

LUNG MICROMECHANICS OF PULMONARY FIBROSIS: A FINITE ELEMENT ANALYSIS

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INTRODUCTION

Human lungs consist of a branching network of airways that become narrower, shorter and more abundant from the trachea to the bronchiole, eventually terminating at the alveolus. There are approximately 300 million alveoli, which are microscopic balloon-like sacs found in the form of small clusters. This offers a large surface area for gas exchange estimated at about $1 \text{ m}^2/\text{kg}$ of body mass or more [2].

The alveolar wall has a complex composition, containing elastin and collagen fibers, and is coated on the inside with a layer of fluid. Surface tension at the air-fluid interface is regulated by surfactants secreted from epithelial cells that line the alveolar wall. Tension in the fibrous tissue in combination with surface tension at the air-fluid interface maintains the internal lung structure by exerting a deflating force, often referred to as elastic recoil [3]. However, it has been shown that the contribution of each type of tension force to the total elastic recoil is not necessarily equally distributed [4].

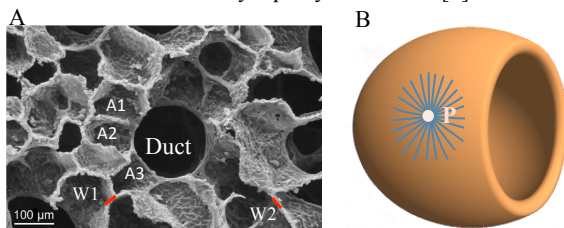


Fig. 2: (A) Electron micrograph of human lung parenchyma [2]. Alveoli (A1-3) and wall thickness (W1-2) used to define model geometry. (B) Alveolus model and an arbitrary point (P) with 12 groups of fibers.

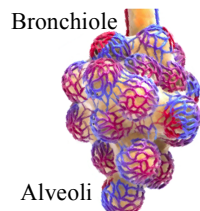


Fig. 1: Lung micro-structure [1].

Lung function is often characterized in the literature through Pressure-Volume (PV) curves. Specific aspects about alveoli function, including pulmonary tissue mechanics, cannot be elucidated from PV curves. A better understanding of pulmonary tissue mechanics is critical for improving treatment strategies for certain lung diseases. For example, a recent study utilized a multi-scale computational model to investigate ventilator-induced lung injuries [5]. In this paper, we develop a finite element model that specifically determines the effect of pulmonary wall fibrous tissue mechanics on alveolus function. After validation with PV curves in the literature, the model is used to study pulmonary fibrosis (PF), which is a disease where both the alveolar wall thickness and stiffness increase [6].

METHODS

The alveolus geometry was obtained from an electron micrograph of the human lung (Fig. 2A) [2]. A single alveolus formed an ellipsoidal shell, with a major axis of $122 \pm 6.1 \mu\text{m}$, a minor axis of $93 \pm 3.5 \mu\text{m}$, a circular opening of $70 \pm 3.0 \mu\text{m}$, and a wall thickness of $7 \mu\text{m}$ (Fig. 2B). The representative alveolus geometry was processed with a custom-written algorithm to create a 3D mesh (53760 hexahedral elements; MATLAB R2016b, Mathworks Inc.).

The mesh was imported into Preview (preprocessor of FEBio Package [7]), where boundary and loading conditions were specified. The alveolar wall was composed of collagen fibers embedded in a ground matrix that encompassed elastin, different types of cells, capillaries, etc. In order to evaluate the importance of collagen fibers in lung diseases, such as PF, we added tension-only fibers. Fibers were described with an exponential stress-strain response (three material coefficients: ξ , α , and β), while the ground matrix was described as a Neo-Hookean material (two material coefficients: E and ν). Due to the paucity of data on the alignment of collagen fibers in the alveolar wall,

the following fiber arrangement was assumed: twelve groups of fibers (15° between two adjacent groups) of equal strength were laid in the tangential plane of the alveolar wall (Fig. 2B). The opening of the alveolus was constrained in all directions, and varying pressure was exerted on the inner surface, resulting in cycles of inflation and deflation.

The material coefficients were determined by parameter identification of the PV response from our simulation with data in the literature [8]. Because our specific interest is alveolar tissue mechanics, we used PV curves determined quasi-statically from saline-filled lungs, which eliminates the contribution of surface tension forces during lung recoil [3]. Furthermore, we assumed that the PV curve of the whole lung applies to a single alveolus, due to the fact that major changes in lung volume are attributed to changes in the alveolar configuration [3]. Results were validated with PV curves of saline-filled cat lungs, due to the absence of saline-filled human lung data. The model was considered valid if the coefficient of the determinant (R^2) between the model simulation and data was greater than 0.9.

Once the material coefficients were determined, stresses and strains on the inner and outer wall were evaluated with an applied internal pressure of 8 cmH₂O, which is pressure at total lung capacity for the saline-filled lung experiment [8]. Then, the alveolar wall thickness (t) and fiber modulus (ξ) were increased by 30%, to represent changes noted with pulmonary fibrosis (three simulated cases).

RESULTS

After parameter identification of the matrix and fiber material coefficients ($E = 1$ KPa, $\nu = 0.45$, $\xi = 0.03$ KPa, $\alpha = 0.1$, and $\beta = 2.5$), we obtained a PV curve that matched well with experimental data (Fig. 3A; control, $R^2=0.97$). The alveolar wall thickness decreased at different rates with pressure (Fig. 3B). At low pressures that represent normal inhalation (~ 1 cmH₂O), a steep descent in wall thickness was observed, while at higher pressures, the thickness plateaued near 2 μm . The inner wall of the alveolus had an effective strain of $\sim 200\%$, corresponding to an effective stress of 40 kPa. The outer surface had a lower effective strain at $\sim 160\%$, with an effective stress of 11 kPa (Figs. 3C&D).

All three simulated cases of PF resulted in lower PV curves than the healthy lung (Fig. 3A). Furthermore, total lung capacity decreased by 10% for a thicker alveolus with stiffer fibers (red line). The change in alveolus capacity was more pronounced at lower pressures, where the volume decreased by 25% at 2 cmH₂O.

DISCUSSION

A FEM model of a single alveolus was developed to study pulmonary tissue mechanics. The material properties of the alveolar wall were described by a combination of constitutive relations for the matrix and the fibers.

PV curves from the model allowed us to investigate the effect of pulmonary fibrosis on lung behavior. The two symptoms associated with PF, thicker wall and stiffer fibers, both caused the lung to become less compliant. Moreover, a combination of the two symptoms, which represents a severe case of PF, had a more drastic effect on tissue compliance. The decrease in alveolar volume during inhalation suggests a lower surface area available for gas exchange, which agrees well with observations in patients suffering from PF [6, 9, 10].

The strain and stress distributions revealed that an alveolus undergoes asymmetric expansion and contraction during breathing. This can be mainly attributed to the boundary conditions at the airway opening. Future work will incorporate the surfactants that line the alveoli wall to investigate the effect of surface tension due to surfactant concentration on alveoli mechanics. Also, it is apparent that

the inner and outer walls experienced different strain and stress values, which suggests that a thin wall assumption may not be an accurate approach in modeling.

It is worth mentioning that the results of our preliminary model are limited by the lack of necessary information and data in the literature. A notable improvement to our model would be the replacement of the homogeneous material description with a more specific one that contains information on fiber arrangements, and elastin and collagen densities. Also, the implications of assuming equivalence between the PV curve of a single alveolus and that of a whole lung are not well understood; nor are the limitations of the quasi-static PV curves determined from saline experiments clear.

This study is part of an ongoing project that aims to estimate the work of breathing and gas exchange rates in human lungs as a function of multiple biological parameters, such as breathing cadence, pulmonary surfactant properties, and pulmonary tissue mechanics. The model presented here demonstrates that finite element analyses of the alveolus can appropriately describe tissue compliance of both healthy and unhealthy lungs, which will be important for understanding disease mechanisms.

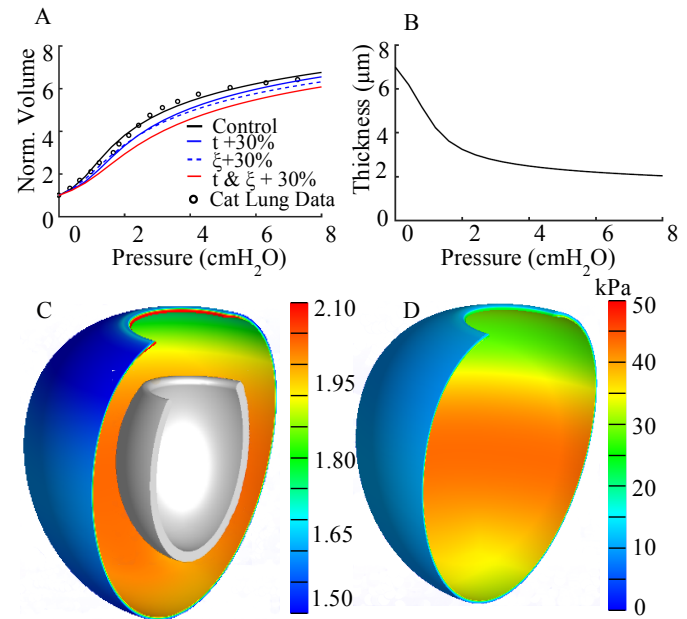


Fig. 3: (A) Volume (normalized by Residual Volume) vs. Pressure for the model, cat lung experiment, and different cases modeling PF. (B) Alveolar wall thickness vs Pressure. (C) Cross sectional view of alveolar reference configuration (grey), effective Lagrangian strain and (D) stress distribution at 8 cmH₂O.

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REFERENCES

- [1] MedicalGraphics, <http://www.medicalgraphics.de/en/>;
- [2] Hsia, CCW et al., *Compr Physiol*, 6:2:827–895, 2016;
- [3] Hoppin, FG et al., *Handbook of Physiol*, ch.13:195-215, 1986;
- [4] Von Neergaard, K et al., *Z. Gesamte Exp. Med*, 66:373-394, 1929;
- [5] Wall, WA et al., *Int. J. Numer. Meth. Biomed. Engng*, 26:807-827, 2010;
- [6] Muhlfield C et al., *Am J Physiol Lung Cell Mol Physiol*, 305:205-221, 2013;
- [7] Maas, SA, *J Biomech Eng.*, 134.1:011005, 2012;
- [8] Harris, RS, *Respir. Care*, 50.1:78-99, 2005;
- [9] Selman, M et al., *Ann. Intern. Med.*, 134.2, 136-151, 2001;
- [10] Gunther, A et al., *Am. J. Respir. Crit. Care Med.*, 168.11:1358-1365, 2003