INTRODUCTION:
In tissue engineering research it is common practice to seed cells on a scaffold and expose them to strain in a bioreactor. Often, cells proliferate and form layers of cells on top of the scaffold rather than infiltrating the scaffold as the surface is the most nutrient rich environment. Moreover, cells may not penetrate the scaffold as they preferentially become embedded in their own secreted matrix. The purpose of this research was to quantify and illustrate how strain is transmitted to cells growing on a scaffold in monolayer or multi-cell-layered constructs versus cells attached within a scaffold.

METHODS:
Three different three-dimensional parametric finite element models representative of eukaryotic cell scaffold seeding were created: (1) cells embedded within a scaffold, (2) a monolayer of cells growing on a scaffold, and (3) five layers of cells growing on a scaffold. The cells were modeled utilizing an idealized ellipsoid volume for the cell body and nucleus, while an ellipsoid shell was utilized for the cell membrane. The models were created using TrueGrid Version 2.3.0 (XYZ Scientific, Livermore, CA) and a mesh density convergence study was conducted. The geometric and material properties used in the models were previously published in the literature [1,2]. In all cases, the cells were attached to the scaffold and to the neighboring cells where present. A prescribed axial displacement was applied to the scaffold face perpendicular to its long axis resulting in an applied 10% strain. Symmetry boundary conditions were applied to all remaining faces of the model. The simulations were run using LSDYNA Version 971 and post processed using LS-PrePost Version 2.2 (LSTC, Livermore, CA). The resulting 1st principal strains were analyzed for the cells of each of the models.

RESULTS:
In the finite element model where the cells were embedded within the scaffold, the imposed strain was distributed throughout the entire cell. In fact, a small amplification in strain was noticed, due to strain concentration at the pores of the scaffold (Figures 1-2). In the monolayer model of cells seeded on a scaffold, the strain was transmitted evenly to each of the six modeled cells, regardless of location on the scaffold with respect to the application of the strain. The imposed 10% strain was effectively transmitted to the base of all of the cells; however, the strain diminished to nearly zero approaching the apex of each cell. In the model of the cells seeded in multiple layers on the scaffold, the greatest strains were seen by the cells directly attached to the scaffold; these cells had a similar strain distribution to the mono layer cell model, with the maximum strains occurring at the base of the cells. However, as the cell layer’s distance from the substrate increased, the strain transmitted to the cells decreased markedly (Figures 2-3). The average cell strain in the first layer of cells directly attached to the scaffold was 5.4%, 1.2% in the second layer, 0.7% in the third layer, 0.5% in the forth layer, and 0.1% in the fifth layer of cells. These results indicate that cells not directly attached to the scaffold receive very little of the imposed strain.

DISCUSSION:
When utilizing a bioreactor, it is important to consider the strain environment that each cell will experience. If improper cell-scaffold constructs are produced, or allowed to develop during culture, strain-induced biological responses could be muted. Subsequent global assays, such as PCR wherein all of the cells are harvested and their RNA mixed together, can produce averaged data where the contribution from those cells correctly attached to the scaffolds is severely diluted. Only the cells directly attached to the scaffold will demonstrate the full effect of mechanotransduction on many biological outcomes.

REFERENCES: