

Mechanical Stimulation of Mesenchymal Stem Cells for Cartilage Tissue Engineering

Articular cartilage is a durable, load-bearing surface whose mechanical function is defined by a set of inhomogeneous (depth-dependent) and anisotropic (direction-dependent) properties. Mechanical forces play a vital role in cartilage development; loading-induced tissue remodeling increases compressive and tensile properties and the development of tissue anisotropy. The limited intrinsic repair of cartilage has motivated numerous efforts to engineer functional replacements; toward this end, mesenchymal stem cells (MSCs) have emerged as a promising cell source due to their ability to undergo chondrogenesis in 3D culture. To date, however, generating MSC-based constructs with the mechanical complexity and integrity of cartilage remains a challenge. In free swelling studies, the compressive and tensile properties of MSC-seeded hydrogels are consistently lower than those of the native tissue. Dynamic compression improves chondrocyte-based construct properties, and we have recently demonstrated that a similar approach can improve the compressive modulus of MSC-based constructs, but only when loading is initiated after a period of pre-culture (**Figure 1**). Despite the promise of these findings, these studies were not designed to generate either depth-dependence or constructs with improved tensile properties. We hypothesize that a new bioreactor system that can better recapitulate the mechanical environment that arises with joint motion may further refine constructs. To that end, we developed a sliding contact bioreactor mimicking two contacting cartilage layers that move relative to one another. Preliminary findings suggest that tensile properties improve and depth-dependent inhomogeneity is induced with long-term sliding contact (**Figure 2**). This is consistent with finite element analysis showing that the tensile strain and fluid efflux/influx generated by sliding contact were depth-dependent and localized to the construct surface (**Figure 3**). Future and ongoing work will focus on application of sliding contact over longer culture durations, and evaluate the efficacy of this loading system on directing mechanical inhomogeneity (depth dependent compressive properties) and structural anisotropy (collagen fiber alignment).

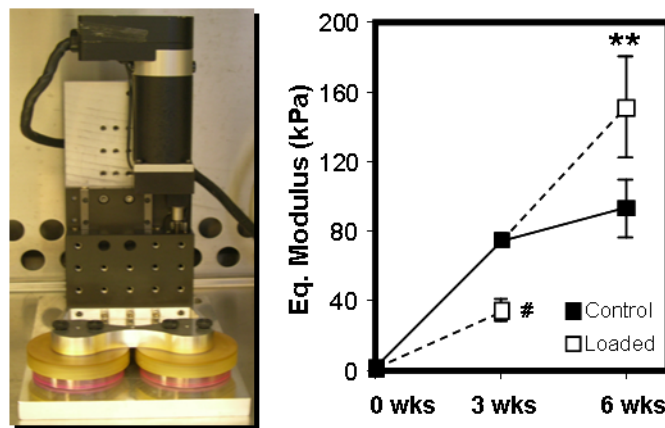


Figure 1: Long-term dynamic compression enhances the mechanical properties of MSC-laden constructs when initiated after 3 weeks of pre-culture.

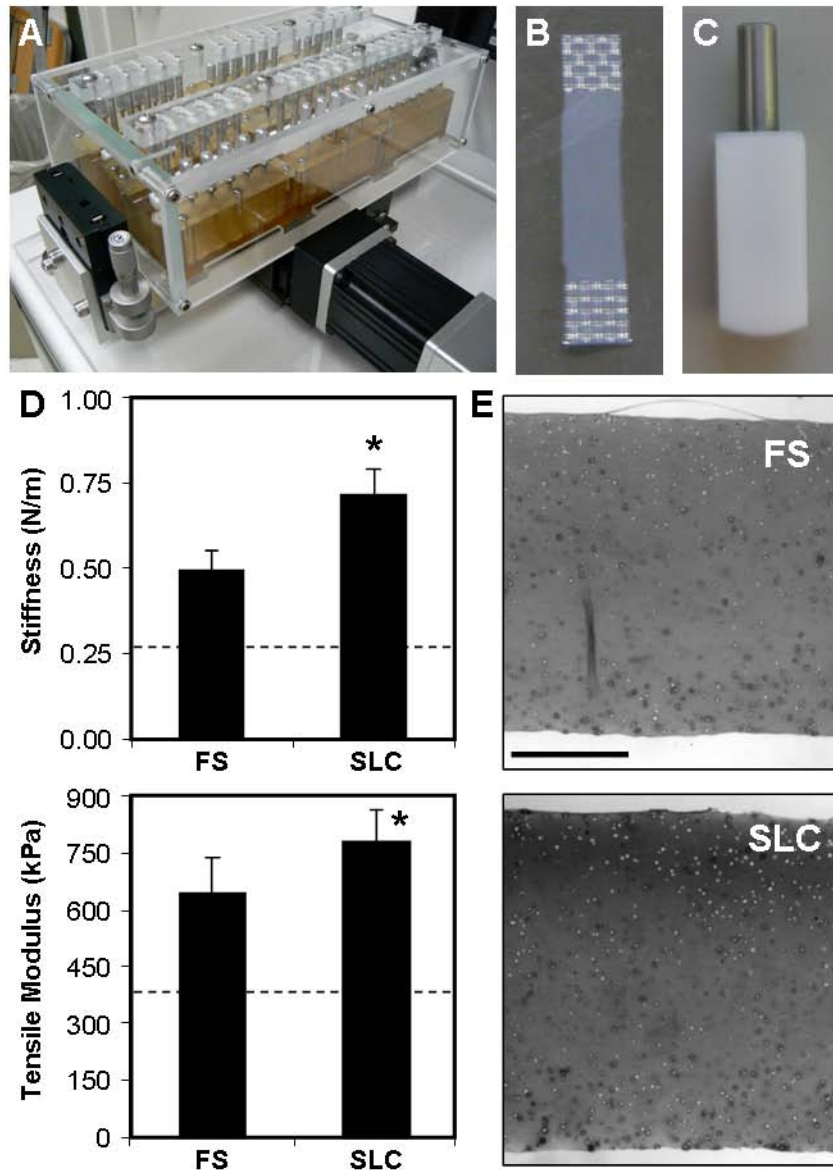


Figure 2: (A) Custom sliding contact bioreactor. (B) Agarose strip cast into nylon meshes. (C) Spherical indenter ($\text{\O}25$ mm). (D) Tensile properties and (E) matrix inhomogeneity of day 42 MSC-laden constructs. Dashed line indicates day 21 values. * greater than FS ($p < 0.05$), + greater than FS ($p < 0.1$), $n=6-8$ per group.

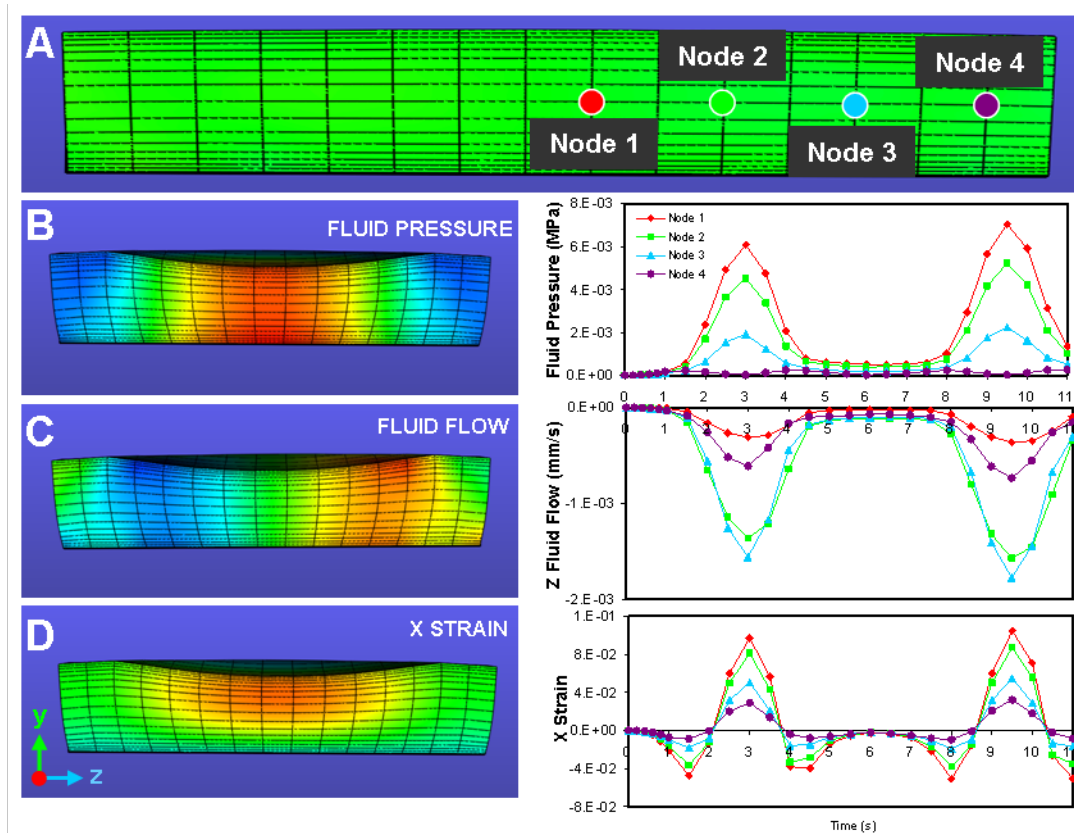


Figure 3: Finite element model of sliding contact where x, y and z represent length, depth and width of construct, respectively. (A) Location of nodes within construct. Cross-sectional views and graphical representations of (B) fluid pressure, (C) fluid flow and (D) x strain as the indenter traveled along the construct length (time = 0-6) and back (time = 6-11).

Recent Publications:

1. Huang AH, Farrell MJ, Mauck RL. "Mechanics and Mechanobiology of Mesenchymal Stem Cell-Based Engineered Cartilage," 2009, *Journal of Biomechanics*, in press (PMID: 19828149).
2. Huang AH, Yeger-McKeever M, Stein A, Mauck RL. "Tensile Properties of Engineered Cartilage Formed From Chondrocyte- and MSC-Laden Hydrogels," 2008, *Osteoarthritis and Cartilage*, 16(9):1074-1082.
3. Huang AH, Baker BM, Ateshian GA, Mauck RL. "Sliding Contact Enhances Mesenchymal Stem Cell Chondrogenesis in 3D Culture," *Transactions of the 56th Annual Orthopaedic Research Society Meeting*, New Orleans, LA, March 6-9, 2009, 35:315.
4. Huang AH, Farrell MJ, Mauck RL. "Dynamic Compression Initiated After Chondrogenesis Improves Mechanical Properties of Mesenchymal Stem Cell Seeded Hydrogel Constructs," *56th Annual Orthopaedic Research Society Meeting*, New Orleans, LA, March 6-9, 2009, 35:1336.
5. Huang AH, Farrell MJ, Mauck RL. "Delayed Dynamic Compression Improves the Mechanical Properties of MSC-Laden Constructs," *Biomedical Engineering Society Meeting*, Pittsburgh, PA, October 7-10, 2009.

6. Huang AH, Mauck RL. “Repeated Dynamic Loading Modulates Cartilage Gene Expression but Does Not Improve Mechanical Properties of MSC-Laden Hydrogels,” *Proceedings of ASME 2009 Summer Bioengineering Conference*, Lake Tahoe, CA, June 17-21, 2009, paper 204339.
7. Mauck RL, Byers BA, Yuan X, Tuan RS. “Regulation of Cartilaginous ECM Gene Transcription by Chondrocytes and MSC in 3D Culture in Response to Dynamic Loading,” *Biomechanics and Modeling in Mechanobiology*, 6(1-2):113-125.

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