# A Simulation of Heart Valve Interstitial Cell Contractile Behavior in 3D Gels


Xinzeng Feng[1], Alex Khang[1], Jake Sansom[2], Nicholas West[2], David Ilitzky[3], Emma Lejeune[4], Michael Sacks[1]

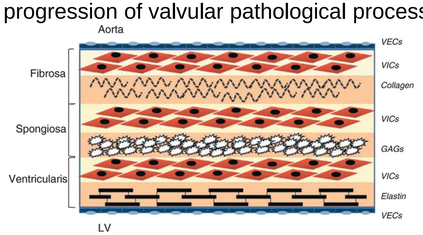
[1] James T. Willerson Center for Cardiovascular Modeling & Simulation
Oden Institute for Computational Engineering & Sciences • Department of Biomedical Engineering
The University of Texas at Austin • Austin, TX

[2] Department of Aerospace Engineering and Engineering Mechanics
[3] Department of Computational Chemistry • Department of Applied Mathematics
The University of Texas at Austin • Austin, TX

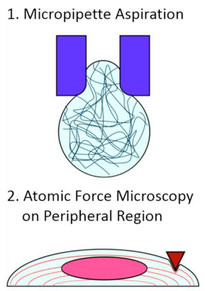
[4] Department of Mechanical Engineering
Boston University• Boston, MA


## Introduction

- Heart valves are specialized cardiac structures that ensure unidirectional blood flow.
- Heart valve interstitial cells (VICs) are located throughout heart valve tissues whose function is intimately connected to heart valve remodeling and repair, as well as the onset and progression of valvular pathological process [1].



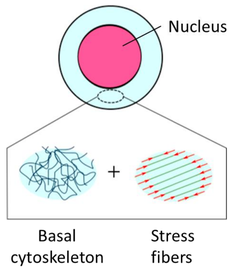

- Yet, there is limited knowledge and extant models regarding their behavior under varying activation levels and dynamic valve tissue environment.
- Previously, we developed a VIC computational continuum-mechanics model and studied the contractile behavior of VICs with micropipette aspiration and atomic force microscopy experiments.
- However, cells behavior differently in these experiments from a fully 3D environment.




- Toward a better understanding of VIC function in 3D, in this study, we aim to apply our VIC model to simulate the contractile behavior of VICs in real cell geometry and investigate the effect of stress fibers and contraction strength based on 3D single-cell traction microscopy measurements.

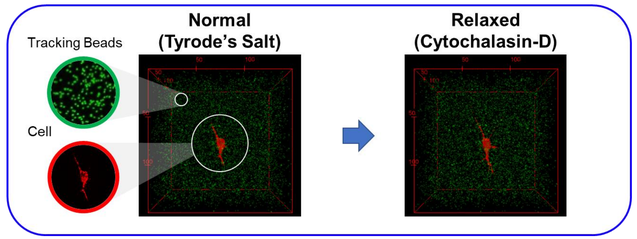
## Hypothesis

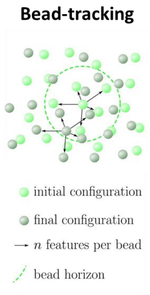
- A VIC is modeled as an elastic body that actively contracts through the stress fibers. Key modeled components includes the (basal) cytoskeleton, cell nucleus, both considered as hyper-elastic materials, and stress fibers, which behave as actively contracting elastic structures.




## Methods

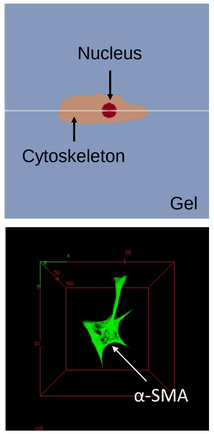
### 3D singe-cell traction microscopy




- VICs were seeded in a 3D PEG gel environment surrounded by a dense population of fluorescent beads (0.5μm in diameter, density=3x10$^9$ beads/ml).
- The state of VICs (e.g., normal/hyper-contractile/relaxed state) were modulated using chemical agents that affect their contractility.
- The resultant displacements of the fluorescent beads were tracked by FM-Track, an open-source feature-vector-based bead tracking algorithm [2].

### Sakamoto cell model[3,4]




Nucleus: nearly incompressible, Neo-Hookean
Cytoskeleton (basal): compressible, Neo-Hookean
Gel: compressible, functionally gradient material
Fiber: specified by an orientation distribution function $\Gamma_0(\mathbf{m}_0)$ where $\mathbf{m}_0$ is mean fiber direction in the unstressed state (direction guided by the stained fluorescence imaging data). A common choice for $\Gamma_0$ is the constrained von-Mises distribution.
Cauchy stress:

Active contracting
Passive contracting

$$\mathbf{T}^{sf} = \int_S \Gamma_t(\mathbf{m})\left[H(I_4-1)\mathbf{T}^p(\mathbf{m}) + \mathbf{T}^a(\mathbf{m})\right]dS$$

where $\mathbf{m}$ is the deformed fiber direction, H is the Heaviside function, $I_4 = \mathbf{m}_0 \cdot \mathbf{C}\mathbf{m}_0, \mathbf{C} = \mathbf{F}^T\mathbf{F}$ is the square of the fiber stretch along $\mathbf{m}_0$ and S is the surface of the unit sphere.

**Active contraction**:

$$\mathbf{T}^a = f\frac{I_4}{J}\mathbf{m}\otimes\mathbf{m}$$

is proportional to the local intrinsic contraction strength f.

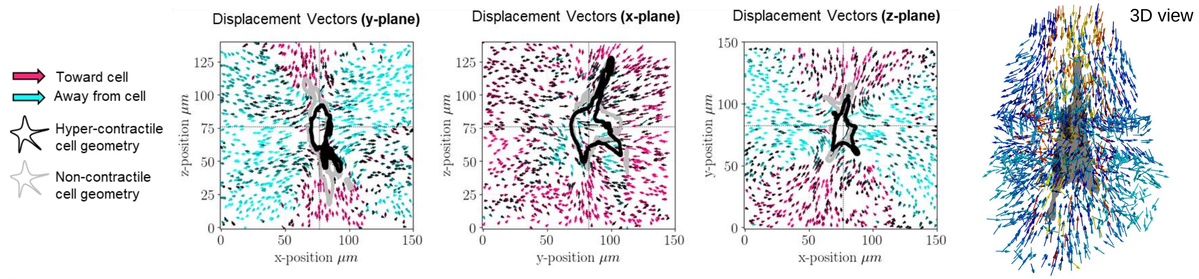
**Passive contraction**:

$$\mathbf{T}^p = 2\frac{I_4\partial\psi_p^{sf}}{\partial I_4}\mathbf{m}\otimes\mathbf{m}$$

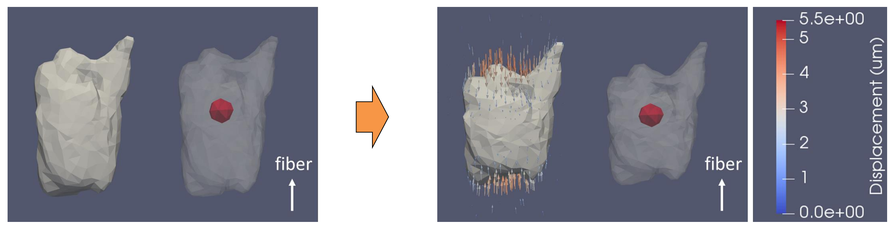
depends on the directional stretch and strain energy density of the fibers.

## Results

### Tracked displacement field from single cell traction microscopy




### Simulated cell contraction




The 3D geometry of a VIC in the relaxed state. The red volume inside the cell represents the postulated nucleus position.

Simulated shape of the same VIC after active contraction of uniformly aligned fibers in the major direction (y). Arrows indicate the model-predicted displacement in the gel.

- Full cell model was implemented in FEniCS
- The finite element mesh includes ~ 9000 tetrahedra P1 elements

## Discussion & Future Work

We presented a computational cell mechanics model to simulate the VIC contractile behavior in 3D.
Our future work will focus on

- Using the cell model to investigate the fiber distribution and contraction strength of VICs based on the single cell traction microscopy data, and
- Connecting down to cell signaling, e.g., providing mechanistic link between cell forces and changes in expression of key genes/proteins/protein modification.

## Acknowledgments & References


This work was supported by the National Institutes of Health [R01-HL 142504].



1 Leopoid, Jane A "Cellular mechanisms of aortic valve calcification." *Circulation: Cardiovascular Interventions* 5:4 (2012).
2 Lejeune, Emma, et al. "FM-Track: A fiducial marker tracking software for studying cell mechanics in a three-dimensional environment." *SoftwareX* 11 (2020).
3 Sakamoto, Yusuke, et al. "On intrinsic stress fiber contractile forces in semilunar heart valve interstitial cells using a continuum mixture model." *Journal of the mechanical behavior of biomedical materials* 54 (2016).
4 Sakamoto, Yusuke, et al. "On the functional role of valve interstitial cell stress fibers: a continuum modeling approach." *Journal of biomechanical engineering* 139.2 (2017).