Multi-scale Computational Modeling and Characterization of Cell Encapsulated Alginate Tissue Constructs

Kalyani Nair,[1] Karen Chang Yan,[2] Wei Sun,[1]
Laboratory for Computer Aided Tissue Engineering, Drexel University[1], Philadelphia, PA, USA
College of New Jersey[2], Ewing, NJ, USA

Introduction

In scaffold guided regenerative therapies, cellular responses are affected by multiple cues arising from the extra-cellular matrix (ECM) components, chemical and/or biological signals from neighboring cells [1]. In this regard, developing mathematical models to predict the stresses at the micro-environment of encapsulated cells would aid in maintaining and controlling the cell phenotype to form functional tissue in an engineered construct.

The objective of this study is to develop a multi-scale numerical model that predicts the stresses and deformations at the cellular level when the tissue construct is subjected to macro-level loads. This study quantifies the effects of micro-level physical and geometrical heterogeneity on cell deformation, providing details of cell injury as well. Specifically, it examines the effects of the matrix material stiffness, and cell geometric distribution in terms of location and size on cell deformation. Subsequent statistical analyses provide insight for the degree of influence from these factors [2].

Materials and Methods

Initial experiments were conducted to characterize the macro-scale biomechanical properties of the scaffold under compressive load. Rat heart endothelial cells were encapsulated in 1.5%(w/v) alginate concentration and cross linked with 0.5% $CaCl_2$ solution to form 4.2mm thick, 9mm diameter alginate discs. Compression tests were carried out on six samples to obtain the stress-strain curve. A non linear axisymmetric finite element model was then developed to validate the experimental results and provide the macro deformation and stresses. The hyper-elastic nature of alginate hydrogel was modeled using the Ogden polynomial. Detailed micro-structures are restored to a region of interest, and micro-level analyses are performed to determine the local deformation and stresses in the region. The cells are modeled as two-phase inclusions using the Neo-Hookean material model to capture the properties of the nucleus and cytoplasm.

Results and Discussion

A nonlinear numerical model has been developed and validated for the mechanical characterization of bulk alginate-cell discs. Fig 1 depicts the geometry of the RHEC-alginate disc used in experimental studies along with the stress-strain curves for both the experimental and numerical studies. The graph indicates that the numerical model follows a very similar trend to that of the obtained experimental data.

A second non linear micro-level model is developed to quantify the stresses and deformations at the cellular level. Fig 2 shows the geometry of the micro-structure along with the applied boundary and loading conditions. Fig3 compares the stress contour plots from the multi-level analysis for 1.5% (w/v) and 3% (w/v) alginate concentrations respectively. The alginate gel with 1.5% (w/v) concentration is less stiff in comparison with that of a 3% (w/v) concentration; hence the stress concentration between cells and 1.5%w/v alginate strands is less severe due to the stiffness mismatch. Fig 4 compares the stress contours of three cases where variations have been made to cell geometry and cell distribution. The stress concentrations are significantly different between the model with uniform radii and distribution and that with random cell radii and distribution. Higher stress concentration can be observed in areas where cells are clustered together compared to areas where cells are relatively isolated.

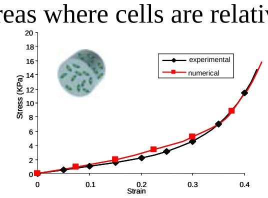

Fig 1: Predicted stress strain curve of bulk 1.5% alginate-cell discs validated with experimental data.

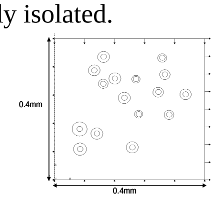

Fig 2: Geometry of the micro-structure with the applied boundary and loading conditions

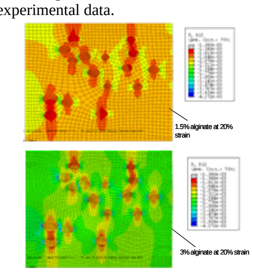

Fig 3: Stress (MPa) contour plots for cells embedded in 1.5% (w/v) and 3% (w/v) alginate concentrations

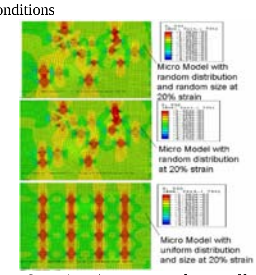

Fig 4:Stress(Mpa) contour analyzing effects of geometrical distribution in size and location of cells within the microstructure

Conclusions

This modeling technique enables to effectively quantify the stresses and deformations in the cell's micro-environment when a tissue construct is subject to macro-level loads. The micro-scale analysis quantifies how the stiffness of matrix material, the microstructure of the cell, and the geometric heterogeneity at the micro-level affect the local stress and deformation in the cell's surrounding. This method provides an effective means to characterize cell encapsulated scaffolds and can be further used to analyze cell injury in tissue engineering applications.

References

1. Lauffenburger, D, A and Griffith, L, G., Who's got pull around here? Cell organization in development and tissue engineering, Proc. Natl. Acad. Sci. 98,2001
2. Nair, K, Yan, K. and Sun, W., A Multi Level Numerical Model for Quantifying Cell Deformation in Encapsulated Alginate Structures, J. Journal of Mechanics of Materials and Structures, accepted for publication.