Quantifying the 3D Mechanical Tractions of the Aortic Heart Valve Interstitial Cell

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Introduction: Heart valves ensure unidirectional blood flow throughout the heart and are dynamic tissues that adapt to the local stress environment. This is made possible by the biosynthetic activity of the underlying heart valve interstitial cells (VIC). VICs can become activated in response to growth or pathology and transition into a highly-contractile, myofibroblast state. Previous work has characterized the effects of aortic VIC (AVIC) contraction on the bending stiffness of native valve tissue [1] and within synthetic poly (ethylene glycol) (PEG) hydrogels [2]. However, the exact mechanism of how cell contraction directly effects bulk level properties is currently unknown. To address this, we combine extant flexural deformation testing data of AVIC seeded PEG hydrogels [2] and new data from 3D traction force microscopy (TFM) experiments to develop a multi-scale model of the AVIC-gel system.
Materials and Methods: AVICs were seeded within PEG gels containing degradable peptide cross linkers, CRGDS adhesive peptide sequences to allow for cell attachment, and fluorescent microbeads used to track local deformation. The samples were first incubated within Tyrode's Salt Solution and a 'normal' z-stack of images was captured of a cell and surrounding fluorescent beads using confocal microscopy. The sample was then exposed to 50 pM of Endothelin-1, which incites AVIC contraction, and a 'hypertensive' z-stack of the same field of view (FOV) was acquired. Finally, the samples were treated with 4 uM of Cytochalasin D to stop the contraction and an 'inactive' z-stack of the same FOV was acquired. From the images, we analyzed the changes in cell volume with respect to the different treatments and we computed the bead displacements using a custom bead tracking algorithm. A finite element (FE) model of the 3D TFM experiment was developed within the open-source FEniCS framework.
Results and Discussion: We note a reduction in cell volume within the hypertensive state and we observe a recovery of this volume when the AVICs are in an inactive state (Figure 1). In addition, our bead tracking algorithm is capable of identifying and tracking the beads from the confocal images and is capable of computing bead displacements and local deformation gradient tensors reliably.

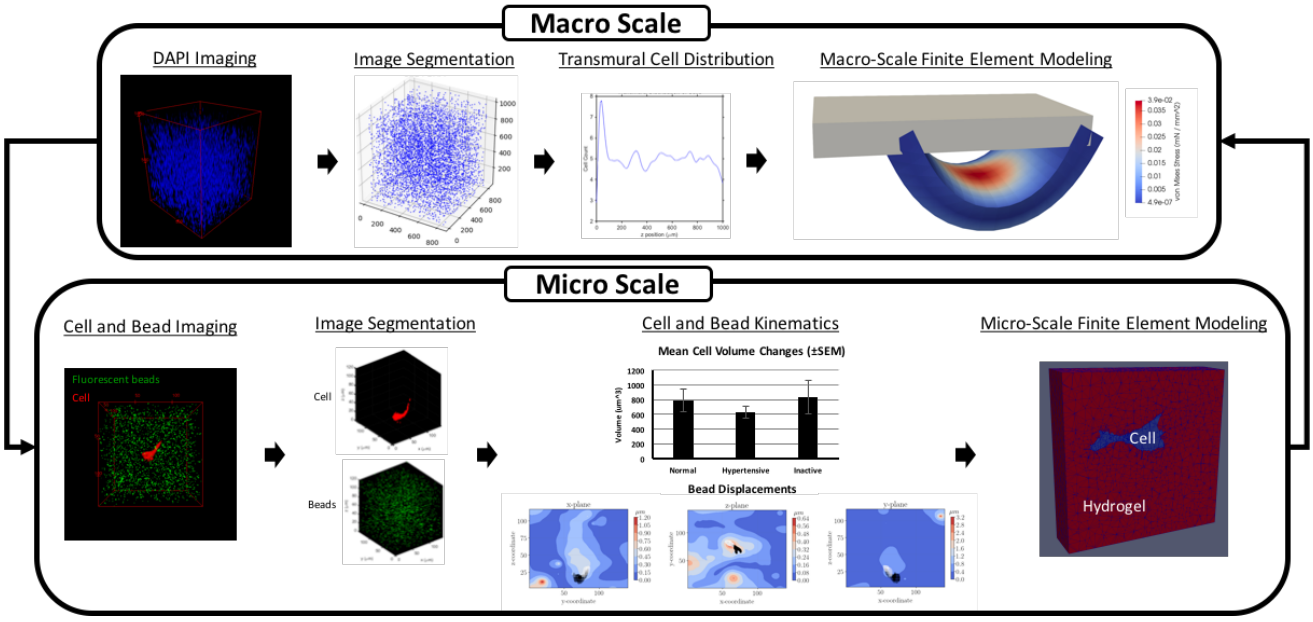

Figure 1: Extant flexural deformation testing data [2] is combined with new 3D TFM data to establish a coupled macro-micro FE model of AVIC seeded PEG hydrogels. The macro scale model is informed using the real spatial distribution of cells acquired through transmural imaging of cell nuclei (DAPI). The micro scale model is informed with 3D TFM data which provides cell volume changes and local bead deformations.

Conclusions: We successfully measure AVIC volumetric changes and local bead displacements from the 3D TFM experiments. These results suggest that AVIC contraction can regulate intracellular volume. Future work will focus on further development of our micro AVIC model and coupling this to our established FE model of an AVIC seeded PEG hydrogel undergoing a bending deformation [2].

References: [1] Merryman W, J Biomech, 2006, 39:88-96. [2] Khang A, Acta Biomater, Submitted, 2019.