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FINITE ELEMENT ANALYSIS AND EMPIRICAL SOLUTION FOR FLEXIBLE SUBSTRATES UNDERGOING LARGE EQUIBIAXIAL STRAINS*

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INTRODUCTION

Studies of cellular mechanobiology have depended heavily on the use of *in vitro* experiments. Many devices have been developed to probe those basic physical mechanisms responsible for cell culture mechanostimulus. The work reported here uses a system that imparts equibiaxial loading on a flexible substrate, similar to the Bioflex in Flexcell [1] family of products, to study cell response to mechanical load. The objective of this study is to incorporate an adaptive loading algorithm (ALA) in a finite element analysis (FEA) to update loading conditions, to obtain an accurate correlation between the substrate stain and applied pressure in the culture system. There is a good agreement between the strain predicted from the analysis and that from the direct measurement. Also, based on the mechanistic condition of physical constrains and a regression analysis of finite element results, we have developed an empirical formula to predict the pressure-strain relationship for large substrate strain levels (up to 15 %) to circumvent experimental measurement or FEA for the substrate strain. The results from this study can be used to validate experimental observations and provide a framework for advancing the apparatus to next level involving other loading cases and geometries.

METHODS

Figure 1 gives a schematic of the equibiaxial strain culture system, which consists of a flexible silicone membrane, a circular solid loading post, lubricant between the membrane and post, and vacuum. The membrane is stretched across the loading post by the application of vacuum pressure, such that it creates an equibiaxial stress state on the cells cultured on the membrane. A commercial finite-element code, Abaqus [2], was employed to analyze the pressure-strain relationship of the equibiaxial strain culture device shown in Fig. 1. In the analysis, the geometry and material nonlinearities were invoked. Consistent with experiment, friction between the membrane and post was also considered in the analysis (a value for the friction coefficient of 0.03, [3]). The membrane was assumed to follow a hyperelastic material model while the post was assumed to be rigid. The result in Figure 2 indicates that silicon membrane used in this study could be effectively described as a linear elastic material with an equivalent elastic modulus of approximately 1.75 MPa.

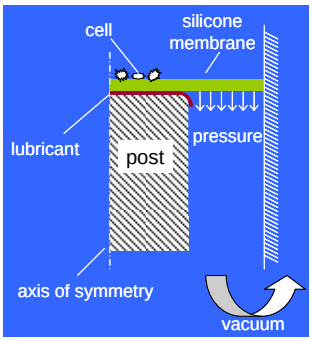

Figure 1. The schematic of the equibiaxial strain culture system for studying cell response to mechanical stimuli.

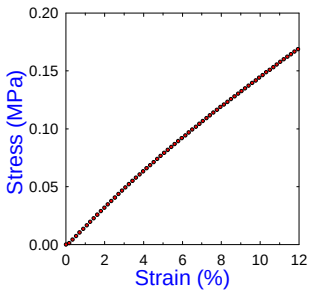

Figure 2. The stress-strain relationship of silicone membrane used in this study.

During the loading, the membrane

will be stretched from on-post region to off-post region where the vacuum pressure is applied. Practically, the pressure should be instantaneously applied to this new incoming material pulled into the off-post region, Fig. 3. Therefore, in order to properly analyze the pressure-strain relationship of the equibiaxial strain culture system, we have implemented the ALA through an Abaqus user subroutine to update the pressure to the incoming material from on-post to off-post. In the analysis, the criterion for updating the load is that if the material (membrane) coordinates are greater than the radius of the post, the pressure would be updated to the current level. Figure 4 gives the difference in strain estimation between the finite element analyses with and without the ALA. This difference depends on the post geometry as well as the ultimate loading level. For example, for an actual strain of 15%, the strain estimate without updating the load can be 35 % lower than the actual strain if the post diameter is 80% of the membrane diameter.

RESULTS AND DISCUSSION

In our study, pressure-strain relationship predicted from the finite element analysis is compared with that obtained from experimental measurement. From the result in Figure 5, one can see there is a good agreement between the prediction and the direct measurement. The directly measured strain was determined from multiple measurements of the changes in distance between two reference points on the membrane surface. To confirm that membrane stretching was biaxial, the distance measurements were monitored in horizontal, vertical, and diagonal directions. Data was collected on multiple substrates to ensure system reproducibility. Values for measured strain are an average of all directions and samples.

The result in Figure 5 also indicates that the pressure and strain have a linear relationship. Although the nonlinearities due to geometry, material and boundary were considered in the FEA, based on two linearities shown in Figures 2 and 5 (stress-strain and pressure-strain), we have developed an empirical formula to estimate the pressure-strain relationship as follows:

$$\varepsilon = \lambda \frac{L}{h} \frac{(L-l)}{l} \frac{P}{E} \qquad (1)$$

where ε and P are the membrane strain and applied pressure, respectively. E is the effective modulus, which is the slope of stress-strain curve in Fig. 2. λ is a universal dimensionless constant (= 2.4±0.2 x 10^{-4}) obtained from a regression analysis of finite element results obtained from various combinations of geometry and material properties. *L* and *l* are the radii of the membrane and post, respectively. *h* is the thickness of membrane. The formula is formed to satisfy some mechanistic constrains. For example, if the post is as large as the membrane, the formula gives a zero strain, while the post diameter becomes very small, the strain grows very large (infinitive due to a point load). The result in Figure 6 shows a good agreement on the pressure-strain relationship between the prediction of eq. (1) and the direct measurement. Therefore, this formula can be used to replace a tedious experimental measurement or finite element analysis for the substrate strain where cells to response.

References:

1. http://www.flexcellint.com. Certain commercial materials, equipment, and software are identified in this paper in order to specify adequately the experimental and analysis procedures. In no case does such identification imply recommendation or endorsement by the National Institute of Standards and Technology (NIST) nor does it imply that they are necessarily the best available for the purpose.

2. ABAQUS Finite Element Analysis Code and Theory, Version 6.5. Hibbitt, Karlsson & Sorensen, Inc. RI, USA.

3. J.P. Vande Geest, E.S. Di Martino, D.A. Vorp, An Analysis of the Complete Strain Field Within Flexercell Membranes, J. of Biomechanics, 37, 1923-1928 (2004).

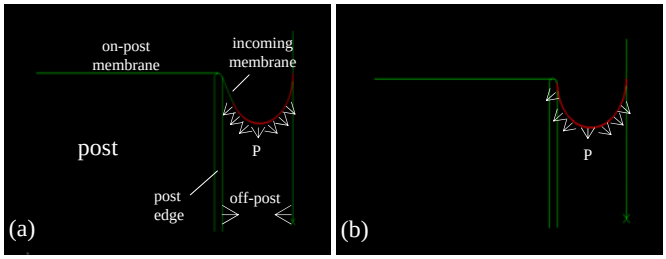

Figure 3. A typical membrane deformation of the culture system, the results are from finite element analyses: without (a) and with (b) updating the load to the current level for incoming material.

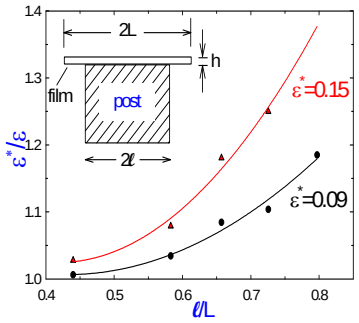

Figure 4. Relative difference in strain estimation as a function of post geometry; ε and ε* are the strains obtained from the model with and without adaptive algorithm, respectively.

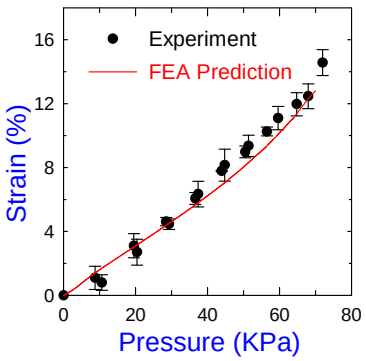

Figure 5. Comparison of strains obtained from different approaches as a function of applied pressure.

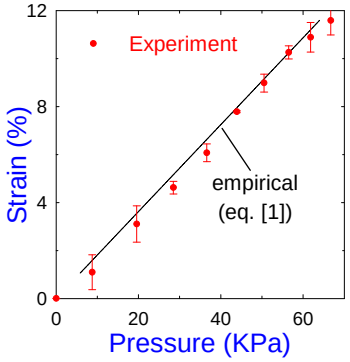

Figure 6. Comparison of strain estimation of the empirical formula to that of the direct measurement.