting to the larger-scale paradigm of bioengineering partial or whole joints in complex shapes. Such biological joints could ultimately allow for replacement of large areas of joint damage by providing transplantable anatomically-shaped grafts that function and adapt under physiological joint loading and motion.

This paper provides a forward-looking view of scientific and engineering challenges along the path to creation of partial or whole synovial joints, with particular emphasis on the roles of shape and motion in joint mechanobiology. Design considerations include biomedical need and biological-biomechanical targets. Solution development includes component identification, assembly, cultivation, and testing.

2. SYNOVIAL JOINT GEOMETRY, MOTION, AND CARTILAGE CONTACT

The native structure and function of synovial joints in the body provide design goals for joint engineering. Surface geometries, whole-joint motions, and relative motions of cartilage surfaces give rise to the spectrum of native joints. The complex shapes and motions of normal and engineered joints can be quantified.

2.A. Synovial Joint Geometry

The surface geometry of joints affects joint congruence and contact mechanics. Atypical geometries predispose joints to certain diseases through altered biomechanics (Beck, et al., 2005, Colombo, et al., 2008, Daniel, et al., 2005, Ganz, et al., 2003, Noble, et al., 2003). The geometries of synovial joints can be generalized into five shapes according to predominant curvatures of articulating surfaces (Fig. 2).

Planar joints have a flat or slightly curved surface geometry. *Cylindrical* joints have surfaces that are curved in one direction and flat in the orthogonal direction. *Spherical* (or “ball-and-socket”) joints, have approximately constant radius of surface curvature. *Elliptical* joints have radii of curvature that differ in orthogonal directions. *Saddle* joints have an articulating surface that is concave in one direction and convex in an orthogonal direction.

2.B. Joint and Cartilage Surface Motion

Cartilage-capped long bones can articulate against an opposing surface in three basic motions (Fig. 3A). *Translation* results in a change in position along an arbitrary axis. *Spin* motion involves rotation about a longitudinal axis of bone and occurs with internal and external rotation of the limbs. *Swing* motion is defined as rotation about an orthogonal axis and occurs during flexion, extension, adduction, and abduction. These motions are limited by the presence of ligaments, joint capsules, and muscles, and dependent on the geometry of the opposing surface. The combination of these three basic motions leads to the complex kinematics of the body.

Relative motions between two cartilage surfaces in contact can be decomposed into sliding, rotation, and rolling movements (Fig. 3B). as illustrated for a simple joint viewed as a fixed (F) and a moving (M) surface. *Sliding* occurs when the contact points of F remain the same while the contact points of M change. *Rolling* occurs when there is a one-to-one correspondence between the points on F and M (i.e. each point in F always comes into contact with the same corresponding point on M within one revolution). During *rotation*, the same points on F and M are involved in the articulation, while the relative positions between F and M points change. Combinations of sliding and rolling, sliding and rotation, and rotation and rolling result in changes of F and M contact points as well as their correspondences. While all types of motion do not occur physiologically in all joints, examples of each occur to certain degrees in various joints.

2.C. Quantitative Shape Analysis of Joints

Analysis of joint surfaces allows definition of local and global shape features with a limited number of parameters. Various laboratory (photogrammetry, stereophotogrammetry, laser scanning) and *clinical* (radiography, arthrography, B-mode ultrasound, computed tomography, magnetic resonance imaging) methods have been used to acquire surface data at various resolutions. Data can be fit to mathematical representations of joint geometry such as bicubic patches, B-splines, and thin-plate splines (Ateshian and Eckstein, 2005, Ateshian, et al., 1991, Gu, et al., 2008). Joint shape descriptors include mean and Gaussian curvatures calculated at points along the surface. Alternative representations are from 2D and 3D statistical shape modeling of biological structures (Cootes, et al., 1995, Lorenz, 2000). Accurate and efficient methods of surface quantification will facilitate the design of shaped grafts for joint repair.

2.D. Joint Motion Analysis and Cartilage Contact Mechanics

Quantification of joint mechanics and cartilage surface interactions provides constraints and boundary conditions for theoretical models as well as design targets for the movement of bioengineered joints. Traditionally, optical, magnetic, or optoelectronic systems have been used to track surface motions (Khumsap, et al., 2004, Wilson, et al., 2009), while 2D (biplanar radiography, fluoroscopy) and 3D (CT and MRI) scanning methods have been used to estimate joint-scale forces and moments (Freeman and Pinskerova, 2005, Muhle, et al., 1999, You, et al., 2001). The advancement of experimental and computational methods has allowed for estimation of contact areas and surface deformation during joint motion.

Such information from joint-scale analyses can be used with experimental and theoretical analyses at the cell and tissue scale in order to elucidate tissue deformations and surface

interactions at a finer scale during the relative motion of two contacting cartilage surfaces (Fig. 3C) (Gratz and Sah, 2008). Compressive (Schinagl, et al., 1997) and shear properties (Buckley, et al., 2008, Wong, et al., 2008) of cartilage tissue vary with depth from the articular surface. In turn, tissue-scale cartilage deformation has been related to local stresses and strains at the cellular level both experimentally using high resolution microscopy (Guilak, et al., 1995, Szafranski, et al., 2004) and theoretically using multi-scale biphasic finite element models (Guilak and Mow, 2000), yielding estimates of fluid flow and strain amplification in the pericellular matrix (PCM) around chondrocytes (Alexopoulos, et al., 2005, Gupta and Haut Donahue, 2006). Features of chondrocyte deformation and load appear to regulate chondrocyte matrix metabolism and membrane transport (Huselstein, et al., 2008, Lammi, 2004). Further development of multi-scale methods for describing and analyzing motions and forces in natural joint geometries will improve the understanding of mechanobiology of native and engineered cartilage during development, homeostasis, and degeneration.

3. DESIGN CONSIDERATIONS FOR JOINT-SCALE TISSUE ENGINEERING

The shift to designing joint-scale osteochondral constructs will be driven by consideration of biomedical need and by the customization of size, maturity, and shape.

3.A. Biomedical Need

The biomedical need for a large-scale tissue engineered construct for an individual joint is dictated by the incidence and prevalence of degeneration, severity of functional impairment, and efficacy of current treatments. For example, the prevalence of osteoarthritis is higher in the knee than the ankle (Brown, et al., 2006, Cushnaghan and Dieppe, 1991); however, both joints are important in mobility during daily activities, and the general effectiveness of treatment of osteoarthritis by joint replacement is poor for the ankle relative to the knee (Clifford and Mallon, 2005). In addition, with the predicted increase in osteoarthritis prevalence to almost epidemic levels associated with increasing longevity in the general population (Lawrence, et al., 2008), there are clear needs for therapies before, or instead of, traditional total joint replacement to avoid difficult revision surgeries and improve biological and kinematic joint function. This is especially true for young patients with advanced osteoarthritis (Dorr, et al., 1994). Thus, the greatest impact of biological joint replacement will be in joints afflicted with osteoarthritis at a high incidence, and with a major impact on quality of life and an unmet clinical need.

3.B. Graft Size and Maturity

The extent and severity of joint degeneration dictate the size and load-bearing capabilities of an engineered graft. For cell-based cartilage repair therapies that recapitulate normal development and growth, tissue formation progresses from cell isolation and proliferation to chondrogenesis, tissue expansion, and tissue maturation (Fig. 4). Most current therapeutic tissue engineering treatments are immature compared to native tissue and intended primarily for relatively small defects. However, existing allograft and tissue engineering treatments are shifting toward larger defects. Constructs for biological hemi-, unicompartmental, or total joint arthroplasty will benefit from being more mature in terms of biomechanical function in order not only to contribute effectively to load-bearing but also to minimize rehabilitation time *in vivo*. Biomechanically mature grafts may also help restore the mechanical environment of the joint from a chronically abnormal state, contributing to further degeneration, to a healthier one. It remains to be determined how mature joint-scale constructs should be at the time of implantation into particular lesions.

3.C. Graft Shape

In joint-scale engineering, both a custom-fit shape and a “shoe-size” approach to shape may be appropriate for the implant. Traditionally, joint arthroplasty has been performed with limited sizes of off-the-shelf, modular implants because of their reliability and high costs associated with customization (Dennis and Lynch, 2005, Laskin, 1976). However, the range of available implant sizes has increased in recent years to allow for customization as anatomical variations associated with race, stature, and gender are being elucidated (Weng and Fitzgerald, 2006). Joint shape-matched implants (Zimmer Gender Solutions Knee™, Warsaw, IN) target women and specific patients (ConforMIS, Burlington, MA). Patient-specific surgical guides and instruments allow surgeons to make cuts and select implants that match the normal anatomy of each patient (OtisMed, Alameda, CA; Biomet, Warsaw, IN; Depuy, Warsaw, IN). In joint-scale engineering, customization would allow surgeons to treat unique joint geometries and may be useful for partial resurfacing surgeries, where the opposing articulating surface is left intact. On the other hand, a “shoe-size” approach would simplify the process of construct creation and may be more applicable for total joint arthroplasties, where both joint surfaces are replaced.

4. TISSUE ENGINEERING STRATEGIES FOR PARTIAL AND WHOLE JOINTS

Advances in tissue engineering of cartilage (Klein, et al., 2009), bone (Khan, et al., 2008), meniscus (Sweigart and Athanasiou, 2001), and ligament (Woo, et al., 2004) serve as the foundations for generating partial or whole joints. Critical additional areas for scientific investigation and engineering development include the creation of multi-tissue units, specialized tissue interfaces, complex tissue shapes, and bioreactors capable of applying loads and motion to joints (Fig. 5).

4.A. Engineering Environments for Multiple Tissues

Several repair strategies for dysfunctional synovial joints use the common approach of transplanting functional units consisting of soft tissue (cartilage, ligament, or meniscus) attached to bone. Compared to soft-tissue grafts alone, multi-tissue grafts can offer enhanced integration between graft and host through strong fixation and bone-to-bone healing (Bugbee, 2004, Cole, et al., 2003, Schoderbek, et al., 2007). Such grafts restore bulk tissues and preserve the specialized interfaces between soft tissues and bone.

To engineer a multi-tissue unit such as an osteochondral construct, distinct local environments are needed for promoting tissue-specific formation (Hwang, et al., 2009). The available cell sources can dictate the use of multiple cell types or a single population of stem cells capable of differentiation into multiple tissues. Within a single construct, regulation of distinct cell functions is achieved through spatially heterogeneous biochemical or physical stimuli. Gradients of biochemical factors can be produced by tethering and diffusion (Wang, et al., 2009), while multiphasic scaffolds can present distinct physical cues for chondrogenesis and osteogenesis (Tampieri, et al., 2008). Porous osteoconductive scaffolds have also been widely investigated as substrates supporting the formation of cartilage by chondrocyte encapsulation in hydrogel (Buschmann, et al., 1992, Lima, et al., 2008) or scaffold-free techniques (Allan, et al., 2007, Masuda and Sah, 2005).

4.B. Engineering Integrated Tissue Interfaces

Functional integration of engineered tissues within a construct may benefit from additional understanding of the physical, chemical, and biological properties found at native tissue interfaces. Recent studies have focused on quantifying components of the structure, composition, and function of the calcified cartilage interface between articular cartilage and subchondral bone (Ferguson, et al., 2003, Hwang, et al., 2008), the fibrocartilage interface

between ACL and bone (Moffat, et al., 2008, Wang, et al., 2006), and the ligament-fibrocartilage interface between meniscus and bone (Maes and Haut Donahue, 2006, Villegas, et al., 2008). Co-culture studies using chondrocytes, osteoblasts, fibroblasts, and mesenchymal stem cells are elucidating the biological crosstalk between neighboring tissues (Gerstenfeld, et al., 2003, Jiang, et al., 2005, Nakaoka, et al., 2006, Sanchez, et al., 2005, Wang and Lu, 2006). These studies elucidate concepts that may serve as biomimetic strategies to reproduce functional interfaces in engineered grafts and provide benchmarks against which the properties of engineered interfaces can be compared.

Physical integration of engineered tissues to form a functional unit can be achieved from initial assembly of components, as in a biphasic scaffold, or else by separate culture of tissues with subsequent bonding by sutures, fibrin glue, and other methods (Martin, et al., 2007, O'shea and Miao, 2008). While these strategies may yield physical integration, engineering design principles are needed to recreate the specialized features found in native interfaces (Yang and Temenoff, 2009). Making use of specific cellular phenotypes, such as the ability of deep zone chondrocytes to initiate matrix calcification, can facilitate the biomimetic formation of a zone of calcified cartilage in osteochondral constructs (Allan, et al., 2007). Analogously, larger scaffolds support transitional fibrocartilage phenotypes for bridging the ACL-bone interface (Spalazzi, et al., 2006).

4.C. Engineering Lubricated Tissue Surfaces

Within the synovial joint, interfaces occur not only between two adjacent tissues but also between tissues and the synovial fluid compartment with specialized lubricated tissue surfaces. The tissue-fluid interface is critical to the low friction, wear resistant properties of a synovial joint. Lubricant molecules, such as hyaluronan (HA) and proteoglycan 4 (PRG4), are secreted into the synovial space by the surrounding tissues including synovium, articular cartilage, menisci, and intra-articular ligaments (Jay, et al., 2000, Schumacher, et al., 1999, Schumacher, et al., 2005, Smith and Ghosh, 1987, Sun, et al., 2006). Articular cartilage constructs which actively secrete PRG4 at the superficial surface were generated by stratifying zonal populations of chondrocytes (Klein, et al., 2003). Lubricant secretion from engineered tissues may be further modulated by biomechanical and biochemical stimuli (Grad, et al., 2005, Khalafi, et al., 2007, Schmidt, et al., 2008). Functionally lubricious fluid mimicking synovial fluid containing HA and PRG4 has also been generated in a bioreactor through biomimetic co-culture of synoviocytes and chondrocytes (Blewis, et al., 2009).

4.D. Forming Anatomical Shapes

When formed into appropriate anatomical shapes, osteochondral constructs and other engineered functional units may become useful as grafts for joint repair or parts for constructing whole bioengineered joints. Several techniques exist for imparting anatomical contours to tissue constructs. Most scaffold materials can be cast, milled, printed, or otherwise formed into anatomical shapes to serve as positive templates for tissue growth. Hydrogels with encapsulated cells are typically conducive to shaping by injection into molds and polymerization *in situ*. Anatomical geometries have been created with scaffold-free approaches by seeding primary or alginate-recovered chondrocytes at high density into molds (Aufderheide and Athanasiou, 2007, Han, et al., 2008). Anatomical imaging data, obtained from MRI or CT, can serve as the inputs for computer-aided machining or solid freeform fabrication of scaffolds or molds with high shape fidelity (Ballyns, et al., 2008, Feinberg, et al., 2001). However, the shape fidelity of a construct may diminish with subsequent tissue growth or scaffold degradation. Growth may need to be controlled or predicted *a priori* with the aid of mechanobiological growth models (Davol, et al., 2008, Heegaard, et al., 1999). Tissue shape may also be modulated *in vitro* through physical or biochemical means as demonstrated by the

contouring of immature cartilage (Williams, et al., 2007) and the lengthening of ligaments and tendons (Esther, et al., 2008, Wood, et al., 2003).

The application of shaping techniques is evident in examples of anatomically-shaped (hemi-) joint fabrication. These include phalanges formed with solvent-cast synthetic polymer scaffolds in combination with periosteum and isolated chondrocytes (Isogai, et al., 1999, Landis, et al., 2005, Sedrakyan, et al., 2006), patella formed from a milled trabecular bone substrate with a molded chondrocyte-agarose layer (Hung, et al., 2003), and mandibular condyle formed from molded PEG hydrogel with stratified layers of encapsulated stem cells (Alhadlaq, et al., 2004). Whole-joint bioengineering has been attempted by apposition of engineered distal and middle phalanges with a joint capsule formed by a tenocyte-seeded PGA mesh (Isogai, et al., 1999, Landis, et al., 2005), and resurfacing devitalized chick knees with chondrocyte-seeded collagen sponges (Warden, et al., 2004, Zaleske, et al., 2003). In these whole-joint studies, anti-adhesion sheets of silicone or ePTFE were used to prevent fusion of opposing articular surfaces during *in vitro* or subcutaneous *in vivo* culture.

4.E. Bioreactors for Joint Loading and Motion

The tissues which comprise a joint are typically mechanosensitive, altering their biological activities and, in turn, their biochemical and physical properties, in response to the local physical environment (Allori, et al., 2008, Grodzinsky, et al., 2000, Guilak, et al., 1997). In addition to biochemical stimuli and nutrient and waste exchange, many bioreactors provide specific mechanical cues to guide the growth, remodeling, and maturation of engineered musculoskeletal tissues (Vunjak-Novakovic, et al., 2005, Williams, et al., 2008). Physical stimuli may be transmitted through the fluid medium in bioreactors producing hydrostatic pressure gradients or fluid flow across or through a construct. Mechanical stimuli may also be applied directly to constructs in the form of static or dynamic tension, compression, or shear.

While simplified loading regimes may facilitate the development of models and an understanding of mechanobiological processes, bioreactor designs have been evolving to incorporate complex loading and motion, with opposing surfaces that compress, shear, and slide. One approach is to apply loading and traction to a tissue surface, such as that achieved when a chondral tissue pin is articulated against a ceramic hip prosthesis which can undergo compression and biaxial rotation (Wimmer, et al., 2004). Certain types of applied articulation modulate chondrocyte gene expression, including that of PRG4 lubricant and cartilage oligomeric matrix protein, in a velocity dependent manner (Grad, et al., 2006, Wimmer, et al., 2009). A different approach is to apply loading to joint components in a biomimetic configuration. When a continuous passive motion device was transformed into a whole-joint bioreactor, PRG4 synthesis by articular chondrocytes in knees joints was upregulated in a manner dependent on surface loading and motion (Nugent-Derfus, et al., 2007). These studies suggest that mechanical conditioning of engineered joints may affect the tribological properties of the bathing medium and synovial interfaces, which in turn would affect the local mechanobiological environment of the cells within articulated tissues.

5. MECHANICAL TESTING AND ANALYSIS OF SYNOVIAL JOINTS

The success of a tissue or graft for joint repair may depend on its load-bearing properties and its ability to survive within a demanding joint environment. A variety of mechanical properties can be evaluated for a tissue or graft at scale levels ranging from tissue-level to intact joints. The time scale and conditions over which properties are evaluated may address properties at steady-state or evolving under the influence of mechanobiological stimuli.

5.A. Load-Bearing Properties of Articular Cartilage

Mechanical testing is often performed on localized regions of a joint or on excised tissue samples to simplify experimental configurations and analyses. With appropriate boundary conditions and with assumptions about sample (in)homogeneity and (an)isotropy, material properties can be estimated. Indentation testing, for example, has been widely used to characterize the health and function of cartilage because it is relatively easy to perform, nondestructive measure, and interpretable in terms of structural (Kempson, et al., 1971) or material biomechanical properties (Mow and Huiskes, 2005). Indentation measures are sensitive to the structure and composition of the tissue (Jurvelin, et al., 1988, Lu, et al., 2004) and, therefore, can reflect cartilage degeneration (Bae, et al., 2003, Froimson, et al., 1997, Kempson, et al., 1971) and repair (Messner and Gillquist, 1993, Wakitani, et al., 1989), as well as tissue edges and interfaces (Bae, et al., 2004, Smith and Mansour, 2000). Compressive and tensile testing methods have also been used to assess the structural and material properties of cartilaginous repair tissue. Compressive testing of engineered tissue before implantation (Bastiaansen-Jenniskens, et al., 2008, Lebourg, et al., 2008, Obradovic, et al., 2001, Pfeiffer, et al., 2008, Spiller, et al., 2008) and at the time of retrieval (Ando, et al., 2007, Chu, et al., 1997) reflect load-bearing properties while tensile properties of repair tissue between an implant and host cartilage reflect the degree of integrative repair (Gratz, et al., 2006). These tests, however, utilize excised tissue samples of specified or measured geometry for calculation of material properties.

5.B. Assessment of Tribological Properties

In the synovial joint, cartilage slides against cartilage, meniscus, synovium, and ligament, and lubrication of these tissues by synovial fluid appears critical to reducing friction and wear. Friction is the resistance to motion between two bodies in contact. The friction coefficient is the ratio of the forces transverse (frictional) and normal to the contact area (Ateshian and Mow, 2005, Swanson, 1979). Wear is the progressive loss of the bearing substance from a body in contact with another body as a result of mechanical action, whether through relative sliding or cyclic loading. A wear coefficient can be defined as the ratio of the volume of material lost to the load normal to the contact and to the total sliding distance (Stachowiak and Batchelor, 2005). *In vivo*, wear can be estimated from serial MRI scans (McCann, et al., 2009). *In vitro*, wear volumes for a hydrated tissue such as cartilage can be estimated from the amount of collagen or proteoglycan released into the test solution and thereby account for tissue swelling that occurs with OA (Maroudas, 1976). Cartilage surface roughening is another index of wear, visualized classically as India ink up-take on the tissue surface (Meachim, 1972) and quantified through digital imaging methods (Chang, et al., 1997) or estimated by surface profilometry to determine surface roughness (Northwood, et al., 2007).

5.C. Tissue-Scale Tribological Testing

A variety of *in vitro* lubrication tests apply linear translation or rotation to excised tissue samples (Fig. 6A,B). At this scale, tissues are isolated from their surroundings, sample geometry is simplified from that of the joint, and fluid depressurization paths and characteristic times can be controlled. A variety of lubrication regimes are generally operative during linear translation of two deforming surfaces, while the boundary lubrication regime is predominantly operative with rotational motion, since the same two surfaces remain in contact (Bowden and Tabor, 1950, Malcom, 1976). Cartilage has been tested in contact with artificial materials (Forster and Fisher, 1996, Radin, et al., 1971, Wang and Ateshian, 1997) or with cartilage (Davis, et al., 1979, Katta, et al., 2009, Malcom, 1976, Schmidt and Sah, 2007). Such tests have been used to evaluate the lubricity of synovial fluid in health and disease, as well as to assess the friction-reducing capabilities of putative lubricating molecules (Davis, et al., 1979, Forster and Fisher, 1996, Schmidt, et al., 2007). Engineered cartilage tissue exhibits friction

coefficients that decrease with increasing maturation time and increasing water content (Morita, et al., 2006, Plainfossé, et al., 2007).

Analogous tests assess the wear of cartilage against a variety of counter-surfaces. Cartilage wear has been analyzed with counter-surfaces of polished stainless steel plates (Berrien, et al., 2000, Lipshitz and Glimcher, 1979, Owellen, 1997) and polymers used for tissue engineering applications (Katta, et al., 2007, Kobayashi and Oka, 2004), as well as cartilage with various lubricants (Temple, et al., 2007). Wear testing of engineered tissues may be useful for material and fluid characterization, with the advantage of well-defined sample geometries and fluid depressurization times.

5.D. Joint-Scale Tribological Testing

Whole-joint systems for testing lubrication function offer the advantage of tissue geometries and loading patterns that may be physiological (Fig. 6C) and thereby indicative of *in vivo* articulation. A whole joint testing system, such as a continuous passive motion device, allows evaluation of the ability of a defect repair strategy to withstand joint motion (Drobnic, et al., 2006) or to quantitatively evaluate the joint friction or wear resulting from a repair strategy. Intact joints have been tested, either in passive or active pendulum instruments or with robotic arms to assess the effects of experimentally-induced cartilage degeneration (Jay, et al., 2007, Obara, et al., 1997) and synovial fluid lubrication (Linn, 1967) on the frictional properties between two joint surfaces. The large contact areas, however, reflect lubrication mediated by fluid pressure and the complex geometry may require complex motion and loading patterns (Frank, et al., 1984). In addition, the presence of ligaments, menisci, and synovium may modulate the lubrication mechanics, and complicate interpretation of the contribution of cartilage-on-cartilage contact. Unicompartamental knee joint testing systems have also been used to assess the friction between cartilage surfaces with and without a meniscus (McCann, et al., 2009) and between cartilage and metal surfaces (McCann, et al., 2009).

Articular cartilage wear has also been assessed using an actively-loaded pendulum-style instrument on partial and whole joints. In *ex vivo* studies of whole bovine metatarsophalangeal joints, very mild disruption of the articular surface appeared after $>1 \times 10^6$ cycles of articulation under static load and was accelerated with a superimposed impact load (Radin and Paul, 1971). Cartilage wear can be modulated by treatments simulating the degradation of cartilage and the stiffening of cartilage or bone (Radin, et al., 1982). Other studies using a unicompartamental pendulum system to articulate a femoral condyle against a tibial plateau (McCann, et al., 2009) or other metal plate (McCann, et al., 2009) have induced wear after only 3600 cycles of dynamic loading. Such results may indicate that the unicompartamental test system may be useful as an accelerated test system of tissue structure and lubrication function; or they may reflect abnormal loading patterns and a lack of biological response. As joint-scale tissue engineering strategies evolve, evaluation of the ability to articulate with little friction between and low wearing of the bearing surfaces, under physiologically-motivated loads and motions, will be increasingly important.

6. CONCLUSION

Anatomically-shaped, engineered synovial joints that could adapt to the functional demands of the host environment may have enormous clinical applicability in the future, especially for the treatment of large and extensively damaged or degenerated articular surfaces. Engineering tissues at this scale poses exciting challenges in design, assembly, culture, and testing. Success will require not only the biological understanding, quantitative characterization, and bioengineering analysis of multiple components and environmental cues, but also thorough analyses of the role that joint shape and motion play in mechanobiology. With the advancement

in fields such as imaging, biomaterials, and biomechanics, therapeutically-useful engineered joints are “the shape of things to come.”

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Current Treatment Paradigms for Articular Cartilage Degeneration

Figure 1.

Current treatment modalities for articular surface damage of varying size and severity. Focal defects (<1 cm², arthroscopy image) treated with microfracture. Focal defects (1–2 cm²) treated with autograft mosaicplasty or (matrix-assisted) autologous chondrocyte implantation (ACI/M-ACI). Single or multiple large (2–4 cm²) defects treated with allografts. End-stage osteoarthritic degeneration treated by total joint replacement. Microfracture photo is reprinted with permission from Elsevier (Steinwachs, et al., 2008). Mosaicplasty and ACI photos are reprinted with permission from The Journal of Bone and Joint Surgery, Inc. (Hangody, et al., 2004, Jones and Peterson, 2006).

Joint Geometry	Examples
Plane	<ul style="list-style-type: none"> • intercarpal (hand) • intermetatarsal (foot)
Cylinder	<ul style="list-style-type: none"> • atlantoaxial (head-neck) • humeroulnar (elbow) • interphalangeal (finger)
Sphere	<ul style="list-style-type: none"> • femoroacetabular (hip) • glenohumeral (shoulder)
Ellipse	<ul style="list-style-type: none"> • tibiofemoral (knee) • radiocarpal (wrist)
Saddle	<ul style="list-style-type: none"> • carpometacarpal (thumb) • patellofemoral (knee) • talocrural (ankle)

Figure 2.
Synovial joint classifications based on geometry and examples.

(A) Joint Motions **(B) Cartilage Surface Motions** **(C) Tissue and Cell Deformations**

Figure 3. Schematic of the types of A) whole-joint motions and B) cartilage surface contact motions. C) Tracking of tissue and cell deformations due to joint loading.

Tissue Engineering Therapies for Articular Cartilage

Figure 4.

Developmental progression of biomimetic tissue engineering therapies for articular cartilage repair. Current therapies using ACI, M-ACI, and small chondral and osteochondral constructs, are advancing incrementally towards larger, more phenotypically stable and mature tissues at the time of implantation. Future engineered partial or whole-joint constructs may require or benefit from further *in vitro* maturation of tissues. Chondro-Gide®, ChondroCelect®, DeNovo®ET, and NeoCart® are products of Geistlich Pharma AG (Wolhusen, Switzerland), TiGenix (Leuven, Belgium), ISTO Technologies, Inc. (St. Louis, Missouri), and Histogenics Corporation (Waltham, Massachusetts), respectively.

Key Challenges for Synovial Joint Tissue Engineering

Multiple Tissue Environments

- Cell Types
- Multiphasic Scaffolds
- Biochemical Gradients

Specialized Interfaces

- Soft Tissue - Bone
- Tissue - Synovial Fluid

Complex Shapes

- Shaped Scaffolds
- Scaffold-less Molding
- Controlled Growth

Joint Loading & Motion

- Compression - Shear
- Translate - Spin - Swing

Figure 5.

Key challenges for advancing tissue engineering of partial or whole synovial joints include creating multiple tissue environments, specialized interfaces, complex tissue shapes, and bioreactors for the application of joint loading and motion.

Friction and Wear Testing of Cartilage and Joints

Figure 6. Configurations for friction and wear testing of lubricated cartilage with varying complexity and physiological relevance. Friction and wear tests can be performed with small samples of cartilage in apposition to (A) a material or (B) cartilage, or with (C) whole-joint testing systems. Lubricant solutions within these systems may be varied to reflect various physiological states.