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Computational modeling helps uncover mechanisms related to the progression of emphysema

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Abstract

Emphysema is a progressive disease characterized by deterioration of alveolar structure and decline in lung function. While morphometric and molecular biology studies have not fully uncovered the underlying mechanisms, they have produced data to advance computational modeling. In this review, we discuss examples in which modeling has led to novel insight into mechanisms related to disease progression. Finally, we propose a general scheme of multiscale modeling approach that could help unravel the progressive nature of emphysema and provide patient specific mechanisms perhaps suitable for use in treatment therapies.

Introduction

Emphysema is a progressive disease of the lung parenchyma with gradual loss of tissue mass, deterioration of the fine alveolar structure and subsequent decline in lung function (30, 37). It is believed that the progression is maintained by enzymatic digestion of the tissue mostly driven by cigarette smoke-induced inflammation, cell apoptosis and aberrant tissue repair (5, 8, 21, 36). However, modern molecular and cell biological efforts and morphological studies have not uncovered the mechanisms underlying the progressive nature of the disease nor have they advanced new therapies.

Within the last 5 years, there has also been a growing interest and activity in developing computational models of the normal and emphysematous lung. One reason is that understanding the primary function of the lung, gas exchange, requires the knowledge of regional deformation, stiffness and mechanical forces of breathing all of which naturally lend themselves to computational modeling. There are several avenues of computational modeling within the context of emphysema that are aimed at better understanding lung function, tissue degradation, failure mechanics, binding kinetics and even drug design.

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Conflict of interest

The authors have no conflict of interest to declare.

The purpose of this brief review is to overview several selected modeling studies related to the spatial scale at which they operate in 2 or 3 dimensions (2D or 3D, respectively). The discussion will focus on mechanisms that these models can examine and their limitations. Finally, we also propose new directions where computational modeling could make an impact on emphysema research by uncovering actual mechanisms related to the persistent progression of tissue destruction.

Modeling organ level mechanical function

One type of models that has often been used to describe organ level function is the impedance model of the respiratory system. These models are usually composed of lumped parameters describing the respiratory system as a series combination of airway resistance, airway inertance, tissue resistance and elastance (3, 6, 12, 15, 16, 18). Measured impedance spectra usually fit with these models to obtain subject specific information. More recently, models with distributed tissue elastance have been introduced that allow estimation of the elastance of the softest and stiffest tissue compartment which was shown to correlate with structural heterogeneity (16). These models should be useful in following the progression of the functional aspects of the disease in individual patients or evaluating the response to interventions such as lung volume reduction (15). It is also possible to combine such modeling with histology and biochemistry (12), computed tomography (CT) imaging (22) or crackle sound measurements (13) to obtain more specific structure-function relations. Nevertheless, the impedance modeling approach does not lend itself to mechanistic insight into disease progression.

A more mechanistic approach to organ level function is based on the microstructural model of Wilson and Bachofen (41), later modified by Stamenovic (28). This model partitions recoil pressure into tissue and surface-tension components to account for quasi-static lung inflation. The model was then adapted by Ingenito et al. (14) to simulate emphysematous tissue destruction and predict the corresponding pressure-volume curve. For this, the number of peripheral fibers and alveolar ducts were decreased, fiber length and alveolar duct size were increased, but the mechanical properties of the tissue were kept the same as in the normal lung. Simulations provided realistic average alveolar dimensions and surface area-to-volume ratios as well as pressure-volume curves, but the model does not account for heterogeneity of the disease. A more complicated variant of the model consists of a large collection of alveoli with elastic properties subject to regional heterogeneity and changes in transpulmonary pressure due to gravity (38). While this model is valuable because it explains why upper lobe lung volume reduction provides better lung function than lower lobe lung volume reduction, it cannot predict the evolution of disease due to a lack of interactions among regions and specific molecular mechanisms driving the progression at the microscale.

Modeling alveolar structure in 2D

Changes in lung micro-structure during the progression of emphysema are well known from animal and human studies. With the introduction of modern CT imaging, lung structure at a larger spatial scale was also analyzed in human patients. The first significant effort to model

lung structure was by Mishima et al. (23) who reported that the distribution of low attenuation areas (LAA) followed a power law with an exponent that was very sensitive to early changes in lung structure not picked up by the traditional measurement of fractional changes in LAA. These findings were interpreted via an elastic spring network model of the parenchyma in which tissue degradation was mimicked by breaking springs based on how much force they carried. When a spring separating two small clusters of LAA broke, the clusters coalesced. Since only a single spring was eliminated from the network, the LAA did not increase appreciably (Fig. 1). However, since two small clusters disappeared from and one large showed up in the LAA distribution, the likelihood of finding small clusters decreased while that of larger clusters increased. This phenomenon retained the power law shape, but decreased the exponent. Thus, network analysis at the microscale provided novel insight into how progression of tissue destruction may have occurred and hence was able to explain why patients with early emphysema had normal LAA but lower exponent than normal subjects.

At the microscale, numerical modeling of the stresses in the alveolar septal wall in emphysema suggested that severe stress concentration can develop (11), a mechanism subsequently shown experimentally to lead to rupture of collagen and the alveolar wall (20). Furthermore, Suki et al. (31) showed that assuming random elimination of springs predicted a uniform distribution of LAA not a power law reinforcing the idea that mechanical forces play a key role in the structural deterioration of the emphysematous lung. Next, utilizing the theory of percolation (29), Bates et al. (2) linked the microscopic progression of both emphysema and fibrosis to clinically observable lung bulk modulus. More recently, adding pressure boundary conditions and calculating the changes in both compliance and structural heterogeneity from the network was able to correctly predict measured structure function relations in mice treated with elastase, suggesting that lung function decline is closely related to an increase in alveolar structural heterogeneity (12).

A different kind of structural modeling of CT images was introduced and applied to individual patient CT images by the Mishima group (33–35). In this case, the CT image of a given patient was taken as the initial structure and various algorithms were applied to the image to mimic tissue destruction. The outcome of these procedures was then compared to the CT image of the subject taken at a later time. This modeling approach not only confirmed the original force-based coalescence of LAA clusters, but also revealed that the model works only when small LAA clusters merge into nearby larger clusters providing evidence that diseased areas tend to grow possibly due to larger than average stresses around the perimeter of existing already damaged regions (34).

While the elastic networks led to the realization that mechanical forces are a key contributor to tissue deterioration, the static modeling of CT-based structures can shed light on the details of how this can occur in individual patients. Nevertheless, both approaches have limitations including their 2D nature and the lack of binding kinetics and mechanotransduction. In the next two sections, we discuss what new insight may be obtainable by extending these models to 3D and by including the interactions of binding and cleaving with mechanical forces.

Modeling alveolar structure in 3D

Advances in micro-CT imaging have made it possible to visualize and quantify the microscopic structure of the parenchyma in 3D (25, 39, 40). In an elastase-induced mouse model of emphysema, micro-CT imaging showed that the earliest structural alterations were characterized by an increase in standard deviation of the alveolar volumes (25). What is the functional consequence of the observed changes in alveolar geometry? Two dimensional models of parenchyma may be inappropriate to answer this question as sections of 3D structures in mechanical equilibrium can exhibit non-convex geometries that 2D spring networks cannot recreate (4, 24). Y.C Fung (10) proposed a 3D model structure which uses a space filling polyhedron, the tetrakaidecahedron (a 14-hedron also known as Kelvin solid), as its basic building block. Polyhedra in the interior of the model were removed to mimic alveolar ducts. Several 3D models of the alveolar duct with octahedra (9) or dodecahedra (19) as the basic building block have also been used to predict pressure-volume curve and elastic moduli of the lung. Furthermore, a similar model also predicted that disruptive high stresses in the acinus of emphysematous lung can occur even at low lung volumes (7). However, simulations using these models were limited to only a few alveoli. Therefore, these models would not be efficient in describing the large scale destruction and coalescence of many alveolar units that occurs in emphysema.

To overcome these limitations, Parameswaran et al. (26) developed a 3D computational model of lung tissue in which a pre-strained cuboidal block of tissue was represented by a tessellation of space filling polyhedra (both cubic and tetrakaidecahedral tessellations were considered), with each polyhedral unit-cell representing an alveolus (Fig 2.A). Destruction of alveolar walls was mimicked by eliminating faces that separate two polyhedra either randomly (Fig.2 B) or in a spatially correlated manner, in which the highest force bearing walls were removed at each step (Fig 2C) based on previous experimental data (20) or a combination of random and force based destruction (Fig 2D). Following the removal of a face, the new equilibrium configuration was calculated numerically by minimizing the total free energy of the system. Simulations were carried out to establish a link between the unit-cell volume distributions that emerged during the process of tissue degradation and the rate of decline in bulk modulus of the tissue block. The spatially correlated process of the force-based destruction led to a significantly faster rate of decline in the bulk modulus and was accompanied by a highly heterogeneous structure compared to the structure due to random destruction (Fig. 2E). Furthermore, an estimator of the change in bulk modulus from the first four moments of airspace cell volumes was established. Simulations were then obtained for tissue destruction with different idealized alveolar geometry, levels of pre-strain, linear and nonlinear elasticity assumptions for alveolar walls and also mixed destruction patterns in which both random and force-based destruction occurs simultaneously. In all these cases, the change in bulk modulus could be accurately predicted from the distribution of airspace volumes. These results suggest that microscopic structural changes in emphysema and the associated decline in tissue stiffness are indeed linked by the spatial pattern of the microscale destruction process in 3D. Such modeling approach should be linked to smaller scale events at the level of single fibers exposed to enzymatic digestion and mechanical forces.

Modeling fiber mechanics and failure

A recent study reported that the rate of elastase digestion-induced stiffness decline in parenchymal tissue strips was accelerated in the presence of static stretch (17). Two mechanisms were identified for this experimental finding: both the binding off rate of elastase from its binding site and the binding site availability along the elastin increased with stretch, which motivated us to develop a model of the enzymatic digestion of elastic fibers under tension (1). The enzymes particles were allowed to do random-walk along the fiber and bind to available binding sites with a given probability. An unbinding event also weakened the fiber by decreasing its stiffness which in turn locally stretched the fiber and hence increased the density of binding sites. Simulations revealed that the stiffness decreased exponentially and the time constant in the early part of the decrease increased with tension. Incorporating this single fiber model into a multiscale network of the extracellular matrix retained the exponential nature of stiffness decay during digestion that was experimentally verified. This modeling exercise demonstrated somewhat counter-intuitively that in the absence of rupture, the local interaction of fiber digestion and mechanical force on the fiber serves to attenuate the spatial heterogeneity of tissue deterioration and hence the microscale processes of digestion directly manifest at the macroscale. While this type of modeling can be used to describe remodeling processes in general, it has not been specifically applied to tissue destruction in emphysema in which fiber failure is a key contributor to airspace enlargement at the microscale (20).

Modeling drug interactions and treatments

Several modeling studies have addressed the issue of treatments. Based on simulations using network models, Ingenito et al. (14) suggested that surface tension contributes to lung recoil in emphysema and that possible drug treatments that increase surface tension of the air liquid interface could be designed to increase transpulmonary pressure, reduce hyperinflation, and hence improve general lung function. In another network analysis, Suki et al. (32) introduced the concept of depercolation – eliminating the large coalescing airspaces by adding new tissue material - as a basis for the rational treatment of both emphysema and fibrosis. The network modeling predicted that the functional improvements that a hypothetical biological or tissue engineering repair could achieve would significantly benefit from imaging-based targeted interventions compared to random repair such as systemically administered drugs. At a much smaller scale, molecular dynamic simulations tested several variants of alpha1-antitrypsin as an effective inhibitor of neutrophil elastase (27). The simulations suggested that smaller molecules retaining the catalytic site can be stable and comparable in their inhibitor function to the native alpha1-antitrypsin. The above approaches address certain aspects of treatments. However, there is a need to combine modeling at small and large scales to predict possible clinical and physiological benefits of any future treatments that operate at the molecular level.

Recommendations

In this section, we propose further directions to advance the understanding of emphysema. First, the currently existing models could immediately be used to address several important

issues. For example, 2D and 3D network models of the parenchyma could be extended to incorporate realistic lung shapes and the effects of gravity in order to more directly compare model predictions of failure mechanics and progressive tissue destruction with histology and CT imaging. Second, an important feature of next generation models should be the ability to evolve given the initial and boundary conditions and the stimulus history. Evolution of simpler 2D and 3D models have already been introduced as described above. More realistic 3D models with proper boundary conditions can also be achieved. Such models could be used to predict not only the outcome of lung volume reduction surgery, but the recovery phase and the subsequent rate and pattern of tissue deterioration. Third, introduction of novel multiscale models that incorporate gravity, cyclic breathing and the effects of mechanical forces on fiber rupture and binding kinetics will be necessary. Such models should be able to explore the specific roles of various extracellular constituents such as collagen and proteoglycans in alveolar wall failure and hence emphysema progression. We note that these multiscale models require careful considerations. The challenge is how to carry information from one scale to the next higher without compromising the mechanism the model tries to capture but maintaining computational feasibility. Fourth, these models should attempt to incorporate cellular level mechanotransduction although currently very little experimental data exist on which such models could be based. Binding of drugs onto cell receptors and fibers could also be incorporated into models that link mechanotransduction to regional tissue remodeling and functional mechanics of the parenchyma. Finally, some of the models are already used in a patient specific manner. More of these advanced multiscale models should be applied to individual patients should proper data become available. These concepts related to such multiscale modeling both in terms of time and length scales are outlined in Figure 3.

Conclusion

In this review, we have discussed several computational modeling examples in which the results have led to novel insight and in some cases even mechanisms related to the progression of emphysema. We have also examined these models in terms of their short comings and proposed a general scheme of multiscale modeling approach that could potentially help unravel the progressive nature of emphysema as well as provide patient specific mechanisms suitable for use in treatment therapies.

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Figure 1.

A large square lattice (500×500) of nodes connected by linearly elastic springs were used to generate apparent CT images by course graining during the simulated progression of emphysema (23). The different colors represent different low attenuation (LAA) clusters in which several nodes have been removed from the network due to mechanical failure whereas black corresponds to normal parenchyma tissue. (A) Zoom into a small area (50×50) of the lattice. Notice that the three larger red clusters and the smaller neighboring green clusters are separated by normal tissue. (B) The same network as in B but after

equilibrium solution was obtained following the elimination of 554 additional springs (whose tension was higher than 80% of the maximum tension) from the original 500×500 network. The tension in the walls separating the red and green clusters in A was high, and the alveolar walls broke. As a result, the green clusters are now part of the larger red clusters. This leads to a change in the LAA distribution such that the exponent of the power law decreases. (C) Exponent D of the cumulative distributions of cluster sizes as a function of the percent LAA (LAA%) in normal (open symbols) and emphysematous (filled symbols) subjects. Solid line is model simulation. Note the good correspondence between data and model. Based on Ref. (23) with permission.

Figure 2. Networks of cubic cells with the top removed to reveal their internal structure (A) Initial geometry; (B) Result of the random destruction pattern (C); Result of the force-based destruction pattern; and (D) Result of the mixed destruction pattern. Networks B–D have the same drop in bulk modulus, but their internal structure is very different. (E) Change in bulk modulus (K) of the network as faces are removed randomly or based on the force. Note that for the same number of faces removed (mimicking the extent of tissue destruction), the decline in elasticity can be very different depending on the pattern of destruction.

Figure 3.

Schematic representation of component interactions in a hypothetical multiscale model of emphysema. The initial and boundary conditions can occur at multiple length scales and both at short time scales such as a sudden exacerbation (minutes to hours) or long time scales (years) such as, lung shape, continuous smoking or breathing related tissue stretching. These inputs to the models will affect cell and extracellular matrix processes mostly at small length scales (microscale). Such processes may include secretion of cytokines, mechanotransduction, fiber failure etc that operate on relatively short time scales or remodeling that occurs on short to moderate time scales (hours to days). The microscopic changes at moderate time scales can alter both structure and function at the whole lung scale (macroscale). This is the outcome where emergent phenomena might be seen as a result of the complexity of the incessant microscale interactions within the system. The eventual goal of the modeling is to reveal mechanisms by predicting how structure and function evolve on long time scales (months and years) as a function of the initial and boundary conditions together with the stimulus history. Various models can link structure and function via microscopic processes at various length and time scales. Ultimately, a full multiscale model is required that can also be personalized.