Comparison of the predicted axial strain amplification in the cells in the peripheral region (Figure 2) of pressure for cells of either shape moved from the central location to peripheral locations. Although strain amplification was observed in the compared to the more spherical chondrocyte in both the central and discoidal chondrocyte experienced greater relative shear stresses in the peripheral location. Chondrocyte morphology also had a large effect: the proportion of the ECM shear that a chondrocyte experienced increased as the cell was moved from the region beneath the indenter to the peripheral regions of the joint [3]. The ECM was extended about the chondrocyte morphology [3, 4]. These variations in cell shape may represent an adaptation to previous loading history; however, a shift in loading could create a substantial change in cellular stresses due to these differences in cell shape. These changes could be large enough to cause deleterious metabolic response in cells and lead to the degradation of cartilage following changes in joint loading. The purpose of this study was to determine whether the mechanical loads experienced by superficial zone chondrocytes are sensitive to cell morphology and cell location with respect to applied load.

METHODS:
A multiscale approach was used to simulate the deformation of chondrocytes in response to tissue-level loading by using the results of a macroscale (tissue-level) model to drive a microscale (cell-level) model. The macroscale model simulated indentation of a 12mm diameter articular cartilage plug, loaded with a 5mm diameter flat indenter at a pressure of 50kPa. The cartilage was modeled as a linear elastic solid with a Young’s modulus of 1MPa, Poisson’s ratio of 0.3 [5], and thickness of 1mm. Each microscale model consisted of a chondrocyte surrounded by a spherical pericellular matrix (PCM), embedded in an extracellular matrix (ECM). The geometry of the chondrocytes (modeled using linear hexahedral elements) was obtained by assembling voxels from a set of confocal microscope z-stack images of viable chondrocytes in the superficial zone of porcine tibial cartilage from central and peripheral regions of the joint [3]. The ECM was extended about the PCM and cell to form a cubic model with edges of length ~40µm. The cell and PCM were modeled as linear elastic with moduli of 0.6kPa and 1.5kPa, respectively [6]. Displacement results from the macroscale model were applied as essential boundary conditions to nodes on the free faces of a microscale model by registering the microscale model within a macroscale element and linearly interpolating the macroscale nodal displacements.

Cells of different shape (spherical vs. discoidal) were placed directly beneath the load and away from the applied (Figure 1), respectively [3, 4]. To simulate a shift in loading, the cell locations were switched such that the more spherical cell was at the periphery and the discoidal cell was at the center. The primary output variables were peak von Mises shear (σ) and peak pressure (p) experienced by the cells, given the opposing roles of these two types of loading on modulating chondrocyte metabolism [7]. To facilitate comparison between regions with different stress magnitudes, these values were normalized by the von Mises shear and pressure in the surrounding ECM. The model validity was tested by comparing predicted cell deformation to experimental measurements of in situ chondrocyte deformation [8].

RESULTS:
Chondrocyte shear stresses were strongly dependent on cell shape as well as location relative to the applied load (Figure 2). In general, the proportion of the ECM shearing that a chondrocyte experienced increased as the cell was moved from the region beneath the indenter to the peripheral location. Chondrocyte morphology also had a large effect: the discoidal chondrocyte experienced greater relative shear stresses compared to the more spherical chondrocyte in both the central and peripheral locations. Although strain amplification was observed in the chondrocytes relative to their surrounding ECM, the cellular stresses were smaller in magnitude than the ECM stresses. There was a reversal of pressure for cells of either shape moved from the central location to the peripheral region (Figure 2).

Comparison of the predicted axial strain amplification in the cells in the central region of the macroscale model with experimentally reported values was favorable: cell strain was 1.12 times that in the surrounding ECM compared with a value of 1.34 reported experimentally [8].

DISCUSSION:
The results suggest that the stresses experienced by a superficial zone chondrocyte may depend not only on the cell’s location within the joint, but also on its morphology. Specifically, the chondrocyte with the discoidal geometry experienced larger peak stresses in each loading scenario than the cell with the more spherical morphology. Thus, a shift in loads to peripheral locations could elicit heightened metabolic response in those cells, consistent with experimental observations of increased biosynthesis in the peripheral regions of the canine knee following ACL transaction [9].

This model represented the actual chondrocyte geometry from regions with high compressive load in the center of the contact region and regions distant from the contact. While a novel three-dimensional multiscale simulation was employed, the model assumed a linear elastic material model. This representation seemed reasonable when limiting analysis to the superficial zone where fluid exudation allows for considerable solid matrix consolidation during loading, and was supported by model agreement with experimental results.

The results suggest cell shape is adapted to loading history and conditions that shift joint loading to new contact regions could cause substantial changes in the stress of a cell not conditioned to the new stress. This change in stress could lead to degradation of the tissue if the cell cannot metabolically adapt to the new stress history. These observations may help to identify a potential pathway to OA following conditions that cause kinematic or laxity changes to the joint.