ABSTRACT FACE PAGE

1. **Presenting Author's name: Dylan Casey**
2. **Presenting Author's affiliation: University of Vermont**
3. **Presenting Author's title: _____**
4. **Presenting Author's email: dtcasey@uvm.edu**
5. **Presenting Author's gender (optional): _____**
6. **Presenting Author's race (optional): _____**
7. **Presenting Author's ethnicity (optional): _____**
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A RANDOM FIBER NETWORK MODEL OF ALVEOLAR WALL MECHANICS

[1]Dylan Casey*, [2]Samer Bou Jawde, [2]Jacob Herrmann, [1]J. Matthew Mahoney, [2]Bela Suki, and [1]Jason H. T. Bates
[1]University of Vermont, Burlington, VT, USA; [2]Boston University, Boston, MA, USA
email: dtcasey@uvm.edu

INTRODUCTION: Interstitial lung diseases (ILDs) are characterized by progressive and irreversible scarring of the parenchyma. As a result, the bulk mechanical properties of the organ are altered, but how this occurs is not fully understood. At the lowest length scale relevant for lung mechanics, the properties of the extracellular matrix (ECM) are determined largely by flexible elastin and loadbearing collagen fibers. Additionally, collagen has a wavy structure that straightens out before it takes on a loadbearing role. In ILD such as fibrosis, this structure is modified considerably by increased collagen deposition and/or reorganization due to crosslinking. Ex vivo experiments have demonstrated that human alveolar wall tissue has a nonlinear stress-strain curve that is altered by fibrosis [1]. Previous models focus on a network of alveolar walls, assuming the walls are linear, but these cannot investigate the effects from changes in fiber properties and their reorganization. We thus developed an alveolar wall model composed of two populations of randomly orientated springs that is more faithful to the structure of real tissue while recapitulating its emergent nonlinear mechanical behavior.

METHODS: Lines with random slopes and initial positions were laid over a square. To represent crosslinking, a fraction (default: 85%) of intersecting pairs of lines were split into four segments joined at the intersection. Line segments were randomly assigned to be collagen or elastin in a 2-to-1 ratio. Elastin fibers were given unstressed lengths equal to their initial lengths, whereas collagen fibers were given unstressed lengths greater than their initial lengths that were chosen from experimentally measured probability distribution functions (Figure 1, inset, Bou Jawde et al. unpublished). Fiber spring constants were inversely proportional to initial lengths, with collagen being scaled by their unstressed lengths using a heavy-tailed probability distribution. The equilibrium state of the fiber network was determined at each step of incremental uniaxial stretching using a MATLAB® nonlinear solver. Parameters were tuned to fit the stress strain curve of young, healthy lung tissue (Figure 1) as the baseline configuration. Parameters were tuned again to represent a fibrotic condition whose stretching stopped when it reached the average amount of force at the end baseline stretch.

RESULTS: The stress-strain relationship of the model exhibited substantial strain stiffening as the collagen fibers were progressively recruited, mirroring experimental data (Fig. 1). Fibers also gradually aligned in the uniaxial direction with increasing stretch, which added to the nonlinearity of the force-length relationship. Additionally, the waviness of the fibers scaled with the stiffness, so that stiffer fibers were recruited later. To produce the fibrotic condition, crosslinking and collagen fiber stiffness was increased, while collagen waviness was decreased. These networks stopped at a stretch ratio similar to that reported by Sugihara et al.

CONCLUSIONS: The stress-strain behavior of lung parenchymal tissue derives in large part from the distribution of collagen fiber waviness that determines their stiffness and how they recruit with stretch. Our model suggests that emergent nonlinear behavior is related to a link between collagen waviness and the stiffness of the individual fibers. The fibrotic condition requires an increase in tissue stiffness through collagen reorganization and changes to properties of individual fibers. We anticipate this model to be a precursor for modeling alveolar and pulmonary mechanics on a larger scale and under various disease conditions.

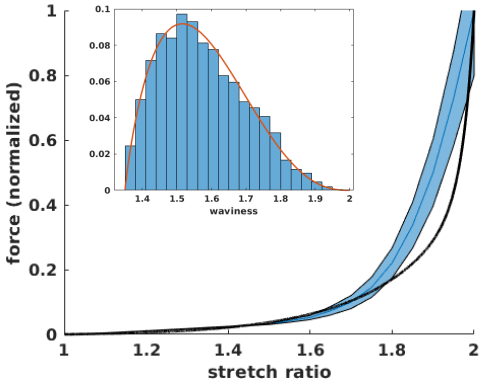

Figure 1: Stress-strain curve (blue) from 64 runs with 95% confidence interval (shaded). Black curve is experimentally measured curve from Sugihara et al. Inset graph: collagen waviness distribution.

REFERENCES:

1. Sugihara, T et al. *J. Appl. Physiol.,* 30:874-878, 1971.