

UNCERTAINTIES IN TISSUE MECHANICAL RESPONSE WITH INCREASED CELL DENSITY: MICROSTRUCTURAL AND HOMOGENEOUS MODELS REVISITED

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INTRODUCTION

Finite element analysis, using models of single cells embedded in an extracellular medium, has provided new insights into cellular loading in cartilage [1] and meniscus [2]. Commonly, these models are driven by stress-strain state obtained by simulating tissue deformations with constitutive models representing homogeneous materials. A major assumption of this process is that the stress-strain behavior of the homogeneous tissue model is equivalent to the nominal stress-strain response of the cellular level model. While the extent of violating this assumption may be considered negligible for a single cell in a given volume [1], reportedly higher cell densities [3] may considerably increase uncertainty in simulation results. Therefore, the objective of this study is to quantify the mismatch in elastic response of cartilage models; based on a homogeneous tissue model and with increasing cell densities. Multiscale coupling approaches targeting prediction of cell deformations from tissue and/or organ level loading will likely benefit from this investigation while balancing computational demand with accuracy requirements.

METHODS

The effect of cell density on the mechanical response of a 100 μm by 100 μm square was examined by conducting finite element analysis on three plane strain models (Figure 1): i) homogeneous model with extracellular matrix only, ii) with a single cell at center, and iii) with three cells distributed randomly within the area [3]. During random placement, a minimum pericellular-to-pericellular spacing of 25 μm and a minimum pericellular-to-tissue-edge spacing of 12.5 μm were enforced. The cells have radii of 5 μm , surrounded by a layer of pericellular matrix with a thickness of 2.5 μm [1]. Linearly elastic materials were used for all regions, with properties estimated from Guilak and Mow [1]. The extracellular matrix had a Young's modulus of 1.0

MPa and a Poisson's ratio of 0.125. For the pericellular matrix these were 0.5 MPa and 0.125; for the cell, 0.001 MPa and 0.25. All models were meshed with quadrilateral elements using TrueGrid (XYZ Scientific Applications, Inc., Livermore, CA).

On each model, two different simulation conditions were performed using Abaqus (Simulia, Providence, RI): i) a non-confined uniaxial compression, and 2) a simple shear. For compression, the top edge was moved downwards to a final displacement of 15 μm (nominal compressive strain of 0.15). For shear, the top edge was displaced by ~ 30 μm sideways to obtain a final nominal shear strain of 0.30. In each case, nominal stress was calculated as the sum of reaction forces divided by area of action (100 μm x unit out-of-plane thickness). Nominal strain was the displacement normalized by model height (100 μm). Finite element analysis also provided the local stress distribution.

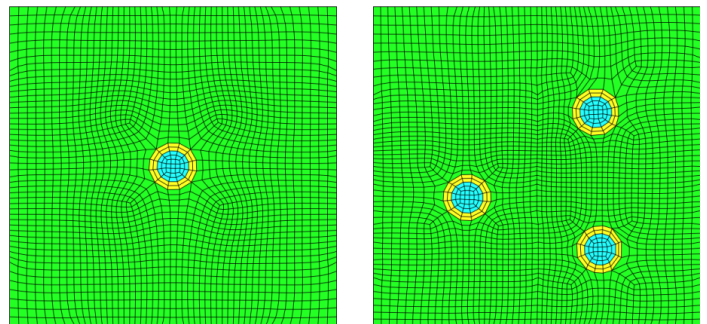


Figure 1: Single-cell and three-cell models illustrating the extracellular matrix, pericellular medium, and cells.

RESULTS AND DISCUSSION

It is not surprising that as generally softer cells were placed inside the extracellular medium, the overall mechanical response became less stiff (Figure 2). At a given nominal compressive strain, overall compressive stress was 3.0% to 3.6% lower for the single-cell model predictions, when compared against the homogeneous extracellular matrix model. It was

decreased by 8.5% to 9.7% for three-cell model. Percentage error increased as nominal compressive strain became larger. For shear loading, single-cell model predicted 4.0% to 4.6% lower nominal shear stress. Comparisons between three-cell model results and those of the homogeneous extracellular matrix model revealed decreased stress values, from 8.9% to 10.2%. Under shear loading, the percentage error was higher at small strains. While error predictions for single cell agree well with previously reported discrepancies [1]; three cell model illustrates the amplification of such errors due to higher number of cells in a region of interest. One should note that the error estimates will likely be influenced in a three-dimensional representation under combined loading; with a detailed representation of the extracellular matrix architecture and tissue mechanics, e.g. biphasic materials.

Identification of cell deformations from body level loading is vital to relate cell vitality and cell mechanobiology to human movement. It is clear that cell deformations and stresses depend on their surrounding medium (Figure 3). In macroscopic modeling of the mechanical deformations in joints and organs, homogeneous representations of tissues are rather attractive due to computational cost. At desired regions in the tissue, a microscopic finite element representation can predict cell deformations by post-processing the stress-strain predictions of the macroscopic model. This study portrays that an increasing level of error in prediction of cell deformations is likely, based on mismatches in predictions of homogeneous and microstructural representations, and depending on cell density and macroscopic strain level. If such inaccuracies cannot be afforded, one may choose direct coupling of macro/micro models using computational homogenization techniques [4], with the expense of an increased computational demand. Alternatively, homogeneous constitutive models, representative of underlying cell distribution and mechanics, can be developed [5].

REFERENCES

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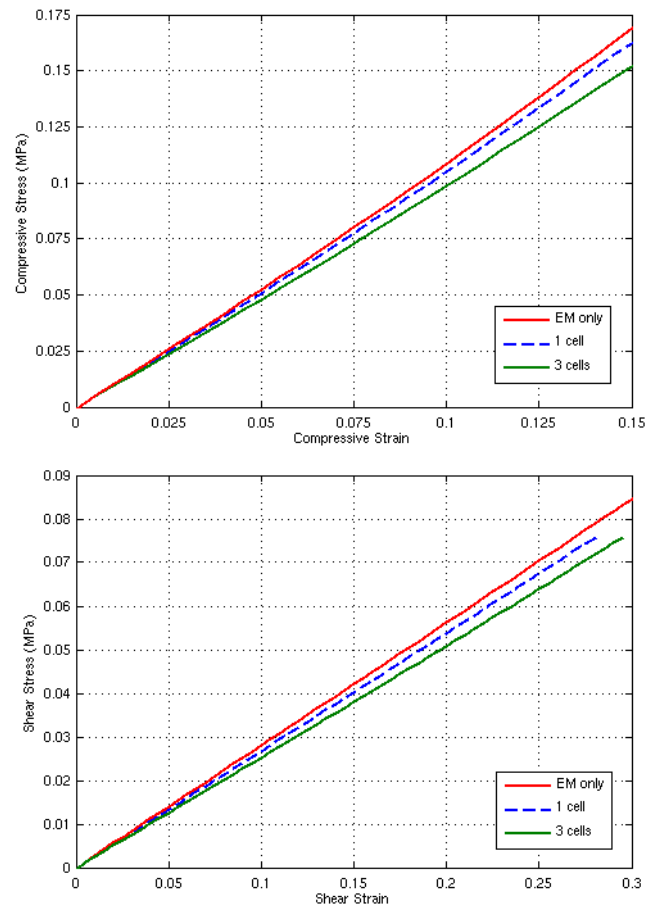


Figure 2: Nominal mechanical response of models under uniaxial compression (top), and in simple shear (bottom). EM: extracellular matrix.

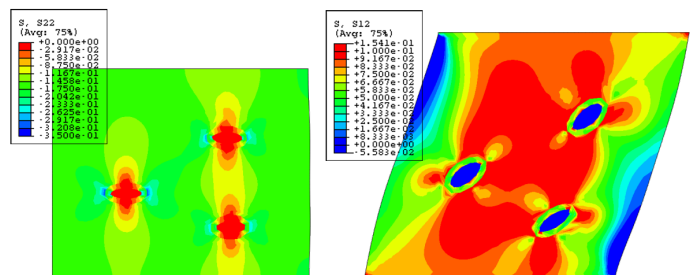


Figure 3: Localized uniaxial stresses along compression axis for compression (left), and shear stress distribution for simple shear (right). Three-cell model predictions are shown.