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VIRTUAL TENSILE TEST EXPERIMENTS TO RECONCILE THE MESO- AND MICRO-SCALE MECHANICAL PROPERTIES OF THE LUNG PARENCHYMA

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INTRODUCTION

Many respiratory system pathologies can disrupt lung function by altering the mechanical properties of the parenchyma. Computational models can provide a non-invasive and patient-specific approach to understanding the mechanics of breathing and the effects of heterogeneous damage distribution on lung function. The geometry and spatial scale of *in silico* models are essential in creating realistic models that produce accurate and reliable results. Similarly, it is vital to consider the accuracy of the constitutive mechanical behavior used to model tissue behavior. Many computational models have been developed for the lung at various spatial scales, while morphological studies combined with increased computing power have allowed for model expansion to smaller length scales. Yet, the wide range of experimental techniques and reported constitutive models for lung tissue at different length scales can lead to uncertainty when utilizing such material properties in computer modeling. Hence, reliable alveolar stiffness values are essential when using multiscale models that incorporate the mechanical properties of the parenchyma.

To compare the mechanical properties of tissue reported across length scales from different studies, the differences in experimental protocols should be considered. Also, other factors, such as tissue preparation technique and loading rate, may affect the reported stiffness values. Thus, reconciling the reported stiffness values of lung tissue across spatial scales may give insight into how well the reported stiffness values represent lung tissue behavior across different scales. As the emergent mesoscale mechanical properties of the parenchyma depend on the microscale properties of the alveolar tissues, reported values at the microscale must be accurate before they can be used in meso- and macro-scale lung models.

Hence, this study aims to use *in silico* modeling to compare, reconcile, and resolve the differences reported in lung tissue mechanics at different length scales. Specifically, the objective of this research is to utilize computational modeling for the purpose of studying whether the emergent mechanical properties of lung tissue at the mesoscale, based on micro-scale mechanical testing data, can be reconciled with the experimental data reported at the mesoscale.

METHODS

A finite element (FE) analysis was performed at the mesoscale by assigning microscale-based properties to alveolar septa based on previously reported *in vitro* and *in situ* experiments. The 3D geometry comprised an array of alveoli represented by truncated octahedra [1]. The geometry modeled the tissue slices used in the uniaxial tension testing of Birzle et al. [2]. SolidWorks 2022 (Dassault Systems, France) was used to build the geometry where each truncated alveoli had the average dimensions of a rat alveolus as measured by Cavalcante et al. [3]. The geometry was imported to COMSOL Multiphysics v6.0 for FE analysis (COMSOL Multiphysics, MA, USA). The entire structure had overall height, width, and depth dimensions equal to the average dimensions of lung tissue slices used for uniaxial tension testing in Birzle et al. [2], and was simulated for up to 80% strain. The FE model was meshed using 2.2 million quadratic tetrahedral elements.

Mechanical properties at the microscale were taken from the results reported by two different research groups that determined the mechanical behavior of rat lung tissue using atomic force microscopy (AFM) and *in situ* mechanical testing, respectively [4], [5]. The emergent properties from the FE analysis were then compared to mesoscale data from a study that utilized a comprehensive approach to determine the mechanical behavior of rat parenchyma [2] and reporting the strain energy density function below:

$$\varphi = c(I_1 - 3) + \frac{c}{\beta}\left(I_3^{-\beta} - 1\right) + c_1(I_3^{-\frac{1}{3}}I_1 - 3)^{d_1} + c_3(I_3^{\frac{1}{3}} - 1)^{d_3} \quad (1)$$

Where I_1 and I_3 are invariants of the right Cauchy-Green deformation tensor, c_1, c_3, d_1 and d_3 are material constants that characterize the

isochoric and volumetric elastic response of the tissue, and c and β define Young's modulus E and Poisson's ratio v as:

$$E = 4c(1 + v) \quad (2)$$
$$v = \beta/(1 + 2\beta) \quad (3)$$

Additionally, based on a study by Birzle and Wall [6], the standard linear solid viscoelastic model was added to the microscale hyperelastic constitutive models to account for the effect of rate of loading [6]. The viscoelastic stress (σ_q) of the standard linear solid model was determined by the equation:

$$\sigma_q = 2n_1\dot{\gamma}_1 \quad (4)$$

Where n_1 is the viscosity and is related to the stiffness (G_1) and relaxation time (τ_1) by $n_1 = G_1\,\tau_1$. Also, $\dot{\gamma}_1$ is the strain rate. This visco-hyperelastic model of the alveolar tissue was used to determine the emergent mesoscale behavior of the tissue.

RESULTS

The tensile test simulation results (Figure 1) from the visco-hyperelastic model [5] showed reasonable agreement with the reported mesoscale data [2] at strains between 0.0-0.3. Specifically, the simulated curve based on the work of Perlman and Wu [5] showed slightly lower stiffness compared to the reported mesoscale behavior model below ~28% strain. Above 30% strain, the disagreement between the simulated microscale-based curve and the mesoscale dataset increased.

The mean error was determined for each simulated case concerning the reported mesoscale data to quantify the difference in the resulting stress-strain curves. Overall, the visco-hyperelastic microscale model [5] showed the lowest mean error compared to the mesoscale data across all strains (error of 39%) with an even lower error (error of 26%) when only accounting for strains of up to 40%. Conversely, the AFM-based microscale model [4] resulted in a larger mean error overall (error of 61%) with a larger mean error in lower strain ranges (error of 94%) than over the whole strain range of the experiment.

DISCUSSION

In this study, we utilized computational modeling to investigate whether the emergent mechanical properties of lung tissue at the mesoscale, based on micro-scale mechanical testing data, can be reconciled with the experimental data obtained using mesoscale tensile testing. We picked two of the most comprehensive and high-fidelity mechanical testing datasets published by other researchers for the purpose of this study: the microscale data reported by Perlman and Wu [5] and the mesoscale multimodal data of Birzle et al. [2]. An additional comparison to a linear model based on the AFM experiments of Melo et al. [4] was also made for comparison purposes. Overall, the comparative study successfully reconciled the mechanical properties of lung tissue across micro- and mesoscales when comparing the microscale study of Perlman and Wu [5] to the mesoscale data reported by Birzle et al. [2]. By comparing the emergent properties of simulated microscale-based models to the material behavior reported at the mesoscale, this research further confirmed the reasonable accuracy of the mechanical behavior reported for lung tissue in both experimental studies. Furthermore, this study showed that FE modeling could be used as an informative and guiding tool to investigate and potentially resolve the differences in reported lung tissue mechanical properties across spatial scales.

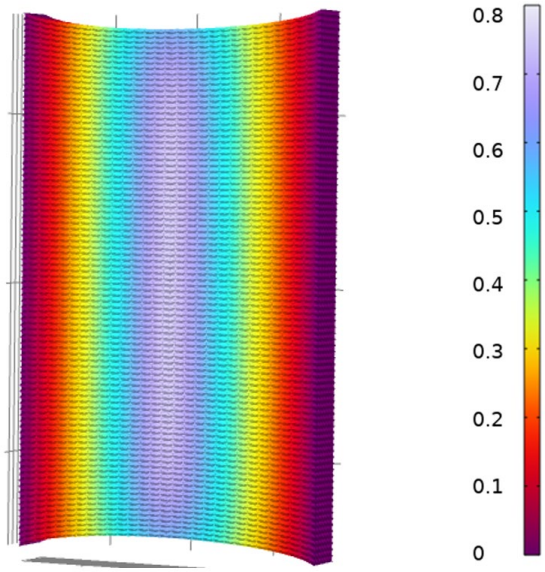

Figure 1: Strain distribution in the uniaxial tension model of 3D model at maximum displacement. The microscale constitutive models are applied to the walls of the truncated octahedra.

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