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RESISTANCE TO ALVEOLAR SHAPE CHANGE LIMITS RANGE OF FORCE PROPAGATION IN LUNG PARENCHYMA

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Abstract

We have recently shown that if the lung parenchyma is modeled in 2 dimensions as a network of springs arranged in a pattern of repeating hexagonal cells, the distortional forces around a contracting airway propagate much further from the airway wall than classic continuum theory predicts. In the present study we tested the hypothesis that this occurs because of the negligible shear modulus of a hexagonal spring network. We simulated the narrowing of an airway embedded in a hexagonal network of elastic alveolar walls when the hexagonal cells of the network offered some resistance to a change in shape. We found that as the forces resisting shape change approach about 10% of the forces resisting length change of an individual spring the range of distortional force propagation in the spring network fell off rapidly as in an elastic continuum. We repeated these investigations in a 3-dimensional spring network composed of space-filling polyhedral cells and found similar results. This suggests that force propagation away from a point of local parenchymal distortion also falls off rapidly in real lung tissue.

Keywords

airway-parenchymal interdependence; airway narrowing; continuum mechanics; spring network

INTRODUCTION

The intra-pulmonary airways are intimately embedded within the lung parenchyma such that the outer aspect of the airway wall is connected to multiple alveolar walls. This produces an important mechanical interdependence between the airways and the parenchyma that affects both; when the lung inflates the parenchyma pulls outward on airway walls tending to increase lumen radii, and conversely when the airway smooth muscle contracts to narrow the lumen it causes local distortion in the surrounding parenchyma. In particular, the capacity of the parenchyma to mechanically oppose airway smooth muscle shortening, and

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hence luminal narrowing, has major implications for airway responsiveness and has been a subject of much study.

The conventional wisdom about the mechanics of airway-parenchymal interdependence dates back to the classic work of Lai-Fook (Lai-Fook, 1979; Lai-Fook and Hyatt, 1979; Lai-Fook et al., 1978) who assumed the parenchyma to behave as an elastic continuum. The predictions of the continuum model were also shown theoretically by Wilson (Wilson, 1972) to be similar to those of a network of elastic elements arranged in a hexagonal pattern representing a two-dimensional slice of alveolar parenchyma. Nevertheless, these early studies are based on mathematical idealizations and also cannot easily incorporate the effects of regional parenchymal heterogeneities, something that clearly pertains in reality. Accordingly, we recently developed a numerical model of a contracting airway embedded in elastic parenchyma. We represented the alveolar walls in the parenchyma as pin-joined springs arranged in a repeating hexagonal pattern, as this represents the conventional idealization of the appearance of a thin slice of lung tissue (Mead et al., 1970; Wilson, 1972). We found, somewhat unexpectedly, that such a network produces long-range transmission of forces in response to the distortion produced by the narrowing of the embedded airway (Ma and Bates, 2012; Ma et al., 2013a). By contrast, when the springs are arranged in a repeating triangular pattern, or the parenchyma is represented as an elastic continuum, the elastic forces fall off rapidly with distance from the airway wall (Ma and Bates, 2012), in apparent accord with existing theory about airway-parenchymal interdependence (Lai-Fook, 1979; Wilson, 1972).

We hypothesize that the reason for the differences in behavior of the hexagonal spring network versus the triangular network relates to their different shear moduli. Unlike the triangular network the hexagonal network has limited capacity to resist shear, although this depends on the pre-stress in the network elements (Stamenovic, 1990; Wilson, 1972). Exactly how real lung parenchyma behaves mechanically thus remains an open question, and one that has some important implications; our studies using 2D models have shown that whether the parenchyma behaves more like a network of hexagonal or triangular cells has a major effect on how nearby cells are able to influence the ability of each other to contract (Ma and Bates, 2014). The purpose of the present study was therefore to determine how resistance to shear is in settling this question. We address this in both 2 and 3 dimensions using computational models that exhibit a range of abilities to resist shear.

METHODS

We have postulated previously (Ma and Bates, 2012) that the key to long-range force transmission in a network of elastic elements lies in its shear modulus, the modulus of a hexagonal network of springs being much lower than that of a triangular network. We investigated this concept in the present study by first adapting our previous 2D model of an airway embedded in a hexagonal network of elastic walls (Ma and Bates, 2012, 2014; Ma et al., 2013b) so that it now includes an empirical mechanism for resisting a change in the shape of each hexagonal cell in the network. This mechanism is similar to that which we employed previously for the airway lumen (Ma and Bates, 2014) and is governed by a shape-restoring force applied to each spring junction (node) in addition to the elastic recoil

forces exerted by the attaching springs. Each hexagonal cell in the network is bordered by 6 nodes, and the shape-restoring force that is applied to each node and points toward the hexagonal centroid is

$$F_i = S(R_i - R_{i0}) \quad (1)$$

where $i = 1 \dots 6$. S is a constant that determines the force magnitude and R_i is the normalized radial distance of the node from the centroid of the hexagonal cell following airway narrowing given by

$$R_i = \frac{r_i - r_m}{r_m} \quad (2)$$

where r_i is the radial distance of the i^{th} node from the centroid and r_m is the mean distance for all 6 nodes. R_{i0} is the corresponding normalized radial distance of the node prior to airway narrowing. All nodes, except those at the network border and those around the airway, thus experienced 3 different F_i corresponding to the 3 cells they bordered.

As in our previous studies (Ma and Bates, 2012, 2014; Ma et al., 2013a; Ma et al., 2013b), the middle section of the network was removed to represent the airway lumen. The springs around the perimeter of the resulting hole represent the airway wall, and each has a stiffness that is ten times that of each of the springs in the parenchymal network, which themselves were assigned a stiffness of unity. The equilibrium configuration of the model was determined as that for which the resultant forces acting on each node were zero.

We then developed a 3D version of the model in which each alveolus is represented as a truncated octahedron (14-hedron). Each 14-hedron has 8 hexagonal faces, 6 square faces, 36 edges of equal length, and 24 nodes. These 14-hedra are space-filling, so they share nodes, edges and surfaces. The edges of the 14-hedron are represented by springs connected at the nodes by pin-joints. In order to imbue the 14-hedra with an adjustable shear modulus, additional cross springs were added to the hexagonal and square surfaces so that they connected between alternate nodes as illustrated in Fig. 2. The stiffness of the cross springs is a fraction, α , of the stiffness of the springs along the edges of 14-hedron. Thus, α provides control over the shear modulus of the 3D model in an analogous fashion to the parameter S in Eq. 1 for the 2D model. A small airway in the 3D model is represented by a column of connected 14-hedra as shown in Fig. 1, similar to other 3D models used by other investigators for different purposes (Denny and Schroter, 1997, 2006). The stiffness of each spring bordering the airway is 10 times the stiffness of each spring along the remaining 14-hedron edges in the network.

The procedure we used for simulating airway contraction in both the 2D and 3D models was similar to that used in our previous studies (Ma and Bates, 2012, 2014; Ma et al., 2013a; Ma et al., 2013b). The nodes around the outer boundary of the network were fixed in place such that the length of each spring in the network was 11% above its zero-load length, so the network began in a pre-stressed state. The equilibrium lengths and the elastic constants of the parenchymal springs were both set to unity. Airway contraction proceeded in small steps through gradual reductions in the zero-load length of all springs comprising the airway wall

until airway contraction had reduced lumen area to 40% of its initial value had been achieved. At each step in this process, the elastic equilibrium configuration of the model was determined using a finite element method. The algorithm used is detailed in our previous studies (Ma and Bates, 2012, 2014; Ma et al., 2013a; Ma et al., 2013b). Examples of the model configuration in its initial and contracted states have also been presented previously, see Fig. 1 of (Ma and Bates, 2012) and Fig. 2 of (Ma et al., 2013b). The numerical algorithms were implemented and solved using Matlab (MathWorks, ver. 2010) on a conventional desktop computer.

RESULTS

Figure 3 shows how spring force falls off with distance from the airway wall in the 2-dimensional model for various different values of S . When $S = 0$, so that there is no additional resistance to shear, parenchymal distortion and force exhibit the behaviors we have previously reported in lung slices embedded in agarose (Ma et al., 2013b) and which has been presumed in models (Lai-Fook, 1979; Ma and Bates, 2012, 2014; Ma et al., 2013a; Wilson, 1972). Specifically, force falls off with distance from the airway wall until about 5 airway diameters, at which point it levels off and remains at an essentially constant plateau level out to the network boundary. However, when a resistance to shape deformation is imposed by a finite value of S via Eq. 1, this behavior rapidly changes. For $S = 0.01$ the level of the force plateau is roughly halved, while at $S = 0.1$ the force plateau is all but disappeared and the behavior of the network approximates that of an elastic continuum.

Figure 4 shows corresponding results for the 3D model. With zero stiffness of the cross-springs in the 14-hedron faces ($\alpha = 0$) the behavior of force with distance from the airway wall (Fig 4) is similar to that of the corresponding 2D case (Fig. 3). That is, at a distance of about 5 airway diameters the force reaches a plateau. Also similar to the 2D case, the level of this force plateau decreases rapidly with increasing cross-spring stiffness ($\alpha > 0$). Interestingly, in the 2D model virtually all the parenchymal springs were affected substantially by airway contraction, whereas in the 3D model only a fraction of the parenchymal springs (about 24% in Fig. 4) incurred an increase in force. This is no doubt due to the fact that a significant number of the springs in the 3D model are aligned out of the direction of force transmission and so do not become stretched. Also, the 3D model is anisotropic but the 2D model is isotropic, which may have influenced their respective behaviors. Nevertheless, in those springs that did incur an increase in force, the peak force magnitude (achieved near the airway wall) increased while the plateau force level (far from the airway wall) decreased with increasing α .

Figure 5 (filled circles) shows that the level of the force plateau (measured near the network boundary) falls off roughly exponentially as α increases such that above $\alpha \approx 0.1$ the plateau force level is essentially zero and the network behaves like an elastic continuum. Figure 5 (open circles) shows similar results obtained when the force-length (F - x) behavior of the parenchymal springs was represented by the nonlinear expression $F = x + 10x^2$ (Cavalcante et al., 2005) to produce strain-stiffening, something that is characteristic of the lung parenchyma (Bachofen et al., 1970). The forces are somewhat higher near the airway wall on account of the nonlinearities in spring stiffness, but again the network behavior

approaches that of a continuum as α increases. In fact, continuum behavior is approximated above $\alpha \approx 0.06$, a lower value than in the linear spring case.

DISCUSSION

We were motivated to perform the present study because long-range force propagation emanating out into the parenchyma from a contracting airway could potentially influence the abilities of other airways to contract (Ma and Bates, 2014). This, in turn, could significantly impact the regional heterogeneity of airway constriction, a matter of substantial physiological importance in obstructive lung disease (Venegas et al., 2005). By contrast, we have shown that when the distortional forces in the parenchyma fall off rapidly with distance from a contracting airway then significant airway-airway interactions seem unlikely (Ma and Bates, 2014). Nevertheless, whether this applies to real lung parenchyma remains an open question because of the difficulty of measuring parenchymal distortion and forces *in situ*. The closest we have been able to come experimentally to addressing the matter is with the lung slice preparation in which the contraction of an airway and its influence on the surrounding parenchyma can be observed. We found previously that the parenchymal displacements in this preparation behave as one would predict of an elastic continuum. However, in order to prepare a lung slice the lung must first be filled with agarose in order to preserve the alveolar architecture, which automatically makes its parenchyma a continuum rather than a 2-D network of alveolar wall segments, so this still does not settle the matter.

We speculate that long-range force propagation in elastic networks occurs when the shear modulus of the network is very low, as in the case of the pin-jointed hexagonal spring network. On the other hand, the lung parenchyma is actually a 3D network of alveolar walls that presumably have at least some ability to resist a change in shape. Indeed, this is to be expected because of the surface tension of the air-liquid interface, and also because of the fibrous network comprising the stress-bearing structures in the alveolar tissue (Toshima et al., 2004), so we wondered if this might raise the shear modulus of the lung sufficiently to eliminate long-range force propagation. We cannot prove this one way or the other, of course, using only a computational model, but our numerical results indicate that the transition to continuum-like behavior occurs rapidly with increasing resistance to shape change of the network cells in both the 2D (Fig. 3) and 3D (Fig. 4) cases, and that this effect is relatively insensitive to whether the springs are Hookean or nonlinear (Fig. 5).

How lung parenchyma actually behaves in this regard is a matter of some physiological importance. In particular, if long range forces due to parenchymal distortion do emanate out from a contracting airway then one would expect airways to exert a mutual influence on each other's ability to contract, which could in turn exert a powerful moderating influence on regional heterogeneity of bronchoconstriction. Our prime motivation for undertaking the current study was thus to determine what pertains in an actual lung. All work that we know of from other laboratories related to parenchymal distortion around contracting airways has been based on the continuum mechanics assumption that distortional forces in the parenchyma surrounding a contracting airway fall off rapidly toward zero with distance. Indeed, invoking this assumption has previously allowed us to model the dynamics of

bronchoconstriction, and its dependence on transpulmonary pressure, rather accurately (Bates et al., 2007; Bates and Lauzon, 2007; Cojocaru et al., 2008; Khan et al., 2010). Nevertheless, our recent finding that hexagonal spring networks give rise to long-range force plateaus (Ma and Bates, 2012), coupled with the fact that slices of alveolar tissue can be usefully approximated as a space-filling arrangement of hexagonal cells (Mead et al., 1970; Wilson, 1972), has left us wondering what pertains in a real lung. Furthermore, some studies have shown that bronchoconstriction in the lung is often accompanied by a general stiffening of the lung tissue (Bates et al., 1994; Mitzner et al., 1992), causing us to wonder if this might be due to the force plateau phenomenon predicted for hexagonal spring networks.

In the present study we have extended our parenchymal model studies to include an elastic resistance for shape change of the hexagonal cells in the 2-dimensional model, and of the polyhedral faces in the 3-dimensional model. These additions are motivated, respectively, by the notions that there may be some finite bending stiffness at the junction between alveolar walls, and that the alveolar faces may have some resistance to shape change. The latter in particular seems reasonable to posit given that alveolar walls contain a significant amount of connective tissue and also that the surface tension in the alveolar lining fluid tends to minimize wall surface area for a given boundary length. In both the 2-dimensional and 3-dimensional models we find that including resistance to shape change as the parameter α increases leads rapidly to the abolition of the force plateau and the acquisition by the model of behavior similar to that of an elastic continuum.

We believe these results essentially answer our original question; even with $\alpha = 0.05$ the continuum approximation is a good one for the spring network models, and it seems entirely reasonable to suppose that the lung parenchyma would exhibit some resistance to shape change. Indeed, although the shear modulus of the lung is known to be small compared to its bulk modulus, it is still not zero. In fact, the bulk modulus of the lung is around 4 times the transpulmonary pressure (Lai-Fook et al., 1976), while its shear modulus is about 0.7 in the same units (Lai-Fook et al., 1976), giving a shear to bulk modulus ratio of about 0.18. This is greater than the values of S and α that produced continuum-like behavior in our 2D (Fig. 3) and 3D (Fig. 4) models, respectively. Also, we performed an approximate analysis of the forces acting on a single cell of the 2D model under distortion (see Appendix) which suggests that the ratio of radial to circumferential spring forces relevant to real lung parenchyma lies to the right of the point in Fig. 5 at which the force plateau has descended to become essentially zero. In other words, even though the protein fiber network in the parenchyma may not exert much resistance to shape change (Wilson and Bachofen, 1982), the surface film probably does. We therefore conclude that prior work based on the assumption of rapidly dissipated parenchymal distortion around a contracted airway (Bates and Lauzon, 2007; Brook et al., 2010; Lai-Fook, 1979; Wilson, 1972) remains on solid ground.

Although force plateaus of the kind that pertain for very small values of α would seem not to play a role in airway-parenchymal interdependence in the lung, it is worth considering whether they might play a role in other biological systems. The area of study in which this is perhaps of greatest relevance is mechanotransduction within cells. The direct transmission of a mechanical signal from the cell surface to the nucleus presumably represents the fastest

mode of mechanotransduction, and while this has been demonstrated (Hu et al., 2003; Maniotis et al., 1997) it remains a matter of interest as to exactly how this is achieved. One possibility is that an appropriately oriented pre-stressed fiber could direct force over a long distance (Wang and Suo, 2005). In fact, computational analysis suggests that this may be the dominant mechanism for long-range force transmission in cells (Ma et al., 2013c), and we have shown that the same effect can potentially occur within the lung parenchyma via a line of stiffened scar tissue (Ma et al., 2013a).

The theory known as isostaticity (Blumenfeld, 2006) also predicts long-range propagation of forces in a directed fashion in networks that are marginally constrained, even though such networks can have a shear modulus that is tuned by pre-stress. The long-range force propagation that we have identified in the present study also seems to involve the fact that the spring networks in which this occurs are mechanically underdetermined and have minimal resistance to shear, although whether it is the lack of shear stress or the lack of connectivity that is more important for such long-range forced transmission is still perhaps somewhat unclear. In any case, the amplitude of the force reaching a distant location is necessarily lower than if the force were directed because of the requirement for conserving strain energy. This would make it less useful as a mechanism for transmitting force information between specific locations, but on the other hand it does not require special structures be set up between the communication points. In this sense, the long-range transmission of force in spring networks is similar to what occurs in tensegrity networks (Stamenovic, 2005; Wang et al., 1993).

In summary, we have shown that long-range force propagation induced by a local deformation is possible in elastic networks that have extremely low resistance to shear. However, the conditions under which this applies appear to be rather limited as the transitions to continuum-like behavior occur in our 2D and 3D models well before the parameters defining the resistance to change of network shape approach even 10% of the parameters defining bulk network stiffness. These findings strongly suggest that force propagation away from a point of local parenchymal distortion falls off rapidly in real lung tissue in line with the predictions of elastic continuum theory.

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APPENDIX

The following is an analysis of a single cell in the 2D model. Although cell shape in the 2D spring network model is hexagonal, here we approximate it as a circle in order to apply Laplace's law to the calculation of surface tension forces.

Consider 6 identical Hookean springs arranged in a circle of radius r (Fig. left). Let each of the 6 circumferential springs have elastance E_c , and an equilibrium length of zero. The pressure inside the circle that maintains its radius against the recoil of the springs is P . Laplace's law in 2D (i.e. in the circle) is derived by noting that the total force acting upward

on the top half of the circle is $2rP$, while the force acting to keep this upper semi-circle pinned to the lower semi-circle is equal to the sum of the vertically-acting hoop stresses at the left and right ends of upper semi-circle, or $2T$. That is, $2rP = 2T$, from which we get $T = rP$. The length of each spring is $l = 2\pi r/6 = \pi r/3$, so

$$E_c = \frac{T}{l} = rP \cdot \frac{3}{\pi r} = \frac{3P}{\pi} \quad (\text{A-1})$$

Suppose that at each of the 6 spring-spring junctions around the circle there is another spring connecting radially in to the center of the circle with equilibrium length r (i.e. these radial spring experience zero stress).

Now let a downward force act on the circle such as to compress it by a small amount $2\delta r$ (Fig. right) so that the two vertical radial springs each have radius $(r - \delta r)$. If the perimeter of the circle, and hence the tension in the circumferential springs, remains the same then the two horizontal springs increase their radii to approximately $(r + \delta r)$. The circle thus becomes an oval with a minimum radius of curvature of $(r - \delta r)$ at the left and right ends. The pressure inside the circle must thus increase by an amount δP sufficient to maintain this smaller radius of curvature. That is,

$$P + \delta P = \frac{T}{r - \delta r} = \frac{T}{r} \left(1 - \frac{\delta r}{r}\right)^{-1} \cong \frac{T}{r} \left(1 + \frac{\delta r}{r}\right) = P + \frac{T\delta r}{r^2} \quad (\text{A-2})$$

The increase in internal pressure, δP , pushes outward horizontally on the left and right ends of the oval, and is counteracted by the increased tension in the two horizontal springs that each now carry a force δF which acts over a circumferential distance of $\pi r/2$ to produce δP . That is

$$\delta P = \frac{2\delta F}{\pi r} = \frac{T\delta r}{r^2} \quad (\text{A-3})$$

from which we get

$$\delta F = \frac{\pi T \delta r}{2r} \quad (\text{A-4})$$

The elastance of the radial spring, E_r , is therefore

$$E_r = \frac{\delta F}{\delta r} = \frac{\pi T}{2r} = \frac{\pi P}{2} \quad (\text{A-5})$$

The ratio of the stiffnesses of the radial spring to the circumferential spring is thus

$$\frac{E_r}{E_c} = \frac{\pi P}{2} \cdot \frac{\pi}{3P} = 1.64 \quad (\text{A-6})$$

The above analysis accounts for the effects of surface tension in maintaining the shape of a cell in the 2D model. However, the elastic recoil of the lung parenchyma is a result of two additive factors, the recoil of the protein fiber network and the surface tension of the air-

liquid interface. The relative contributions of these two factors varies greatly with lung volume and are also very different on inspiration and expiration, but roughly speaking they make comparable contributions to lung elastance (Bachofen et al., 1970). If we therefore assume that the circumferential springs in the figure are accompanied by parallel springs representing the stiffness of the fiber network, then the elastance ratio in Eq. A-6 should be halved if it is to apply to an actual alveolar wall.

The above analysis suggests that the value of the spring stiffness ratio plotted along the horizontal axis in Fig. 5 pertaining to a real lung is about 0.8. It should be pointed out that the simple model we consider in this Appendix is not exactly the same as the analysis that was applied to the 2D spring network model. Nevertheless, a spring ratio of 0.8 is far to the right of the point at which the normalized plateau force has approached zero (Fig. 5), strongly suggesting that surface tension forces resist changes in alveolar shape change strongly enough to ensure that the lung parenchyma behaves like a continuum and not like a low-shear spring network.

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Two and 3 dimensional computational models of lung parenchyma with adjustable resistance to shear are developed.

The range of forced propagation into the parenchyma away from an embedded contracting airway is calculated for both models.

As resistance to shear increases from zero the range of forced propagation rapidly decreases to become similar to the predictions of an elastic continuum.

We conclude that real lung parenchyma is appropriate modeled as an elastic continuum.

Figure 1. Illustration of a $5 \times 5 \times 3$ collection of 14-hedral units each with elastic elements comprising the edges. The central shaded line of polyhedral are designated to represent a small airway to which the adjacent polyhedral, which represent alveoli, are attached.

Figure 2.

The hexagonal (A) and square (B) faces of the polyhedral in the 3D model were given additional diagonal spring elements, as shown, to control their finite shear moduli. The ratio of the shear to the bulk moduli of the model was controlled by α , the ratio of the stiffness of the diagonal springs to the stiffness of the edge springs.

Figure 3.

Spring force versus distance from the airway wall for the 2-dimensional model. As the parameter, S , controlling the shape-preserving force in Eq. 1 increases from zero, the parenchymal distortion force at 5 diameters distant from a contracting airway approaches zero. For values of $S > 0.1$ the elastic network model behavior is close to that of an elastic continuum.

Figure 4.

Spring forces (normalized to the peak force near the airway wall) in the 3-dimensional model ($10 \times 10 \times 3$ polyhedral units) for values of α of A) 0, B) 0.01, and C) 0.1

Figure 5.
Effect of α on the force plateau (measured near the network boundary) normalized to the peak force (near the airway wall).

Figure A-1.

A) Model of a single cell of the 2D model consisting of a circular array of 6 identical circumferential springs (each with stiffness E_c) with 6 radial springs (each with stiffness E_r) connected to the center. B) Cell under vertical compression.