# Possible role of differential growth in airway wall remodeling in asthma

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#### Abstract

Airway remodeling in patients with chronic asthma is characterized by a thickening of the airway walls. As has been demonstrated in previous theoretical models, this change in thickness can have an important mechanical effect on the properties of the wall, in particular on the phenomenon of mucosal folding induced by smooth muscle contraction. However, missing from previous models is an account of how the walls become thicker. In this paper, we present a model for mucosal folding of the airway in the context of growth. The airway is modelled as a bi-layered cylindrical tube, with both geometric and material nonlinearities accounted for via the theory of finite elasticity. Growth is incorporated into the model through the theory of morphoelasticity. We explore a range of growth possibilities, allowing for anisotropic growth as well as different growth rates in each layer. Such nonuniform growth, referred to as differential growth, can change the properties of the material beyond geometrical changes through the generation of residual stresses. We demonstrate that differential growth can have a dramatic impact on mucosal folding, in particular on the critical pressure needed to induce mucosal folding, the buckling pattern, as well as airway narrowing. We conclude that growth may be an important component in airway remodeling.

keywords: mucosal folding, chronic asthma, growth, elasticity, instability

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# **1** Introduction

Asthma is a disease characterized by a narrowing of the airway and reduced lung function. Chronic asthma is often accompanied by irreversible structural changes to the airway wall, collectively referred to as airway remodeling [32]. Airway remodeling is a complex process occuring at multiple time and length scales and involving many different chemical, biochemical, and physical stimuli. Despite a wealth of research it is still not clear how each of the different structural changes individually affects airway function [36], nor is it known whether these different changes are beneficial or detrimental to asthmatic patients [25]. A well documented key feature of airway remodeling is an increase in airway wall thickness, detected at all levels of the bronchial tree and all layers of the airway wall [13, 16, 18, 29].

In this theoretical paper, we focus on the mechanics of airway wall thickening and the mechanism of mucosal folding at a macroscopic level by building a model based on the most sophisticated constitutive theory for elastic tissue available in the bio-engineering literature. In response to certain stimuli, the smooth muscle surrounding the airway wall contracts, and the luminal boundary folds or buckles - this is the phenomenon of mucosal folding. In "normal patients", such an event is marked by only modest narrowing of the airway [26]. In asthmatic patients, however, this airway narrowing tends to occur for lower stimuli, and also leads to exaggerated narrowing [17].

Mucosal folding is also observed in the esophagus [22, 40], blood vessels [21], and gastrointestinal tract [23]. On a mechanical level, this folding indicates an instability of the inner mucosal edge in response to an external pressure provided by the contraction of the smooth muscle. A number of studies have looked at mechanical and geometrical aspects of mucosal folding [27, 19, 20, 38, 12, 40]. Models and simulations have demonstrated that a thicker airway wall can affect buckling pressure (and correspondingly the necessary contraction of the smooth muscle to induce airway narrowing); the extent of the narrowing; as well as the critical buckling mode, i.e. the number of folds in the buckled state. It has been shown geometrically that the buckling mode, or the folding pattern, can have a significant effect on the degree of airway narrowing, although another study [4] suggested that the number of folds may not play a role.

A potentially important assumption in all the above mentioned models is that the mechanical properties of the airway wall do not vary during remodeling, despite evidence that these properties might be altered [15]. Airway remodeling falls into the large category of processes known in the bio-engineering literature as *growth and remodeling of elastic tissues*. Growth in biological systems can be the result of many different processes. Continuum mechanics and the theory of elasticity have long been used to study growth processes and the mechanical properties of growing tissues. Still, it is only in the past couple decades that the complex behavior of biological soft tissues has been fully recognized [6]. It is now understood that biological materials are generally highly nonlinear, anisotropic, and inhomogeneous in their mechanical response and commonly exhibit *differential growth*, that is the tissue does not grow equally in all directions and/or different parts of the tissue grow at different rates.

Differential growth is a common feature in biological tissues and is known to alter profoundly the geometry and mechanical properties of a material. Local changes of mass induce not only a change in the geometry but also elastic stresses which cannot be eliminated geometrically, and thus generate so-called *residual stresses*, which persist in the absence of external loads on the material. Residual stress is a hallmark of biological tissues, and plays a key role in the regulation of many biological systems, including arteries [14, 8, 9], blood vessels [5], the human aorta [10], and plant stems [35].

In this paper we study the possible role of differential growth (including the creation of stress) in airway remodeling. In particular, we study the effect of growth on mucosal folding and show that growth can affect the mechanical response to smooth muscle contraction of an airway beyond the change in geometry. We model the airway as a two-layer cylindrical structure, and take into account both geometrical and material nonlinearities by utilizing the theory of finite elasticity [30]. The growth of the airway is described via the theory of morphoelasticity, and the buckling of the airway is computed using an incremental deformation stability analysis [1]. The model presented here is a radical improvement over previous mechanical investigations for airways [27, 19, 20, 38, 12, 40] as it combines both the nonlinear response of the tissues in large deformation and the effect of growth. (Note Yang et al. recently presented an interesting analysis in finite elasticity for the esophagus [40], but did not consider growth.) Using this model, we demonstrate that differential growth, in particular anistropic growth, can have a dramatic effect on the critical pressure exerted by smooth muscles needed to trigger buckling, the number of folds, the buckling pattern, and the degree of airway narrowing. We demonstrate that differential growth can have a strong impact on stability properties and give seemingly counterintuitive results, for example an airway wall may become thicker while loosing stability. Our results highlight the importance of mechanical effects due to growth and suggest a need for further experimental research along these lines. Indeed, our hypotheses may be tested by direct measurement of residual stress as noted in [24].

## 2 Model and Methods

We model an airway segment as a bilayer cylindrical structure, considering only tissue interior to the smooth muscle. Following the model given by Wiggs et al. [38], a stiff and thin inner layer corresponds to the mucosal region, consisting of the basement membrane, the lamina propria, and the epithelium [2]. Surrounding this is a portion of the submucosa region, consisting of loose connective tissue. The inner layer is much thinner and stiffer than the outer layer.

The smooth muscle surrounds the outer layer, with contraction of the smooth muscle taken into account as an applied normal pressure boundary condition at the outer edge. Since mucosal folding occurs at the mucosal region while the smooth muscle remains roughly circular [20], we impose the boundary condition that the outer edge remain circular in the deformed, buckled state.

The setup is depicted in Figure 1. Material dimensions for the undeformed, reference airway are the inner radius A, the thickness of the inner layer, B - A, and the thickness of the outer layer C - B. We use the isotropic neo-Hookean strain energy function to characterize the nonlinear hyperelastic material [3]. To characterize the difference in stiffness between the two layers, the value of the shear modulus is assumed



Figure 1: Bilayer model of airway wall, consisting of a stiff and thin inner layer, the mucosa, and a soft and thick outer layer, the submucosa. Surrounding the submucosa is smooth muscle, which applies a normal pressure when it contracts.

different in each layer, thus we have the parameters  $\mu_1$  and  $\mu_2$ . From a mechanical perspective, it can be shown that the stiffness ratio  $\mu_1/\mu_2$  is the only important quantity entering the problem.

The model is three dimensional but assumes only plane strain deformation, so that the deformation is uniform along the tube axis. The basic idea behind the numerical computation is that as the smooth muscle contracts, the tube deforms in a symmetric fashion, maintaining its circular shape, until a bifurcation point is reached for a critical pressure (the pressure acting on the inner edge of the cylinder is generated by smooth muscle contraction), at which point the cylinder "buckles" to an asymmetric state. The buckling analysis follows the incremental theory, as described in [37]. Mathematically, it consists of a linear stability analysis for a solution of mechanical equilibrium in finite elasticity. A nonsymmetric perturbation is added to a symmetric finite deformation, and the equations of mechanical equilibrium are expanded in terms of the perturbation parameter, resulting in a 4th order differential equation for the radial displacement of the nonsymmetric deformation. A solution to the bifurcation equation indicates buckling of the tube. A derivation of the growth and bifurcation equations, as well as our approach to solving the bifurcation equation, can be found in [28].

The bifurcation equation has as a parameter the buckling mode number, which is the number of folds in the buckled state. For each mode number, a critical pressure is found that represents the pressure necessary to induce buckling at that particular mode. The actual buckling pressure observed in an ideal experiment is the smallest critical pressure over all modes, and the corresponding mode defines the expected buckling pattern.

Growth is included in the analysis via the theory of morphoelasticity and decomposition of the deformation tensor [34, 7]. The basic concept is that the deformation of the body is due to a local change of mass and to an elastic deformation. That the change of mass is expressed locally enables for neighboring "cells" to grow differentially; this can induce incompatibilities such as overlapping cells. The elastic deformation then brings the material back to a compatible configuration; this step can be seen as an elastic response to the growth, and can induce residual stress in the material.

The effect of symmetric growth in each layer is captured by two parameters per layer, instructing the gain or loss of mass in the radial and circumferential directions. We denote these growth parameters  $\gamma_r^{(i)}$ ,  $\gamma_{\theta}^{(i)}$ ,  $\gamma_r^{(o)}$ ,  $\gamma_{\theta}^{(o)}$ . Here  $\gamma_r$  corresponds to radial growth, with each radial fiber gaining or losing mass if  $\gamma_r$  is greater than or less than 1. The addition or loss of mass in the circumferential direction is captured by  $\gamma_{\theta}$ , where  $\gamma_{\theta} > 1$  corresponds to circumferential growth and  $\gamma_{\theta} < 1$  to circumferential resorption. Figure 2 gives a schematic of radial vs circumferential growth. The superscript differentiates the inner and outer layers. In general, these parameters can be functions of radius, which would signal the case of different "rings" of the airway growing at different rates. Here we consider anisotropic but homogeneous growth in each layer, thus the  $\gamma$ 's are constant but not equal.

As our results are largely focused on varying these parameters, it is instructive to further clarify their meaning via a simple example. Consider a single layer tube with radii A = 1, B = 2, with no applied pressure and three different forms of growth:

- 1.  $\gamma_r = 2$ ,  $\gamma_{\theta} = 2$ . The parameter values imply that both radial and circumferential "fibers" double in mass. Since the growth is isotropic and no other forces are applied to the system, the deformed grown tube has radii a = 2, b = 4, highlighting a doubling of all radial and circumferential lines.
- 2.  $\gamma_r = 1$ ,  $\gamma_{\theta} = 2$ . In this case, circumferential "fibers" double in mass and radial "fibers" do not grow. To account for the anisotropic growth, the tube expands to a larger total radius, while keeping nearly the same length of radial lines. A numerical computation gives that the tube after growth has radii a = 2.48, b = 3.49. The growth induces a slight tensile radial stress; i.e. all radial "fibers" are in tension.
- 3.  $\gamma_r = 2$ ,  $\gamma_{\theta} = 1$ . Here, radial "fibers" double in mass while circumferential "fibers" do not grow. A numerical computation gives the radii after growth as a = 0.69, b = 2.54; in this case radial lines want to double in length but are constrained, thus the anisotropic growth induces a compressive radial stress.

# **3** Results

We investigate the effect of growth on the buckling of a normal versus a remodeled airway. To do this, we keep reference dimensions of the airway fixed, and change the



Figure 2: Transformation of an area element under circumferential versus radial growth.

thickness of the airway by varying the growth parameters. In this way the growth defines a deformation from the normal airway to the remodeled airway. In the prior studies we have mentioned, thicker airways have been studied by changing the reference dimensions themselves, without any particular mechanism to account for the change. By keeping the reference dimensions fixed and altering the growth, we can explore the effect of thickness on the buckling, but we are able to account for the change of thickness as well as the changes in material properties resulting from additional residual stresses. We use as reference "normal airway" dimensions A = 0.98, B = 1, C = 1.5, and stiffness ratio  $\mu_1/\mu_2 = 10$ . The same values have been used in previous models [38, 12].

### **3.1** Isotropic growth

The first effect we consider is isotropic growth, but with different growth rates in each layer. That is, we assume  $\gamma_r = \gamma_{\theta}$  in each region but that  $\gamma^{(i)} \neq \gamma^{(o)}$ . As an example, we let  $\gamma^{(o)} = 1.2$  and vary  $\gamma^{(i)} > 1$ . We plot in Figure 3 the critical pressure (a) and critical buckling mode (b) as a function of  $\gamma^{(i)}$  ranging from 0.9 to 1.4. In Figure 4 the same plots are shown with  $\gamma^{(i)} = 1.2$  fixed and  $\gamma^{(o)}$  ranging from 0.95 to 1.5. It should be noted that the critical buckling pressure only depends on the ratio  $\gamma^{(i)}/\gamma^{(o)}$ . Different values with the same ratio are equivalent up to an isotropic and equal growth multiple in each layer, so that the critical pressure does not differ (note that the airway dimensions will vary by the same scalar multiple). For instance, since  $\gamma^{(o)} = 1.2$  the critical pressure for  $\gamma^{(i)} = 1.2$  in Figure 3 or  $\gamma^{(o)} = 1.2$  in Figure 4, corresponds exactly to the critical pressure in the absence of growth (as shown by the horizontal line on the figures). Comparing the critical pressure to this reference case, it is interesting to note that when the ratio  $\gamma^{(i)}/\gamma^{(o)} > 1$ , the airway is less stable, i.e. it buckles at a lower pressure. On the other hand, a greater pressure is required when this ratio is less than one. In other words, the airway is stronger with respect to buckling when the outer layer grows at greater rate than the inner layer. Observe that this effect is significant as the change in critical pressure increases by a factor of about 8 as  $\gamma^{(o)}$  changes from 1 to 1.5.

The buckling pressure relates the amount of smooth muscle contraction necessary to induce airway narrowing. The other important factor is the amount or degree of airway narrowing. The buckling analysis we present here is a linear stability analysis. It enables us to find critical buckling parameters, but once the buckling occurs we have no direct information on the magnitude of the deformation. Thus, we cannot comment directly on the exact amount of narrowing of the airway once buckling occurs. Nevertheless, we can make relative comparisons of the size of the non-symmetric deformation for different parameters. In this way, we can determine whether buckling at one set of parameters should result in more or less narrowing than buckling at another set of parameter values. Buckling patterns for the points marked I-IV in Figures 3(a) and 4(a) are shown in Figure 5. Comparing I and II, in the case of  $\gamma^{(o)} = 1.2$  fixed, each type of growth can be argued to have advantageous and disadvantageous features. At the lower value of  $\gamma^{(i)}$ , the buckling pressure is much higher but the airway narrows significantly more. If an airway were to grow with the growth rates at point I, it would have a greater resistance to smooth muscle contraction but would have exaggerated



Figure 3: Critical buckling pressure (a) and buckling mode (b) as a function of isotropic growth of the inner layer, for fixed isotropic growth in the outer layer,  $\gamma^{(o)} = 1.2$ 



Figure 4: Critical buckling pressure (a) and buckling mode (b) as a function of isotropic growth of the outer layer, for fixed isotropic growth in the inner layer,  $\gamma^{(i)} = 1.2$ 



Figure 5: Buckling patterns, or tube deformation, after bifurcation for the points marked I-IV in Figures 3(a) and 4(a).

narrowing when buckling occurs. At the higher value, it is the opposite: the airway narrowing is reduced but the buckling pressure is much lower. There is essentially a trade off between the two growth rates. This trade off does not occur in the case of fixed  $\gamma^{(i)}$  (Figure 4). The larger value of  $\gamma^{(o)}$  (point IV) has a higher resistance to buckling *and* comparable narrowing to the smaller value of  $\gamma^{(o)}$  (point III). Between the two stabilizing growths (I and IV), IV might be said to be the "preferable" airway because of the combination of reduced narrowing and increased resistance to buckling. Note that the growth ratio is nearly equal at points I and IV, but both values of  $\gamma$  are higher at IV, and the increased growth leads to a larger airway area. Between the destabilizing growths, III is more detrimental to airway function as it has greater airway narrowing.

Referring to Figures 3 - 4, it seems paradoxical that more growth in the outer layer is required to strengthen the airway wall, since the inner layer is stiffer and intuitively, one would expect that thickening the stiffest layer would have a greater impact in strengthening the wall. Wiggs et al. [38] found that increasing the thickness in the inner layer has a greater impact on the buckling than increasing the thickness of the outer layer. It should be noted, though, that even when the inner layer had a larger growth rate, the actual thickness of the inner layer did not increase much - at point II of Figure 3, the largest value of  $\gamma^{(i)}$ , the inner layer only increased in thickness by approximately 50%. This is an important consideration as it does not match laboratory studies, in



Figure 6: Critical pressure as a function of anisotropic growth of the inner layer. All other growth parameters are set to unity.

which asthmatic patients are found to have a basement membrane roughly doubled in thickness compared to a normal airway [33, 11]. This suggests that isotropic growth is not a suitable mechanism to enlarge the inner layer. Therefore, we now focus on the mechanical effect of anisotropic growth for the inner layer.

## 3.2 Anisotropic growth

Here we only consider the growth of the inner layer. That is we assume that the outer layer does not grow and explore possible buckling as a function of anisotropic growth in the inner layer by varying the ratio  $\gamma_r^{(i)}/\gamma_{\theta}^{(i)}$ . Thickening of the inner layer only occurs with radial growth. In Figure 6, the critical pressure is plotted for  $\gamma_{\theta}^{(i)} = 1$  fixed and  $\gamma_r^{(i)}$  varying from 1 to 2. As  $\gamma_r^{(i)}$  increases, the inner layer becomes thicker – it doubles in size from  $\gamma^{(i)} = 1$  to 2. Correspondingly, the buckling pressure increases, in a linear fashion. The thickness of the inner layer does not tell the whole story as far as stability, though. There are two opposing effects that occur and factor into the strength of the airway. Radial growth creates a radial compressive stress, which further destabilizes the layer [1]. There is also a geometric effect - radial growth causes the inner layer to be thicker, which has a stabilizing effect. Since the inner layer was very thin to begin with, the geometric effect is stronger, and the resultant airway is more stable than before growth.

In terms of the degree of narrowing, with increasing growth the buckling mode decreases monotonically and significantly, from n = 27 at  $\gamma_r^{(i)} = 1$  to n = 14 at  $\gamma_r^{(i)} = 2$ . Included in Figure 6 are the form of the deformation at the values  $\gamma_r^{(i)}$  equals 1.2 and 2. Here the effect of buckling mode is apparent. In both cases, the inner radius at the point of bifurcation is about 0.87, and both plots are produced using the same sized

perturbation in the incremental deformation, but the airway narrowing is exaggerated at the point with the lower mode,  $\gamma_r^{(i)} = 2$ . Defining the inner airway as the shaded gray circles, this area is 18% greater in the case  $\gamma_r^{(i)} = 1.2$ . Increased narrowing with lower buckling mode is essentially a geometric effect, as discussed in [19]. Interestingly, if the anisotropic growth of the inner layer is accompanied by an isotropic swelling of the outer layer, the critical pressure is almost doubled, while the lumen area stays roughly the same.

### 3.3 Fixed outer radius

Note that the model as we have presented it does not restrict outward growth. For instance in Case IV of Figure 5 we see that the outer edge is well beyond the location of the smooth muscle before deformation (the outer radius of the reference state, equal to 1.5). This may not be realistic. It is likely that the smooth muscle, even before contracting, places a geometric constriction on the growth of the outer layer, so that the airway is restricted to grow radially outward, and must otherwise grow radially inward. The exact form of this constraint is complicated by the fact that the smooth muscle also grows during remodeling [17] and would require a detailed understanding of the growth relationships between the various layers of the airway. Nevertheless, some insight on the effect of a geometric constraint can be obtained if we fix the size of the outer radius during deformation. Mathematically, this changes the structure of the problem through the boundary condition since growth and pressure become inter-dependent. Fixing growth parameters automatically sets the pressure – a given growth *creates* pressure at the outer wall since the outer edge pushes against the smooth muscle. In this case, pressure is not a control parameter but is slaved to the growth parameters.

In Figure 7(a), we plot the bifurcation relationship between  $\gamma^{(o)}$  and  $\gamma^{(i)}$  for fixed outer radius. A given value of  $\gamma^{(i)}$  and the corresponding  $\gamma^{(o)}$  represent a form of growth which induces buckling. For each growth pair, the corresponding pressure is plotted in Figure 7(b).

There are different ways to view these plots and this version of the model. If we assume that the smooth muscle is rigid and does not allow any outward growth, then Figure 7(a) shows the critical growth which induces buckling. Then Figure 7(b) is the pressure induced at the smooth muscle due to the growth. In this sense the growth itself is inducing buckling without any required contraction of the smooth muscle. Alternatively, if the smooth muscle is compliant, then some outward growth can occur, and when the smooth muscle contracts the fixed outer radius requirement pushes the outer edge back to its original position. The biggest effect of the fixed outer radius condition is that the amount of growth is greatly restricted. Only the lower-left triangular region in Figure 7(a) constitutes valid growth. Viewing Figure 7(b), growth can be stabilizing or destabilizing. Buckling patterns are included at the select points, indicating again a trade off whereby the stronger airway is also narrower.



Figure 7: Critical outer growth  $\gamma^{(o)}$  (a) or alternatively critical pressure (b) as a function of inner growth  $\gamma^{(i)}$ , for the model with fixed outer radius. The buckling mode at each point is marked in (a). Buckling patterns at the end points are provided in (b).

## 3.4 Inverse problem

It is clearly very difficult to determine experimentally the growth rates in the different layers. However, some geometric parameters, such as the thicknesses of normal airway and asthmatic airways are accessible This raises the question: if we knew exactly how much thicker each layer of the airway wall became during remodeling and the pressure applied by the smooth muscle, could we determine the growth parameters and the amount of differential growth which occurred? We refer to this as the inverse problem: given the details of the deformation and the buckling, can we determine the type of growth which induced the deformation? Surprisingly, this can be done. A detailed analysis of this idea is given in our other paper [28]. Mathematically, the argument can be made by counting equations - there are 4 equations involved in determining the bifurcation of a bilayered cylinder. Since there are also 4 growth parameters, the inverse problem is well formulated, and a solution can be found.

We demonstrate here with two suggestive examples. We start with a reference system in the absence of growth where the critical pressure is  $P^* = 0.2492$ , the buckling mode is n = 27, and the radii at the point of buckling are a = 0.8750, b = 0.8974, and c = 1.4336.

**Case I.** Doubled thickness of inner layer, half the buckling pressure. Keeping the same values of *a* and *c*, but with b = 0.9197 and  $P = P^*/2 = 0.1246$ , we find that the inverse problem has the solution  $\gamma_r^{(i)} = 1.9261$ ,  $\gamma_{\theta}^{(i)} = 1.0514$ ,  $\gamma_r^{(o)} = 1.1357$ , and  $\gamma_{\theta}^{(o)} = 0.8519$ . **Case II.** Half thickness of inner layer, double the buckling pressure. Again, we keep the same values of *a* and *c*, but let b = 0.8862 and  $P = 2P^* = 0.4985$ . Here, the inverse problem has the solution  $\gamma_r^{(i)} = 0.4853$ ,  $\gamma_{\theta}^{(i)} = 1.0239$ ,  $\gamma_r^{(o)} = 0.8862$ , and  $\gamma_{\theta}^{(o)} = 1.1464$ . Physically, the rationale for the existence of these solutions relates to the competing

Physically, the rationale for the existence of these solutions relates to the competing effects of residual stress and geometric effects discussed in Section 3.2. Given the large range of possibilities with anisotropic growth in two layers, there is sufficient flexibility in the growth variables that residual stress effects can be made dominant. In Case I, the growth causes a large compressive radial stress which dominates the geometric effect of the thicker inner layer. In Case II, it is the opposite: the growth creates a large tensile stress, which stabilizes the airway even though the airway is geometrically weaker due to the thinner inner layer.

These results illustrate the powerful effect that differential growth can have in airway remodeling. If one measured the airway dimensions in these examples without knowledge of the growth process, incorrect conclusions on the effect of (and potential reasons for) the structural changes would likely be reached. That different forms of differential growth can produce exact opposite (and seemingly counterintuitive) results gives strong support to the idea that the growth processes may play an important role in airway remodeling and should not be neglected.

## 4 Conclusion

We have investigated in this paper the possible role of differential growth in airway remodeling and the mechanism of mucosal folding. Similar to previous modeling attempts, we have tried to classify the mechanical effect of airway wall thickness on mucosal folding and airway narrowing. The major addition in the present work which has not been included in any prior studies is that we increase wall thickness through a growth mechanism, thus accounting for the means by which the structural changes during remodeling might occur. More importantly, studying increased thickness via differential growth enables us to study changes in material properties, in particular changes in stability properties due to residual stress.

We have explored several growth forms and the resulting impact on airway buckling. Isotropic growth with differing rates in each layer showed the surprising result that a more stable airway is achieved when growth of the soft outer layer exceeds that of the stiff but thin inner layer. Anisotropic growth of the inner layer led to a strengthened airway but significantly decreased the buckling mode. Fixing the outer radius so as to account for the growth constriction of the smooth muscle greatly limited the amount of growth.

Our analysis provides a general framework to understand the mechanical effect of growth and remodeling. It can also be used to gain insight. For instance, isotropic growth with different rates in each layer seems unlikely to be occurring in airways as it does not lead to the substantial increase in thickness of the mucosal layer as observed in experiments. Similarly, it is not clear that thicker airways are more stable, as stability depends on the contractile potential of the smooth muscle [31]. We have shown that particular forms of growth can lead to a thicker and less stable airway wall. Solutions to the inverse problem show that it is possible for a structural change to be doubly detrimental by decreasing the strength and exaggerating the narrowing. It is also possible that the structural changes may be increasing the stability at the cost of increased narrowing. Underlying these possibilities is a need to understand the growth processes.

If airway walls grow differentially and induce residual stress, as we have postulated here, this can be detected by opening-angle experiments, in which a ring of airway wall is cut radially. Any residual stress is relieved by the cut and the ring opens up. Such experiments have been carried out in only one study [24], with the result that human airways are essentially free of residual stress. However, it is important to note that none of the human lungs in that experimental study came from humans with asthma. This is a critical distinction, because our hypothesis is that normal airways are in a zero stress state, and that stress might be introduced through airway remodeling, in which case only asthmatic lungs would show an opening angle. Hence, opening angle experiments would need to be carried out on normal *and* asthmatic airways to confirm or deny the possibility of differential growth.

We now turn to the obvious shortcomings of an idealized model. The airway is a complex structure, composed of multiple layers, which we have modeled as a bilayer cylindrical tube. This is certainly a simplification, although the purpose is to provide insight into the role of growth in mucosal folding and an idealized model is sufficient to investigate these generic effects. Though we have allowed for material nonlinearities in the airway layers, the specific choice of neo-Hookean hyperelastic strain energy may have some effect on results. The two dimensional nature of the model and the plane strain assumption are supported by the fact that folds in airways are observed as longitudinal ridges [39]. The linear stability analysis has the drawback that it only provides information up to the point of the buckling; any further deformation would

require a much more computationally heavy numerical approach.

The results presented here might also suggest a future direction of research. The structural changes associated with airway remodeling are generally considered uncontrollable and detrimental. However, if airways can be stimulated to grow in a particular way, growth can potentially both strengthen the airways against narrowing and reduce the degree of narrowing.

## **Figure Legends**

Figure 1: Bilayer model of airway wall, consisting of a stiff and thin inner layer, the mucosa, and a soft and thick outer layer, the submucosa. Surrounding the submucosa is smooth muscle, which applies a normal pressure when it contracts.

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