ACTIVE AND PASSIVE CELLULAR MECHANICS IN A BIO-ARTIFICIAL TISSUE CONSTRUCT

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Fibroblast cells in structural tissues such as tendon serve a mechanical function by actively remodeling the extracellular matrix (ECM) and by pulling on the ECM to provide tissue tone. Understanding the mechanical behavior of fibroblast cells is important for developing interventions to aid in wound healing, and to develop palliative strategies for tissue injured during heart attacks.

However, determining the active and passive mechanical properties of living cells presents a tremendous challenge because of active remodeling that takes place within the cells themselves. On a timescale of thirty seconds, a fibroblast cell can completely remodel its inner architecture in response to changes in its mechanical environment. Cells grown on a Petri dish adopt a morphology almost completely unrelated to that which the same cells adopt when transferred into a three-dimensional ECM. Cells in a natural tissue are too compliant relative to the ECM to detect passive cellular contributions in testing of a natural tissue. Additionally, the mechanism of applying loads to fibroblast cells may affect measurements of passive stiffness. For instance, we believe that existing methods involving probing a cell's outer membrane may under-predict cellular stiffness in the same way that pulling on an ear would lead to an under-prediction of the stiffness of the human skull.

Our approach is to build simplified tissues from living cells and collagen. The cells actively remodel the collagen over a period of several days, reducing its volume by a factor of 10 while building a realistic three-dimensional network. We stretch these simplified systems mechanically, then test them once more with cells either deactivated or removed through biochemical treatment. From measurements of stiffness and simple mechanical models, we back out the mechanical properties of the cells, and find values that exceed previous estimates of passive cellular stiffnesses by up to two orders of magnitude.

Several features of active cellular response that have been masked by previous testing methods are revealed through tests performed using tissue constructs. An example that will be presented involves a previously unseen cellular protective scheme in which sacrificial cellular structures break in response to a rapid stretch of high magnitude, and remaining structures apply active stresses to quickly restore tone as the cell rebuilds.