Title: **A multi-scale computational model of the extracellular matrix of the lung**

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Summary

Cells create their own biochemical and mechanical environment, and at the same time are exquisitely sensitive to it, displaying a non-equilibrium homeostatic state that ensures normal extracellular matrix (ECM) function throughout life. Two currently incurable lung diseases for which this maintenance fails are emphysema and pulmonary fibrosis. Our overarching hypothesis is that abnormalities in the homeostatic feedback between ECM mechanics and cellular responses are central to the pathophysiology of these two diseases. Our goals are to develop a multi-scale computational model of lung parenchymal mechanics on which autonomous agents representing key cell types, such as fibroblasts and inflammatory cells, will secrete inflammatory and enzymatic factors that remodel elastin and collagen. We will use this model to explore the pathologic factors leading to the histologic patterns of parenchymal abnormality that characterize emphysema and pulmonary fibrosis, with the specific goal of identifying the events that may responsible for starting and perpetuating these two diseases.

Planned Actions for the Coming Year

Our project has been underway for only a few months, so we have only recently begun to implement our research strategy. Nevertheless, since funding started we have held regular weekly skype conferences between the two study sites (Boston University and the University of Vermont) that have already led to significant progress on two fronts:

1. We are nearing completion of a novel analytical model of a pulmonary alveolus based on concentric rings of collagen and elastin fibers that have a distribution of elastic equilibrium lengths. This model exhibits the strain stiffening characteristic of the lung parenchyma based on the progressive recruitment of collagen fibers into the stress-bearing role.

2. We have developed a novel way of numerically generating a model of the alveolus consisting of the random arrangement of interconnected collagen and elastic fibers that also exhibits strain stiffening as seen in nature, and that will allow us to experiment with the differential effects of collagen deposition and cross-linking on bulk tissue mechanical properties.

These two complementary modeling approaches are each contributions to our understanding of alveolar wall mechanics in their own rights, and we intend to publish each as such. However, they will also form the foundation for a multi-scale model of the alveolar parenchyma by comprising models of the alveolar wall that will be stitched together into a space-filling 3 dimensional model of a collection of entire alveoli. A key modeling goal here is to determine how to scale up the behavior of an individual wall into a model of the parenchyma without having to solve for the stress-strain behavior of each wall individually. Our plans for the coming year are to complete the individual alveolar wall models and to incorporate them into complete parenchymal models.

Model Credibility Plan

Our model credibility plan for the coming year rests on the following principles:

1. The use of more than one approach to modeling. By using both analytical and numerical models of the individual alveolar wall in independent models of the parenchyma, we anticipate simulating similar bulk parenchymal mechanical behavior. Each wall model will thus serve as a cross check on the validity of the other.

2. Comparison to data in the literature. There is a great deal of published data about the nonlinear dynamic mechanical behavior of lung parenchyma at many levels of scale from that of the individual alveolar wall to the whole lung. Comparison of our model predictions to these data will provide additional model validation and thus credibility.

3. Feedback from experts in the field. There are scientists at both study sites not associated with this grant who are experts in lung mechanical function, and who are known to the two Co-PI's. We will seek their opinions as to the credibility of our model simulations.

Future Plans

The mechanical models described above will provide the extra-cellular matrix (ECM) substrate upon which agents representing key cell types will be placed. The goal then will be to have these agents imbued with appropriate rules of behavior that lead to the realistic simulation of progressive emphysema and fibrosis. It is crucial, however, to create an appropriate substrate first, since this substrate provides key signals to the cells that determine their behavior. For this reason, we are focusing our efforts during the first year of this grant on the development of a high-fidelity multi-scale ECM model.