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Lung Mechanics: A Review of Solid Mechanical Elasticity in Lung Parenchyma

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Abstract
The lung is the main organ of the respiratory system. Its purpose is to facilitate gas exchange (breathing). Mechanically, breathing may be described as the cyclic application of stresses acting upon the lung surface. These forces are offset by prominent stress-bearing components of lung tissue. These components result from the mechanical elastic properties of lung parenchyma. Various studies have been dedicated to understanding the macroscopic behaviour of parenchyma. This has been achieved through pressure-volume analysis, numerical methods, the development of constitutive equations or strain-energy functions, finite element methods, image processing and elastography. Constitutive equations can describe the elastic behaviour exhibited by lung parenchyma through the relationship between the macroscopic stress and strain. The research conducted within lung mechanics around the elastic and resistive properties of the lung has allowed scientists to develop new methods and equipment for evaluating and treating pulmonary pathogens. This paper establishes a review of mathematical studies conducted within lung mechanics, centering on the development and implementation of solid mechanics to the understanding of the mechanical properties of the lung. Under the classical theory of elasticity, the lung is said to behave as an isotropic elastic continuum undergoing small deformations. However, the lung has also been known to display heterogeneous anisotropic behaviour associated with large deformations. Therefore, focus is placed on the assumptions and development of the various models, their mechanical influence on lung physiology, and the development of constitutive equations through the classical and non-classical theory of elasticity. Lastly, we also look at lung blast mechanics. No explicit emphasis is placed on lung pathology.

Keywords Pressure-volume analysis · Alveolar stability · Lung parenchymal mechanics · Constitutive theory · Lung blast mechanics · Lung computational mechanics

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1 Introduction

The mechanical properties of lung tissue contributes significantly to the physiological functions and the overall behaviour of the respiratory system. These properties are closely associated with elastic and resistive forces [1]. They also play a crucial role in ensuring breathing occurs comfortably and without any obstructions. However, respiration and lung function are heavily impeded by disease. There exist numerous pulmonary pathogens which affect the mechanical functioning of the lung. For example, emphysema is a lung pathogen which results in shortness of breath. This disease affects lung tissue and causes the lung to lose its elasticity. This is due to the destruction of elastic tissue [2]. Despite being affected by disease, the mechanical properties of the lung can act as precise indicators of where and how a disease affects the lung. Through proper evaluation of lung function and gathering data of variables, such as lung tissue resistance, one can analyse disease progression and potentially develop methods or equipment to assist in treating these pathogens [2].

Various studies have been dedicated to understanding the macroscopic behaviour of either the alveolar septa or layers of lung parenchyma. This has been achieved through analysis of pressure-volume plots, numerical methods, as well as the development of constitutive equations or strain-energy functions. In lung mechanics, constitutive equations are capable of describing the elastic behaviour exhibited by lung parenchyma for example, through the relationship between the macroscopic stress and the macroscopic strain. These equations have been modelled under both the classical and non-classical theories of elasticity. Thus, the aim of this research is to establish a descriptive and systematic review of mathematical studies conducted within the field of lung solid mechanics. This review is centered on the development and implementation of the theory of elasticity to the understanding of the mechanical functions and components of the lung. Elastic theory plays a significant role in these studies. Under the classical theory of elasticity, the lung is said to behave as an isotropic elastic continuum undergoing small deformations. However, the lung is also known to display inhomogeneous behaviour associated with large deformations. Therefore, particular focus is placed on the assumptions and development of the various models, their subsequent mechanical influence on lung physiology, and the development of constitutive equations through the classical and non-classical theory of elasticity. Attention is also given to lung blast mechanics and computational models developed through finite element methods, image processing and elastography. Lastly, potential areas of future research are briefly discussed. Note, the list of references used for this study is not indicative of all the work done in lung mechanics. These papers are selected based on their relevance and overall contribution towards the mathematical elastic properties of the lung.

This paper is structured as follows. Section 2 will present a brief overview around pressure-volume analysis. In Section 3, an in-depth review of surface tension and alveolar stability studies will be investigated and discussed. Section 4 will explore the literature pertaining to the development of constitutive equations and strain-energy functions for lung parenchyma. Additionally, this section will also provide a review of the modern day mechanical elastic studies on lung tissue, mostly involving computational models and image processing techniques. Section 5 gives insight into a few studies on lung blast mechanics. Lastly, Section 6 provides a brief conclusion on possible areas of future research in lung mechanics.

2 Pressure-Volume Analysis

The current scientific knowledge and understanding behind lung mechanics has stemmed from analysis of the pressure and volume behaviour exhibited by the lungs [3]. Pressure-

volume analysis is largely performed by plotting the volume of the lung against the corresponding elastic component of the applied pressure over a large volume range [4]. Observations of pressure-volume behaviour is a fundamental tool in determining the compliance of the lung. The compliance of the lung at any particular lung volume is calculated by taking the gradient of a pressure-volume curve, i.e., taking the ratio between the change in pressure and the change in volume. Mead and Martin [4] describe a pressure-volume curve as being a straight line over a large portion of the volume, although at higher volumes the compliance is observed to decrease, i.e., the curve flattens. This sudden flattening of the pressure-volume curve is indicative of a characteristic of elastic bodies or materials. That is, in the case of the lung, a larger pressure is needed for a particular volume change. For example, a rubber band can only be stretched to a certain point before wanting to return to its original state [4]. The above points are only applicable to the lung. Now consider the lung which is actually enclosed within the chest wall and that the chest wall has its own elastic properties [4]. Suppose a balloon is placed within another balloon with equal compliance values. Further, suppose complete collapse of the balloons occurs with no pressure applied across them. Then the total pressure acting across the combined system at any given volume is equal to the sum of the pressures needed to deform each balloon individually. The lung-chest wall system correspond to the above example. However, there is a further complication to take into account. That is, any hollow elastic body may attribute a finite volume when there is no applied pressure acting on the elastic body. This finite volume is known as the resting volume, and is a property of the chest wall [4].

Initially, the relationship between the pressure and volume of the lung was observed to be linear in studies conducted by Hutchinson [5] and Cloetta [6]. This linear pressure-volume relationship was associated with the lungs having perfect linear elasticity [7]. However, these experiments contained several inconsistencies. The observed linear elastic behaviour of the lung was not a direct result of the linearity between the pressure and the volume. The linear behaviour observed by Hutchinson [5] and Cloetta [6] depended on two key aspects, (i) during their experiments the lungs were inflated from a partially inflated state and were kept inflated at all times, and (ii) they did not account for the effects of deflation [7]. Deflation is an important part of lung functionality, and it contributes significantly to the performance of the respiratory system. Mechanically, it is a consequence of the elastic recoil and surface tension of lung tissue. Accounting for these issues and factors in further studies led to the conclusion that the lungs exhibit a nonlinear pressure-volume response [8]. However, obtaining a linear pressure-volume response is still possible by taking into account inflation or deflation, separately.

Svantesson et al. [9] evaluated and further derived a method for the determination of the quantitative characterisation of the elastic pressure-volume relationship. This study was performed with respect to mechanically ventilated human subjects. The experiment was undertaken during a single altered insufflation (the act of blowing or introducing gas into a system), whereby the corresponding resistance within the respiratory system (R_{RS}) could be determined [9]. Svantesson et al. [9] determined a complete sigmoidal elastic pressure-volume curve, described by application of a three-segment model. The model assumption made is that at low volumes, compliance is small and linearly increases with respect to volume. Subsequently, the model then assumes a constant high volume. Thus, at higher volumes, it linearly decreases with volume [9]. These assumptions correlate to an elastic pressure-volume curve with a accurate linear segment of high compliance (C_{lin}) between two nonlinear asymmetrical segments. The elastic pressure-volume curve asymptotically approaches the minimum and maximum volumes (V_{min} & V_{max}) at it's respective lower and upper points. The linear segment is delineated by the lower and upper points of inflection

(LIP & UIP) [9]. The elastic pressure is defined as a function of volume. It is expressed by the following three-segment model [9]:

$$\begin{aligned} V_{min} < V \leq V_{LIP}: &\quad P_{el} = P_{LIP} - \frac{(V_{LIP} - V_{min})}{C_{lin}} \cdot \ln\left(\frac{V_{min} - V_{LIP}}{V_{min} - V}\right), \\ V_{LIP} \leq V \leq V_{UIP}: &\quad P_{el} = P_{LIP} + \frac{(V - V_{LIP})}{C_{lin}}, \\ V_{UIP} \leq V < V_{max}: &\quad P_{el} = P_{UIP} + \frac{(V_{max} - V_{UIP})}{C_{lin}} \cdot \ln\left(\frac{V_{max} - V_{UIP}}{V_{max} - V}\right), \end{aligned} \tag{2.1}$$

where P_{el} is the elastic pressure, V_{LIP} & P_{LIP} are the values of volume and pressure at the lower points of inflection, respectively. Similarly, V_{UIP} & P_{UIP} are the values of volume and pressure at the upper point of inflection, respectively. Note: V_{min}, V_{LIP}, P_{LIP}, C_{lin}, V_{UIP}, V_{max} are all estimated using numerical methods [9], however, the technique used is not specified in this paper. The authors determined, for the constant flow model, that parameter estimation is achieved by minimising the sum of squared differences between the elastic pressure from measured data. Thereafter, elastic pressure is calculated from (2.1). For the sinusoidally modified flow model, the aforementioned parameters and respiratory system resistance are derived by comparing measured data of the tracheal pressure (P_{tr}) to calculated values of tracheal pressure using the following equation [9]:

$$P_{tr} = P_{el} + \dot{V} \cdot R_{RS}. \tag{2.2}$$

From their results, Svantesson et al. [9] conclude that the sinusoidally flow model corresponds better to patients with obstructive lung disease, because it provides values of inspiratory resistance measured concurrently with the elastic pressure-volume curve.

The Drawback of Pressure-Volume Analysis Research in lung mechanics has concerned itself with understanding the elastic and flow-resistive properties of the lung and respiratory system. This includes examining the effects of forces acting on the surface of the lung and how they affect the flow of air and blood throughout the respiratory system. However, this can only be understood through knowledge of the mechanical elastic properties of the lung, i.e., the elastic response of the lung due to its associated stresses and strains. This presents a fundamental flaw with pressure-volume analysis, being that it is incapable of providing a direct indication of the stress-strain properties of lung tissue [3]. However, the importance of pressure-volume analysis in assisting with theoretical and experimental studies should not go without credit. These studies range from investigations into surface tension and alveolar stability, as well as analysing the overall elastic response of lung tissue. Pressure-volume data may not be able to provide information on the stress-strain relationships of the lung, however it may be useful in specifying the tension-area relationship of lung tissue [10], lung hysteresis [11], indicating the overall compliance and resistive nature of the lung [9], and developing models to accurately demonstrate pressure changes corresponding to physiological values [12].

3 Surface Tension and Alveolar Stability

The classical study of Neergaard [13] is widely considered to be one of the first attempts of research on elastic lung properties. Previous efforts to understand the overall elastic behaviour of the lung failed to consider surface tension as an important force acting upon its

surface [5, 6]. Neergaard [13] investigated the importance of surface tension at the air-liquid interface, along with its contribution to the retraction pressure of the lung. Neergaard [13] first considered the formation of a bubble (representing the alveoli) at the top-end of a capillary tube as a model for the surface geometry of the lung, i.e., expanding alveolar surface. The bubble was considered to have one surface. An assumption was made suggesting surface tension to be constant. Further, the bubble was modelled as a spherical segment and exerted a pressure corresponding to the relationship

$$\Delta P = \frac{2\gamma}{r}, \tag{3.1}$$

where ΔP is the change in pressure across the surface, γ denotes surface tension, r represents the principal radii of curvature at a point on the surface. Equation (3.1) is derived from the Young-Laplace equation

$$\Delta P = \gamma \left(\frac{1}{r_1} + \frac{1}{r_2} \right), \tag{3.2}$$

where r_1, r_2 signify the principal radii of curvature at a point on a surface. Neergaard [13] identified two models for bubble formation that he associated with the physiological behaviour of the lungs. The first model describes spherical alveoli which assume a hemispherical shape at maximum lung inflation and never exceeds this limit. In other words, during inhalation lung volume increases whilst pressure and the radius of curvature decreases. The radius of curvature is inversely proportional to lung volume [14]. The second model is an extension of the first model whereby the spherical alveoli are now allowed to exceed the height of hemisphere at maximum lung inflation. Therefore, after maximum inflation has been reached, volume continues to increase but instead of the radius of curvature decreasing, it actually begins to increase. There is a directly proportional relationship between the radius of curvature and lung volume after maximum lung inflation [4, 14]. Neergaard [13] attributed this phenomenon to a lung affected by disease. That is, the second model closely resembles overstretching of a lung or one which is highly compliant. For example, emphysema is a disease which causes a sudden increase in compliance. The first model was chosen by Neergaard [13] as it corresponded with the linear pressure-volume relationship observed in his experiments. However, it was later confirmed that the second model described the actual physiological behaviour of the lung more accurately than the first model [14–17]. Upon inhalation, lung volume increases as pressure and the radius of curvature decreases, whilst the recoil pressures of the lung increase. Upon exhalation, lung volume decreases as pressure inside the lung and the radius of curvature increases. The most important finding to come from this paper relates to the existence of a surface-active material on the surface of the lung, responsible for influencing the behaviour of surface tension on the lung. However, he could not provide direct evidence to support his statement. Despite having a major influence on surface tension studies in lung mechanics, there were several inaccuracies with his findings. Neergaard [13] considered his estimated surface tension values (35–51 dyne/cm) to be too low. However, later studies [15–18], found that his estimates were too high. Moreover, Neergaard [13] only examined pressure-volume curves corresponding to lung deflation. He did not analyse or present data on lung inflation. As a result, he was not able to observe the hysteresis that would occur upon inflation and deflation.

Radford [18] reproduced and extended upon Neergaard's [13] experiments by providing a careful analysis on lung surface area and surface tension. Mathematically, Radford [18] was able to describe an estimate of the elasticity influence to the total free energy. He then

determined the surface area from experimental estimates of the Hemholtz free energy of surface, F_s, as well as knowing the relationship between surface tension, γ, and surface area, A_s, for the lungs:

$$\frac{dF_s}{dA_s} = \gamma. \tag{3.3}$$

Note that in his deductions, surface tension was taken as a specific constant (50 dynes). Equation (3.3) was derived by considering the equilibrium in a two-phase system whereby the surface area is related thermodynamically to the Helmholtz free energy of the surface for a plane interface [18]. Moreover, temperature is assumed to be constant and the total composition of the associated bulk phases are independent of area [18]. Radford [18] approximated surface area values (5–10 m^2) that were less than the surface area estimates gathered from histological data (50–100 m^2), highlighting a contrast with the results obtained by [13]. However, Radford's [18] estimates were thought to have been in error for two reasons. Firstly, he attributed the data based on pressure-volume curves obtained from saline-filled lungs to be applicable for air-filled lungs. Radford [18] suggested that this may have been due to differences in elastic strain at the alveoli emerging due to the air-liquid interface. This was not the case and was later evident in the study on surface tension hysteresis by Mead et al. [19]. Secondly, he assumed that part of the total surface energy could be dissipated through friction as the alveoli and airways began to close. The source of the first error would lead to overestimating the surface energy, whilst the source of the second error would result in underestimating it. Radford [18] cleared up these inaccuracies by stating that the sources of error would nullify and have little impact on the final estimates. Brown et al. [20] provided patient lung surface area estimates that did not correlate with Radford's [18] findings. These estimates were significantly higher than the results presented in [18].

Pattle [21] conducted a microscopic study of air bubbles expunged from lung extracts inflicted with pulmonary edema. Pulmonary edema is a respiratory lung disorder that arises due to excess fluid in the lungs. This condition impedes the process of breathing as the fluid overflow gathers in the numerous air sacs in the lungs. He reported that foam produced by edema showcased a high resistance upon direct contact with anti-foaming agents. This was considered to be an impressive feature as it highlighted that the edema foam formed in the lung introduced a stabilising property. Pattle [21] sampled stable bubbles by squeezing the lacerated surface of normal lungs under water. Despite being in contact with water, these bubbles never lost their stability. However, they lost their resistance to anti-foaming agents. Therefore, Pattle [21] provided estimates of lung surface tension by considering a bubble in an air-saturated liquid. The bubble had a tendency to recoil depending on the magnitude of surface tension. That is, the greater the surface tension, the faster the contraction of the bubble [21]. The following equation defines the lifeline of an isolated gas bubble whereby contraction of the bubble is slow enough such that a steady state of diffusion can be established [21]:

$$T = \frac{\left(Pr^3 + 2\gamma r^2\right)}{(6D\lambda\gamma \ln 2)}, \tag{3.4}$$

where T is the lifetime of a bubble of radius r, γ the surface tension of liquid saturated with gas at P the atmospheric pressure. Further, D denotes the diffusion coefficient of dissolved gas, λ the ratio of concentration to the density of the gas in the equilibrium with it [21]. Substituting values of D, λ, a bubble with a diameter of 21.5μ and with a lifetime of 90 minutes, Pattle [21] obtained the following estimate for surface tension: $\gamma = 0.026$ dyne/cm.

Pattle's [21] surface tension estimate was considered to be extreme and divisive since it implied that surface tension in the lung approached zero. This further added to the confusion around the correct lung estimates of surface tension and surface area. Pattle [21] explained that lung tissue extracts had features responsible for significantly lowering surface tension forces and that stability was a result of an insoluble protein layer lining the alveoli. He explained, "Means of keeping surface tension low must therefore be a part of the design of the lung. It is thus evident that the alveoli of the lung are lined with an insoluble protein layer that can abolish the tension of the alveolar surface" [21]. Thereafter, Pattle [21] developed a method for studying the lung lining layer called the stability ratio of a bubble or surface. The stability ratio is defined as the inverse of the ratio of the surface area of a bubble which needs to be obtained to reduce surface tension to approximately zero [21]. Pattle [21] approximated the stability ratio of the lung lining to be nearly unity.

Brown [15] and Clements [16] were both motivated to resolve the perplexities presented by Neergaard [13], Radford [18], and Pattle [21]. They both investigated the surface tension-area relationship of the lung. Brown [15] reproduced Radford's [18] study and assumed the lung to be composed of many identical hemispherical units, alveoli, in order to evaluate surface tension from the pressure-volume data. He derived a surface tension-area relationship similar to that of bubbles of nasal mucus [21], with a dependence on an assumed area-volume function,

$$A = KV^{\frac{2}{3}}, \tag{3.5}$$

where A denotes the surface area, V indicates volume, and K is a constant of proportionality. Equation (3.5) describes the proportionality between surface area and volume to the two-thirds power [15]. Clements [16] disagreed with this assumption and deemed it unacceptable should the alveoli of the lung deviate drastically from the mean radius. He further critiqued Brown's [15] calculations as they did not account for the tendency of the alveoli to close off above zero volume as transpulmonary pressure decreased. Instead, Clements [16] used isolated lung extracts. Surface tension was measured using a Wilhelmy balance during inflation and deflation [16]. Clements [16] determined that surface tension would decrease to low figures under deflation. His surface tension vs surface area plots also displayed considerable hysteresis [7]. Despite using different methods, they both reached similar conclusions. They determined that lung inflation occurs at a high surface tension estimate ($\approx$ 50 dyne/cm), close to Neergaard's [13] measurements. Additionally, the lung was concluded to deflate with low surface tension ($\approx$ 17 dyne/cm), although not as low as the limit of convergence stated by Pattle [21]. Brown et al. [20] addressed the lack of agreement with regards to the following: (i) The magnitude of surface tension and its contribution to pressure changes throughout the lung, (ii) the surface tension coefficient, and, (iii) lung surface area approximations. They calculated similar estimates of surface tension upon inflation and deflation, respectively. They also estimated the lung surface area of man to be within physiological estimates of 50–100 dyne/cm. Their surface area approximations were considerably higher than the measurements reported by Radford [18]. Lastly, Brown et al. [20] provided conclusive findings on the behaviour and existence of a surface-active material on the alveolar surface.

The Discovery of Surfactant Neergaard [13] explained that a surface-active material "would be useful in the mechanics of breathing, for otherwise the contraction pressures of the lung might become so great as to interfere with adequate expansion" [13, 14]. Macklin [22] explained that the air-liquid interface must be covered by a layer of mucus formed from a

hydrated secretion of granular pneumocytes (alveolar type I and alveolar type II cells) of the alveoli that act as a barrier for gas exchange to occur and are responsible for the discharge of surfactant. Macklin [22] suggested that a layer of mucus lining the alveoli was capable of performing vital functions such as maintaining a constant favourable alveolar surface tension, and facilitating gas exchange. Pattle [21] determined that the mucous layer identified by Macklin [22] was identical to the lung-lining substance discovered in [21]. Pattle [21], Clements [16], and Brown [15] similarly concluded that prevention of the partial or complete collapse of the lung, atelectasis, depends on the presence of a surface-active material, known as surfactant, with very low surface tension lining the alveoli. This prompted Avery and Mead [23] to examine the lungs of small premature infants, inclusive of those inflicted by a respiratory distress syndrome (RDS). They noticed that lungs of premature infants displayed less surface activity when compared to lungs of infants who died from non-pulmonary causes. This implies an absence of pulmonary surfactant in the lungs of premature infants and in infants with hyaline membrane disease [23]. Avery and Mead [23] concluded that the more premature an infant, the more delayed the development of pulmonary surfactant. Therefore, there was an immediate enquiry around the composition of pulmonary surfactant in order to find or develop a replacement for surfactant in defective lungs [24]. A compound known as dipalmitoyl lecithin was confirmed to exist in lung extracts [25–27], with Macklin [22] correctly suggesting its source being the alveolar type-II cells. Similarly, Bondurant [25], Buckingham [26], and Klaus [27] noticed that the development of the surfactant system occurred quite late in the gestation period. Therefore, should a premature birth occur prior to its development, the infant would experience disorders with its respiratory functioning [23]. This discovery has resulted in the saving of lives of thousands of premature infants [7].

Hysteresis describes the mechanical phenomenon where the value of a physical property lags behind changes in the effect causing it. For example, during the breathing cycle, lung volume changes lag the transpulmonary pressure changes which produce them. The lung is said to exhibit hysteresis in this state. Graphically, hysteresis is represented by plotting volume change against pressure change. A single respiratory cycle forms a closed loop, and the enclosed area, in relation to the total change in lung volume, acts as a measure of the degree of hysteresis [19]. Mead et al. [19] explained that measurements on the lung's mechanical characteristics could only be obtained if transpulmonary pressure was separated into its elastic and flow-resistive components, respectively. Mathematically, this is described by

$$\Delta P = f(V) + f\left(V'\right), \tag{3.6}$$

where ΔP is the instantaneous transpulmonary pressure, V is the volume, V' is the rate of change of volume or flow rate [19]. Mead et al. [19] proved that part of the observed hysteresis was a result of surface tension. This phenomenon is associated with the elastic nature of the lungs. Air inhalation causes the lungs to inflate, which results in the elastic recoil forces within the tissues of the lung to exert a pressure back toward the interior of the lungs. These internal and external pressure forces actively contest to inflate and deflate the lung whilst maintaining the physiological curvature of the lung. Hysteresis was found to be almost negligible in the pressure-volume diagram for the saline-filled lung. This was in contrast to the observations made on the air-filled lung, where hysteresis was highly noticeable during inflation and lung expansion was nonuniform. Several considerations were undertaken in developing a plausible theory around how surface forces could lead to nonuniform lung inflation [19]. These considerations were not mentioned in [19], however the mechanism

was described as follows. Mead et al. [19] assume the tension originating at the air-liquid interface as being the result of a pressure difference occurring on either side of the surface. Note that this phenomenon is dependent on the extent of the curvature of the interface or surface [19]. For example, the smaller the radius of curvature the greater the required pressure differences needed to maintain the curvature. Therefore, as air flows along a series of successive small bronchioles during inflation, the opposing pressures to surface tension must increase [19]. Consequently, this leads to an increase in the radius of curvature of alveolar openings. Thus, as air flows past the openings to alveoli of a greater radii, there will be a decrease in pressure. Air will continue to flow and inflate the units beyond until a new state of equilibrium is reached, i.e., airway pressure is balanced by opposing forces of local elastic elements and surface forces of stretched alveoli [19]. The above circumstances contribute to the nonuniform expansion of the lung and Mead et al. [19] used this to further examine the sequence of opening and closing of the alveoli. However, they could not distinguish an obvious pattern relating to the sequential opening and closing of the alveoli [19].

During natural breathing, it was often assumed that the loss of energy as a consequence of quasi-static hysteresis was negligible when compared to that of dynamic hysteresis [11]. Bayliss and Robertson [28] concluded that pulmonary tissue hysteresis decreases as the rate of flow increases. Therefore, Saibene and Mead [11] describe pulmonary pressure-volume hysteresis at low rates of volume change whilst under controlled conditions of volume history. They also sought to separate the quasi-static and dynamic contributions to hysteresis at higher rates of volume change [11]. They discovered that quasi-static hysteresis decreases as respiratory frequency increases. From their findings, under quiet breathing, the overall contribution of quasi-static hysteresis tends toward zero. During exercise, increased tidal volume is countered by an increase in respiratory flow. Thus, the contribution is negligible [11]. Bayliss and Robertson [28] initially suggested that "structure viscance" is a result of some phenomenon other than the flow of a viscous fluid. Saibene and Mead [11] report that the viscance remaining in the lung is independent of frequency. Furthermore, they also highlighted that surface tension on the surface of the lung does not have a constant value during respiration, unless in a state of equilibrium. However, it varies depending on the speed at which the lung surface is stretched (greatest at low speeds), i.e., at low frequencies becoming negligible at higher frequencies [11].

Using data initially obtained by Clements [16], Hills [29] hypothesised that hysteresis is associated with an irreversible surface tension-area ($\gamma - A$) relationship amongst the alveoli. There was much doubt around the existence of surfactant at the alveolar air-liquid interface [29]. Pierce et al. [30] motivated this by presenting results indicating that hysteresis in the lung still occurs upon inflation with mercury. Moreover, Hills [29] questioned whether surface tension-area hysteresis is independent of pressure-volume hysteresis. That is, he examined whether hysteresis can result from a variable or element of the lung surface besides surface tension, and whether the effects of this surface parameter could be eliminated by a substance other than surfactant, such as saline solution [29]. The classical Helmholtz approach is considered to be a suitable alternative method to studying surface tension as a function of surface energy, E_s, because of its benefit of considering the lung to be an general matrix as opposed to the Laplace equation which can only be applied to an individual alveolus [14, 29, 31]. Hills [29] considers the relationship between the total surface area A and the surface energy, such that $E_s = \gamma A$. At equilibrium, $dE = 0$, as a result of the quasi-static conditions under which hysteresis is observed [29]. Therefore, Hills [29] derived the following expression for the inflation pressure:

$$P = \frac{d}{dV}(\gamma A), \tag{3.7}$$

where γ is surface tension, and P and V denote the inflation pressure and inflation volume, respectively. Equation (3.7) reveals that any pressure-volume loop is a result of irreversibility of A, which cannot be described by the Laplace equation (3.1) [29]. This finding supports the theory that geometric irreversibility is exhibited in the lung. Therefore, Hills [29] explains that lung pressure-volume hysteresis is not a result of lung surface tension and surfactant, but rather some unknown surface parameter. Emphasis is placed on lung anisotropic behaviour being the main factor responsible for pressure-volume hysteresis [29]. Hills' [29] argument around lung surface tension-area hysteresis and surfactant not affecting pressure-volume hysteresis was deemed invalid by Ardila et al. [32]. They explain that surface tension-area hysteresis is a reflection of the pressure-volume hysteresis of the lung. That is, suppose a pressure-volume curve exhibits hysteresis, then the plot of surface tension against surface area will display a similar hysteresis loop in general. This is also the case for the perfect isotropic expansion of a lung with a reversible stress-strain curve [32]. Pressure-volume hysteresis is in fact a result lung surface tension and the distribution of alveolar surfactant over surface area of the lung [14, 32, 33]. Moreover, Ardila et al. [32] and Lai-Fook et al. [33] concluded that lung parenchyma undergoes isotropic uniform expansion for both inflation and deflation. However, this conclusion neglects the nonuniform sequential opening and closing of the alveoli during the inflation/deflation cycle.

Accounting for the interfacial effects of the lungs brought about an increase in the understanding of the behaviour of the lungs. However, this also brought about confusion pertaining to the stability of the alveoli. For example, the alveolar surface was described as a fluid which led to the assumption that the alveolar structure was highly unstable [34]. Clements et al. [34] hypothesised that alveolar structure stability is dependent on pulmonary surfactant. Their findings supported this hypothesis. Therefore, Clements et al. [34] developed a stability analysis to describe the mathematical relations governing alveolar stability. This analysis considers the behaviour of a single alveolar unit, as well as its component of recoil due to surface tension which is obtained from: (i) the Laplace equation (3.1), and (ii) the surface tension-area behaviour of a lung extract. The total recoil of a unit is estimated by taking the sum of surface components and tissue components [34]. The alveolar unit is considered to assume the geometry of a hemisphere over a range of volumes necessary for stability [13, 34]. Further, the definite volume of the unit is established under the condition that applied pressure is constant and that the pressure-volume plot has a positive gradient, [34, 35]. Therefore, the following condition for alveolar stability is

$$3R\,E\,\frac{V}{V_{max}} + 4s - 2\gamma > 0, \tag{3.8}$$

where γ is the surface tension, R the radius of curvature of a unit, E the coefficient of tissue elasticity, V the unit volume, V_{max} the largest volume assumed by the unit, P the unit pressure, A the area of the alveolar unit and $s = A\frac{d\gamma}{dA}$ denotes surface elastance, i.e., the reciprocal of the coefficient of surface compressibility K [34, 35]. Thus, taking the total recoil of the individual unit along with the criterion for alveolar stability (3.8) yields, $3P_r > 8\gamma - 4s$, where P_r is the recoil pressure [34]. Hence, R_{min} is taken to denote the radius of the smallest stable units, at given values of γ, s, P, such that

$$R_{min} = \frac{(8\gamma - 4s)}{3P}. \tag{3.9}$$

Alternatively, P_{min} is considered to be the least transpulmonary pressure required to stabilise a unit with given values of γ, s, R, such that

$$P_{min} = (8\gamma - 4s)\ 3R. \tag{3.10}$$

The above stability analysis governs the separation of the alveoli into stable and unstable groups at an initial transpulmonary pressure [34]. Clements et al. [34] defines a normal lung as stable. Subsequently, at high lung volumes, the lung is described as strongly stable [34]. However, the alveoli are vulnerable to atelectasis at low lung volumes, particularly when the alveoli are subjected to an applied compressive force [34]. Moreover, they determined that the lung is unstable at low lung volumes provided surface tension is constant or abnormally large [34]. Film-forming activity is also under examination in this study [34]. Film-forming activity refers to the development and adsorption of pulmonary surfactant onto the surface of lung tissue. A lung with high film-forming activity is found to greatly reduce the effects of surface tension whilst ensuring the alveolar structure of the lung is stable. A lung with low film-forming activity struggles to decrease the effects of surface tension, therefore this lung is deemed unstable [34]. Clements et al. [34] did not consider the stability criteria for different geometries of the alveolar structure.

Bachofen et al. [36] re-examined and adjusted the method used by Brown [15]. This was done to establish suitable surface tension-area hysteresis plots [36]. Most of their results differed from prior evaluations on lung extracts which utilised a Wilhelmy balance [16]. Using the assumption that alveolar surface area is related to the two-thirds power by a constant of proportionality along with (3.5) [15], Bachofen et al. [36] calculated the surface tension using the following equation:

$$\gamma = \frac{3}{2}\, k^{-1}\ (P_A - P_S)\, V^{\frac{1}{3}}, \tag{3.11}$$

where k is a constant of proportionality determined by any initial value of surface tension γ, P_A and P_S the area and surface components of recoil pressure, respectively, and V the volume. A higher maximum estimate of surface tension was noticed. Subsequently, this was observed with minor hysteresis and less surface compressibility. Flicker and Lee [37] calculated similar results and their pressure-volume curves were in agreement with [36]. They both concluded that surface tension decreased as surface area decreased. However, Slama et al. [38] obtained results which did not agree with the observations in [36] and [37]. Instead, their findings emphasised that surface tension decreased as surface area increased. Slama et al. [38] utilised a bubble surfactant technique to develop equilibrium area/surface tension diagrams (ASDs) for surfactant from dog and goat lungs. The following was noted based on their observations on the behaviour and effects of surface forces in lung alveoli: Firstly, surface tension changes with surface area only if surface area changes rapidly. However, this case is avoided as lung surface area changes slowly due to an intake of surfactant at the air-liquid interface [38]. Secondly, lung surfactant produced minimal surface tension values of ≈ 20 dyne/cm, significantly higher than histological surface tension estimates. This implied that surface tension increases as surface area decreases. Reifenrath and Zimmermann [39] used this bubble method, and similarly, they obtained reduced values of surface tension ($\approx$ 18–20 dyne/cm). Furthermore, they also did not observe a direct relationship between surface tension and surface area [39]. They determined that the surface tension differences amongst alveoli of varying radii was inadequate in maintaining the correct pressure requirements for stabilisation of the lung alveolar structure [39]. Reifenrath and Zimmermann [39] questioned whether alternative features are responsible for stabilizing the alveolar structure of the lung, however they did not pose a clear answer. Pulmonary surfactant is the primary constituent responsible for maintaining the stability of the alveoli [24, 34]. One could question and further examine whether the stability of the lungs has more to do with the microscopic elements of lung tissue than the macroscopic elements. This would also include investigating the influence of microscopic properties in ensuring lung stability

and how do they work in relation to the macroscopic properties of the lung. [39] concluded that surface tension had no dependence on the radius of curvature of an individual alveoli and that extremely low surface tension values are responsible for the omission of atelectasis in alveoli with a minor surface area. These particular bubble models [38, 39] oversimplified and neglected surface forces which are dependent on an underlying tissue structure for support. The underlying network of tissue is responsible for maintaining elastic and structural integrity [31].

Reifenrath [14] attempted to provide an answer to the coexistence problem, i.e., how is it possible for alveoli of different radii to exist side by side? [14, 35]. Reifenrath [14] utilized the two models initially presented in [13] to explain the coexistence problem. Neither model could directly justify why this concept could work. However, the second model is said to describe the coexistence problem more accurately, i.e., it describes the dependent behaviour of the surface tension-area relationship [14]. This relationship is similar to the actual observed pressure-volume behaviour of the lungs [15, 16, 21]. Clements et al. [35] consider the dependence of surface tension on surface area as a mechanism which can compensate for differences in recoil pressure. According to the Laplace equation, larger alveoli must be ventilated first due to their lower recoil pressures. Thereafter, smaller alveoli are ventilated, and as a result of their higher recoil pressures, tend to become atelectatic, i.e., the alveolar structure will tend to be unstable under these conditions [14, 35]. However, the Laplace equation and both models by Neergaard [13] have a common characteristic. That is, the surface tension and stability of the whole lung is described with regards to an individual alveolus with a spherical geometry [13]. Mead et al. [31] explain that the elastic behaviour of the whole lung cannot be described accurately with respect to an isolated individual spherical alveoli. Through mechanical interdependence, the actual elastic response of the lung can be described by examining a cluster of polyhedral air spaces separated by the alveolar septa, i.e., lung parenchyma [31]. Therefore, Reifenrath [14] assumes that the alveoli adopts a polyhedral geometry throughout the entirety of the lung, with the exception of those septa which are adjoined by an alveolar space on only one side. Thus, Reifenrath [14] presented a new theory on the alveolar geometry explaining that considering a cluster of polyhedral alveoli enables low surface tension values to be negated, thus being the reason why different alveoli of different radii can coexist at the same time. The geometrical model developed in [14] has no explicit dependence of surface tension to surface area. According to Reifenrath [14], the surface tension-area relationship is not necessary for describing the pressure-volume relationship of the whole lung or needed to support the coexistence problem. This contrasts with the standard definition of alveolar mechanics which made use of equation (3.1) [13]. In this description [14], an increase in recoil pressure during inhalation is anticipated even if surface tension is constant. Thus, surface tension is not responsible for guaranteeing alveolar stability and hysteresis [14]. Instead, the differential covering of surfactant onto the surface of the lung at a given surface area can guarantee stability and hysteresis to a greater extent [14]. Reifenrath [14] concluded by inferring that changes to the surface tension of the alveoli would lead to changes in lung volume.

There was a sudden rise in data indicating that surface tension distorts alveolar geometry [14, 31, 40], tissue energy differs in air-filled lungs and saline-filled lungs [41], and that surface tension plays a vital role in lung recoil [40]. Wilson [42] took into account these effects in establishing correlations between recoil pressure, surface area, and surface tension. Surface tension is considered to behave in two ways: (i) A direct manner, by an added contractile force, and (ii) an indirect manner, whereby the shape of the alveoli is distorted and internal forces within the tissue elements are increased [42]. In this paper [42], the indirect approach is used and two models are considered when analysing the relationship

between surface tension and recoil pressure. That is, the quadratic energy difference model and the large energy difference model. Using the description for the total energy difference, two equations are obtained for each model. For the quadratic energy difference model, at equilibrium, the total energy of the lung is minimum [42]. A saline-filled lung is considered whereby the potential energy is equal to the tissue energy. Further, the state of the alveoli for any particular volume, is one in which the energy is minimum [42]. The assumption is made that if this configuration experiences distortion resulting in changes to the surface area S of a lung filled with saline solution S_s, the tissue energy U must increase regardless of any increases or decreases to surface area [42]. The first term relating to an increase in tissue energy U, corresponding to its minimum, U_s, is a quadratic term for the difference in area, i.e., $S_s - S$ [42]. Therefore, in the case of small deformations where α may be a function of lung volume or an unknown variable and surface tension $\gamma \neq 0$ [42]. Then the stored energy is a combination of both tissue energy and surface energy [42]. The surface energy is expressed by $\int_0^S \gamma \, dS$. Therefore, the total energy of the lung, denoted by E, is defined by

$$E = U_s + \alpha \left(S_s - S\right)^2 + \int_0^S \gamma \, dS. \tag{3.12}$$

Wilson [42] determines the minimum of the surface area by taking the derivative of (3.12) with respect to S, where $S = 0$. That is, $2\alpha \left(S_s - S_A\right) = \gamma_A$. Substituting this expression for α into (3.12) eliminates α in the formulation of E_A. Note that $E = E_A$ and $S = S_A$ [42]. Taking the derivative of E_A with respect to V and letting $P_A = dE_A/dV$ and $P_s = dU_s/dV$ yields

$$P_A - P_s = \gamma_A \frac{d}{dV}\left(\frac{S_s + S_A}{2}\right) + \left(\frac{S_s - S_A}{2}\right)\frac{d\gamma_A}{dV}, \tag{3.13}$$

where P_A, P_s denote the total retraction pressures of air-filled lungs and saline-filled lungs, respectively, and S_A and S_s refer to the total surface areas of air-filled lungs and saline-filled lungs, respectively. Further, γ_A denotes the surface tension of the air-filled lung, and V represents total lung volume [42]. Equation (3.13) describes the relationships between surface tension, surface area, and recoil pressure [42]. For the large energy difference model, Wilson [42] generalised the above quadratic energy model by expressing ΔU as an arbitrary function of the volume V and surface area S. For each volume, Wilson [42] assumes there exists a balanced state with subsequent values for ΔU, S relating to each value of surface tension γ. The total energy E, is expressed by summing together the tissue energy and the surface energy. For a particular lung volume, S equates to the value for when the total energy is minimum [42]. Therefore, the following equation is derived by taking the minimum of total energy and quasi-static changes in lung volume due to V and S [42]:

$$P - P_s - \frac{\partial \Delta U}{\partial V}, \tag{3.14}$$

where $P = dE/dV$ and $P_s = dU_s/dV$. Recall that $\Delta U = 0$ at $P = P_s$. Thus, ΔU can be derived by integrating (3.14). Hence, from (3.12) and by integrating (3.14), [42] obtains this expression for the surface tension as a function of lung volume:

$$\gamma\left(V\right) = -\int_{V_s(S)}^{V} \frac{\partial}{\partial S}\left(P - P_s\right) dV. \tag{3.15}$$

Surface tension values were estimated to be < 20 dyne/cm [42]. These values for surface tension are much lower than the values obtained by ignoring the tissue elastic forces within an air-filled lung [38, 39]. Wilson [42] explains that surface tension contributes to the added recoil of the air-filled lung, and increases with increasing lung volume. It should be noted that (3.13) has a number of disadvantages, especially when compared to (3.11). Firstly, (3.13) is a differential equation rather than a straightforward algebraic expression for surface tension. It requires data on surface area that was not readily available when compared to the generous availability of data on lung recoil pressure. Secondly, it involves derivatives of surface area data. If this data were to be inaccurate, differentiation would yield inaccurate surface tension estimates. On the other hand, (3.13) was advantageous in providing more accurate approximations of surface tension than (3.11) [42]. Wilson [42] did not base his energy analysis on a specific geometric model of the alveolar structure. He may have assumed a standard polyhedral structure for the alveoli. However, if this is not the case, one may question if there is any variation with the results if a certain geometry is imposed on his energy difference models [42].

Wilson [43] provided his finalised approximations of surface tension upon inflation and deflation. Using the energy analysis from [42] and histological data for relations among recoil pressure, surface area, and lung volume, Wilson [43] produced surface tension-area curves from pressure-volume diagrams. In this paper [43], surface tension is calculated from recoil pressure using (3.15). However, unlike previous studies [42, 44], Wilson [43] neglected an important assumption relating to the tissue compensation properties of recoil pressure in both the air-filled lung and the saline-filled lung. That is, they are not the equal at the same lung volumes. Wilson [43] reported estimates of surface tension that reduced to < 2 dyne/cm as surface area decreased upon deflation. Similarly, surface tension was found to increase rapidly with increasing surface tension upon inflation. This value was approximated to be < 30 dyne/cm [43]. This highlighted a particular dependence of surface tension to surface area. His findings were consistent with results relating to inhomogenous lung deformations. Wilson [43] additionally examined alveolar stability by using a positiveness of the bulk modulus of lung parenchyma which was used to develop a basic theoretical criterion for stability. This stability criterion [43] could be considered for future research, whereby one could determine critical values of surface tension for the lung which correlate to certain healthy and pathological states of the lung.

Stamenovic [45] considered lung instability to be the consequence of a type of inhomogeneity that resulted in atelectasis. That is, it was suggested that the dependent behaviour of surface tension on the surface area of the alveoli could describe a particular lung instability. Atelectasis was thought to occur under pathological conditions where portions of the lung suddenly became over-inflated, whilst the remainder of the lung experienced little to no effects of inflation [45]. This instability was associated with the structural network of lung parenchyma [31, 40, 43, 46]. Mead et al. [31] initially identified various types of lung inhomogeneity that may result in lung instability. These include the instability and subsequent collapse of alveoli and airways, i.e., atelectasis, nonuniform dynamic ventilation, lung inflation from a gas-free state, and airway obstruction resulting in collapsed airways leading to atelectasis [31]. Stamenovic [45] utilized an alternative approach to lung instability and atelectasis, while still maintaining the properties of mechanical and parenchymal interdependence. He viewed atelectasis as the simultaneous existence of random stages of expansion which was termed the mixture of phases [45]. With regards to this concept, the lung is neutrally stable and stable. A pressure-volume analysis and an energy analysis were used to examine the stability of the lung. Both methods of analysis were vague in determining how the mixture of phases arises after transitioning from a state of uniform expansion.

Stamenovic [45] questioned whether uniform lung inflation occurs to a degree where a negative slope on the pressure-volume curve is observed, provided the equilibrium configurations are small, and whether this causes the lung to become unstable. Stamenovic [45] explains that the instability present at the smaller, more expanded section of the lung is stabilised through the minor expansive areas since these particular areas also have a larger volume [45]. Therefore, during natural lung inflation, the lung tends to maintain its most stable configurations such that the lung uniformly stretches to a point where it is stable with regards to all surrounding disturbances. If this does not occur, the mixture phase takes precedence. Therefore, the strain-energy function W is a potential [45]:

$$W\left(\frac{V}{V_0}\right) - W\left(\frac{\bar{V}}{V_0}\right) = \int_{\frac{\bar{V}}{V_0}}^{\frac{V}{V_0}} W'(J)\, dJ = P\left(\frac{V}{V_0} - \frac{\bar{V}}{V_0}\right), \tag{3.16}$$

where V is the volume, V_0 the relative reference volume, J the volume stretch, V/V_0 and $\bar{V}/V_0$ denote two equilibrium solutions and $P = W'(V/V_0) = W'\left(\bar{V}/V_0\right)$ is the recoil stress which is uniform at equilibrium [45]. Hence, by the Weierstrass condition [45], the lung is neutrally stable while the mixture of phases takes place. Stamenovic [45] states that the mixture phase exists in a domain where a region of a pressure-volume plot attributes a negative gradient or where an instability may occur. This is inclusive of the sections of minor disturbances where the lung is stable. This suggests that the mixture phase has a stabilising effect on the lungs. Stamenovic [45] stated, "During the mixture of phases, the level of stored elastic energy is reduced by the amount of work done in propagating the transition front between phases, leading to stabilisation". Stamenovic [45] also provides a description for the surface tenion-area relationship using the basic constitutive equation for uniform lung inflation:

$$P = f(V, \gamma), \tag{3.17}$$

where P is the pressure difference across the lung surface expressed as a function of volume V and surface tension γ [45]. The recoil pressure of uniformly inflated lungs is equal to P [45]. While this particular inflation occurs, surface area of the alveoli decreases. The volume elements of lung tissue fibres also decrease. As a result, lung recoil pressure diminishes. However, this outcome can be negated if there is a dependent relationship between surface tension and lung volume [45]. Suppose this relationship is nonexistent, then sections or the lung as a whole would approach a state of atelectasis. This would happen in an attempt to minimise the effects of surface tension on the force-bearing elements. Thus, surface tension must depend on alveolar surface area to prevent atelectasis [45].

Stamenovic and Wilson [10] attempted to provide an accurate theory around alveolar stability. They developed a continuum stability analysis which incorporates local distortions occurring within the transition area between open regions and atelectatic regions, i.e., by including the bounds of the elastic moduli obtained from the microstructural model [10]. Furthermore, their analysis examines the stability of a homogeneous and a nonhomogeneous lung [10]. For the homogeneous lung, [10] considers the answer to a specific question regarding the displacement of a surface with a spherical hole in a elastic material. This solution is explained as a consequential decrease of the inner displacement of the surrounding material as the square distance from the centre of the hole decreases. As a result, volume is preserved and shear distortion occurs. Moreover, the stress at the surface of the hole increases by $4\mu u/R$, where μ is the shear modulus of the material [10]. Thus, the surrounding parenchyma apply an outward stress on the boundary, equal to $P + (4\mu u/R)$.

Subsequently, the inner region of parenchyma exerts an inward stress on the boundary, equal to $P - (3Ku/R)$. In the case the outward stress is greater than the inner stress, $P + (4\mu u/R) > P - (3Ku/R)$. Note that P is transpulmonary pressure, R is the radius of a sphere used to model the parenchyma, K denotes the bulk modulus, μ the shear modulus, and u is the minimum inward displacement [10]. In the case whereby the outward stress is less than the inner stress, any increase in displacement u results in a subsequent failure or collapse of the sphere [10]. Therefore, Stamenovic and Wilson [10] derived the following condition for stability of a homogeneous lung:

$$3K + 4\mu > 0. \tag{3.18}$$

For the stability of a nonhomogeneous lung, Stamenovic and Wilson [10] consider the spherical interior region to have a greater surface-to-volume ratio in comparison to the exterior regions. Therefore, the associated recoil pressure, P_1, of the inner region is greater than the recoil pressure of the outer region, P_0. Shear deformation occurs in the exterior sections upon contraction of the interior sections [10]. Similarly, changes to stresses occur at the boundary proportional to the boundary of u. Therefore, the stresses at equilibrium are equal. Simplifying the equilibrium equation provides the following formula for u:

$$\frac{(3K_1 + 4\mu_0)\, u}{R} = P_1 - P_0, \tag{3.19}$$

where the bulk modulus K_1 corresponds to the interior region, and the shear modulus μ_0 relates to the exterior region [10]. Stamenovic and Wilson [10] explain that the lung continuously transitions from a state of uniform expansion to the mixture of phases state, previously considered to be irregular or discontinuous [45]. From the stability analysis, they determined that both homogeneous and nonhomogeneous lungs are stable [10]. However, if surface tension is extensive or constant, along with no explicit dependence on surface area, then surface forces will greatly influence the elastic behaviour of the lung due to decreases in lung volume or tissue forces with a dependence on volume [10]. This will result in an increase with the surface-to-volume ratio, which is used to describe the mechanism responsible for regional collapse during the transition in [10]. Stamenovic and Wilson [10] explain that should the surface-to-volume ratio be greater in one region of a foam than in another, the gas pressure will be higher in the first region when compared to the second. The resulting change in pressure enables gas diffusion within the alveolar walls [10]. This signified a difference in the ratio between surface tension and volume [10].

4 Constitutive Theory of Lung Parenchyma

Describing the complex elastic behaviour of the lung required the development of constitutive equations. In lung mechanics, constitutive equations can describe the nonlinear elastic behaviour exhibited by lung parenchyma through the relationship between the macroscopic stress and the macroscopic strain. Therefore, understanding the elastic behaviour of lung parenchyma formed the foundation for various theoretical and experimental models within lung mechanics [3]. The governing equations of elasticity have been greatly simplified by assuming small displacement gradients. However, with biological materials (organs, tissue, cells), specifically lung parenchyma, the assumption of small displacement gradients is not entirely valid as the lung actually experiences large deformations. Therefore, in order to

obtain efficient measurements of biological lung material, one must consider large displacement gradients [47]. Thus, using finite-strain elasticity theory is more applicable. Lai-Fook [48] gives a reason for adopting this particular method, stating that large displacement gradients will allow one to measure values that correlate with physiological parameters, such as heart rate or lung volume. These parameters can be used to assess the welfare of human beings and animals. Hence, the elastic behaviour of lung parenchyma was represented through strain-energy functions [41] or through nonlinear stress-strain laws [47]. The models developed under this particular approach exhibit a nonlinear stress-strain relationship for large displacement gradients.

Carton et al. [49] and various other studies [17, 19, 30] utilised pressure-volume curves and data to examine the elasticity of lung tissue. However, pressure-volume curves cannot express the stress-strain response of lung tissue along with the overall elastic response of the lung. Mitzner [7] discussed two challenging aspects that contributed to this issue. Firstly, there was a lack of understanding around how the different mechanical components of the respiratory system interacted and depended on each other. That is, how the forces induced in different parts of the lungs could be divided into their respective mechanical elastic, resistive and inertial components. Mead [50] considered these forces as pressures since the motion of the lung mechanical system is expressed in terms of volume. He provided a theoretical basis around this particular concept by redefining Newton's third law of motion, i.e., any pressure applied to a body is opposed by an equal pressure developed by the body [50]. He determined that the applied pressure at each section of the lung is equal to the pressure difference at each boundary of that particular section. Thereafter, taking the sum of the equations for the opposing pressures of gas and the lung tissue, Mead [50] developed the following equation of motion for the lung:

$$P_L = P_{ao} - P_{pl} = P_{el_L} + P_{res_L} + P_{in_L}, \tag{4.1}$$

where P_{a0} and P_{pl} correspond to the pressures at the respective boundaries of the airway opening, ao, and the visceral pleura, pl [50]. Furthermore, $P_{el_L} = P_{el_{Ti}}$, $P_{res_L} = P_{res_{Ti}} + P_{res_G}$, and $P_{in_L} = P_{in_{Ti}} + P_{in_G}$, represent the opposing pressures of the lung with respect to the elastic, flow-resistive, and inertial parts of the lung [50]. The second challenge discussed by Mitzner [7] is based on the forces acting within the lung that are responsible for its deformation. To explain further, consider the structure of the lung. It is comprised of a complex network of connective tissue. Moreover, there is a complex portion of the lung that is responsible for several important physiological processes, such as gas exchange and blood flow, that are influenced by elastic stresses and strains. This area is known as the lung parenchyma and can be described as the part of lung relating to alveolar tissue and any form of lung tissue involved in lung physiological processes, i.e., the bronchioles, bronchi, blood vessels, interstitium and alveoli. Thus, instead of relying on an individual alveolus to describe the mechanical behaviour of the whole lung, studies dedicated their attention to understanding the macroscopic behaviour of either the alveolar septa or layers of lung parenchyma to describe the complex structural and mechanical elasticity of the lung [31, 41, 51].

This major turning point for research into the elasticity of the lung is credited to the prominent study conducted by Mead et al. [31]. An influential description of the mechanical functioning of the lung was presented which changed how lung elasticity was examined. This was termed mechanical interdependence [31]. During inflation, the pressure in the alveoli must surpass the pressure found outside the visceral pleura. Nonetheless, this pressure difference is not applied to only a single unit, but rather to all alveoli. This includes the units

completely surrounded by other alveoli, airways, and blood vessels. The lung elements situated within surrounding elastic tissue forms an interconnected network. This brought up the question regarding what forces are responsible for inflating the internal structures of the lung, including the airways and blood vessels. Mead et al. [31] showed how the effective pressure (transpulmonary) found around the regions surrounded by parenchyma correlated to the pressure outside the visceral pleura, i.e., the pleural pressure. Transpulmonary pressure may be greater than, less than, or equal to the pleural pressure. In more general terms, mechanical interdependence describes the effects of surrounding lung tissue on the mechanics of local elastic elements. The theoretical simplification adopted from this paper [31] was to now analyse the mechanics of lung tissue as a whole or a cluster of lung parenchyma, rather than observing the behaviour of a single independent unit. This newly detailed concept was applied to their analysis on the distribution of stresses within the lung [31]. Mead et al. [31] analyse the equilibrium of radial forces occurring on a section of the lung wall. The assumption is made to neglect gravitational forces. This assumption is valid because gravitational forces acting across the surface of the lung walls are minimal such that any differences in the distribution of stress as a result of gravity is considered negligible [31]. Moreover, radial stresses were deemed appropriate for the lung walls since the walls of the lung are usually shaped in terms of a cylinder or sphere. The equation for the equilibrium of radial stresses is as follows:

$$(P_i - P_o) + \left(\frac{\sum F_o}{A} - \frac{\sum F_i}{\mathrm{A}} \right) - P_w = 0, \tag{4.2}$$

where P_i, P_o, F_i, F_o refer to the inner and outer pressures and forces, respectively, acting upon A the area of the surface, and P_w is the acting pressure on the lung wall. The term, $(P_i - P_o)$, describes the applied forces acting on two surfaces on the wall (inner and outer surface) through molecular gas/liquid interactions. By Pascal's law, for a liquid, the stress is equal to the pressure in all directions [31]. Therefore, the radial stress is the sum of the pressures at the two surfaces. The second term in (4.2) defines the sum of radial stresses arising from the outer and inner wall components. The last term, P_w, is the resulting radial stress from the circumferential components of stress applied to the parenchymal membrane by neighbouring membranes [31]. Now consider the application of (4.2) to the pleural surface (outer wall), and subsequently to the inner walls of the lung. Through this extension, Mead et al. [31] defined the transpulmonary pressure-radial stress relationship which is responsible for distorting particular areas within the lung. Transpulmonary pressure is equally opposed by the sum of a acting tissue and surface forces (inner forces) acting across the pleural surface. Moreover, since the radii of curvature is greater at normal lung volumes, P_w is omitted [31]. Mead et al. [31] further considered an arbitrary spherical region, re, comprised of a wall of adjacent alveolar septa. This wall experiences both outward and inward tissue and surface forces. Furthermore, P_w is accounted for in this instance since the radius of curvature is minimal. Suppose the airways are open such that the pressure of gases acting on the outer and inner surfaces of the parenchymal membrane are both equal to the alveolar pressure. This results in the first term of (4.2) being equal to zero. Thus,

$$\frac{\sum F_o}{A_{re}} = \frac{\sum F_i}{A_{re}} \mid P_w, \tag{4.3}$$

where A_{re} is the area of the spherical region. From (4.3), the left-hand side refers to the distorting regional stress resulting from parenchymal surface tension and parenchymal tissue stresses [31]. This is equally opposed by the right-hand side of (4.3) describing the application of parenchymal surface and tissue stresses acting within the membrane of the spherical

region as well as through the pressure from within the wall. Mead et al. [31] proposed the following question, "How does the local distending stress, $\frac{\sum F_o}{A_{re}}$, relate to static transpulmonary pressure, $P_{alv} - P_{pl}$"? This question was answered by referring to the transpulmonary pressure. That is, the forces acting outward to any wall is an inner acting force for the next outer wall. Therefore, this interdependent relationship progresses to the pleural surface such that the only external force acting on the surface is transpulmonary pressure [31]. Suppose the lung is homogeneous such that the stress occurring at any surface is equivalent to the pressure at that surface, then transpulmonary pressure is applied to the innermost regions of the lung without distention [31]. Accordingly, suppose the stress is equal at all surfaces in the lung, then transpulmonary pressure is transferred towards the inner part of the lung by

$$P_{alv} - P_{pl} = \frac{\sum F_i}{A_{pl}} = \frac{nF}{A} = \frac{\sum F_o}{A_{re}}, \tag{4.4}$$

where n represents the number of connections per unit area A. Hence, all distorted regions of the lung are susceptible to transpulmonary pressure [31]. The dependence of the attached regions on the distribution of stresses and pressures from the outermost region to the innermost region is a reflection of mechanical interdependence [31]. Mead et al. [31] further applied the concept of mechanical interdependence to the static and dynamic stability of the lung, and collateral ventilation. Mead et al. [31] noted that small airways which are obstructed have high opening pressures, which can result in hemorrhagic atelectasis. Therefore, mechanical interdependence plays a crucial part in reducing the magnitude of pulmonary obstruction by collapsing certain regions of the lung towards a focal point [31]. This can be explained more appropriately by examining the extent of mechanical interdependence with respect to the distribution of stresses in the lung. That is, stress distribution in the lung only occurs during nonuniform lung deformation [31]. Mechanical interdependence results in a less nonhomogeneous deformation due to the interconnected network [31]. If regions or lung elements were examined individually, the deformation observed would be highly nonuniform. Further, they modelled the lung as a network of springs in order to analyse the stress-strain relationship. They concluded from their findings that imposing certain constraints at particular points in the model resulted in deformations that occurred in distant, but connected areas of the lung [31]. These deformations are suitable for study under elastic theory. However, Mead et al. [31] did not provide a mathematical formulation of the constitutive equation. Dayman [52] hinted at the breakdown of the complex interconnected network of lung parenchyma being the main reason for advanced cases of emphysema, even going as far as suggesting that a major loss of elasticity within the entirety of lung was not the reason for the disease. Even though it was not stated explicitly, Dayman [52] may have indirectly provided the first possible indication of lung mechanical interdependence.

Mead et al. [31] did not provide a mathematical description of the constitutive equations for the stress-strain response of lung parenchyma. Instead, the formulation of the constitutive equations was developed by Wilson [53], who considered a two-dimensional spring system. The equations are given by

$$\tau_{xx} = \lambda\left(\frac{\partial u_x}{\partial x} + \frac{\partial u_y}{\partial y}\right) + 2\mu\frac{\partial u_x}{\partial x}, \quad \tau_{yy} = \lambda\left(\frac{\partial u_x}{\partial x} + \frac{\partial u_y}{\partial y}\right) + 2\mu\frac{\partial u_y}{\partial y},$$
$$\tau_{xy} = \tau_{yx} = \mu\left(\frac{\partial u_x}{\partial y} + \frac{\partial u_y}{\partial x}\right), \tag{4.5}$$

where τ is the Cartesian component of stress, u_x and u_y are the x and y components of strain. They also represent small deformations. Further, μ and λ are the material constants. Note that equations (4) are linearised and only account for small deformations. From his observations on the stress-strain response, Wilson [53] details that it is not directly applicable to the lung. Rather, the elastic behaviour displayed in his study is similar to that of a spring network, whose properties are based of the properties of lung parenchyma. For the two-dimensional spring model, the shear modulus of the lung material is observed to increase with increasing initial stretching of the springs [53]. Thus, for a low shear modulus, the effects of local disturbances are seen to spread out and diminish the further away they got from the surrounding material. A high shear modulus is seen to have a greater effect on the surrounding material [53].

Understanding the mechanical elastic properties of biological tissues is considered important to solving physiological problems. In particular, the stress-strain relationship of these tissues is of great importance. For example, consider the elastic behaviour of the lung. If one can accurately describe the stress-strain relationship of the lung, then it can be applied to analysing flow-resistive and fluid mechanical properties of the airways, i.e., the deformation of the airways which result in airway obstruction or reduce the flow of air in the lungs. The fluid mechanical properties of the lung have an explicit dependence on the elastic stress-strain relationship of lung tissue. Fung [54] identified an issue with the application of linearised elastic theory to biological material, that is, biological tissues exhibit finite deformations and are associated with having a highly nonlinear stress-strain relationship. Applying linearised elasticity to a highly nonlinear material presents several inaccuracies with the data [54]. Fung [54] explains that biological materials exhibit a dependence of the stress on not only the strain, but also on the history of the strain, i.e., hysteresis, relaxation, creep [54]. Fung [54] used experimental stress-strain curves to develop a general constitutive equation (containing two or three parameters) for biological materials undergoing simple elongation. The biological material of concern in this paper is not lung tissue, but rather mesentery [54], a membrane connecting the intestine to the abdominal wall and holding them together. The constitutive equation for the mesentery neglects any time-dependent properties and the mesentery undergoes uniform stretch [54]. The Eulerian stress, σ, with respect to tension is

$$\sigma = \frac{P}{A} = \frac{P}{A_0}\lambda = T\lambda, \tag{4.6}$$

where A is the cross-sectional area, A_0 the area in terms of the reference configuration, T the elastic tension, and P is the total tensile force [54]. Equation (4.6) expresses simple tension through a single component of stress σ and a single extension ratio λ [54]. The elastic curve for mesentery is approximated by the quadratic expression, $dT/d\lambda = aT\,(1 - bT)$. Integrating this quadratic expression and substituting (4.6) into the resulting equations yields the constitutive equation describing the stress-strain relationship of mesentery:

$$\sigma = \lambda \frac{\exp(a\lambda)}{c + b\exp(a\lambda)}, \quad \left(1 \leq \lambda \leq \lambda_y\right), \tag{4.7}$$

where a, b are constants of proportionality, and c is a constant of integration. Equation (4.7) is an exponential constitutive equation which describes the nonlinear stress-strain relationship of mesentery. According to Fung [54], exponential constitutive equations can be used to model the elastic response of biological tissue. However, Fung [54] does not state the form of the constitutive equation for lung tissue. Instead, he highlights that lung tissue may

be modelled in a similar manner to materials undergoing simple stretch, by describing the stress as an exponential function of the strain [54]. Note that an actual lung undergoes triaxial loading. Thus, it would be more efficient to model the highly nonlinear elastic response of the lung with respect to triaxial experimental stress-strain data [54]. However, triaxial loading of the lung is difficult and complex to perform experimentally. Fung [54] also applied (4.7) to other soft biological tissues such as heart muscles, muscle fibres, and skin. These are discussed briefly in [54].

Soft tissues are major components of every living organism, composed of collagen, elastin, muscle, cells, and ground substances [55]. The mechanical properties of soft tissue depends on both their chemical and structural composition. For organs, the mechanical properties depend on the material, structure, and the environment [55]. Fung [55] states that soft tissues actually exhibit a pseudo-elastic behaviour, i.e., not elastic, but under periodic loading and unloading a steady-state stress-strain relationship exists which is independent of the rate of strain. Further, hysteresis loops observed on pressure-volume curves are associated with viscoelastic behaviour, rather than elastic behaviour [55]. Since this loop is repeatable, Fung [55] emphasises that preconditioning may be applied in order to use elastic theory since the material or curves will begin to display elastic behaviour after periodic loading and unloading, i.e., the curves can be treated separately to examine the elasticity of the material. Preconditioning is the process of considering the loading and unloading pressure-volume curves separately after repeated cycles. This method could be applied to soft tissues of a viscoelastic nature. Fung [55] further suggests that the mathematical model governing the viscoelastcity of a soft tissue, such as lung parenchyma, must account for all features of hysteresis, creep and relaxation. An example of a popular viscoelastic model is known as the Maxwell model, which displays properties of both an elastic and viscoelastic material [55, 56]. Maxwell models have been exhaustively applied to model the viscoelasticity of the lung [57], however they are attributed with several limitations [57, 58]. This will be discussed later in the paper.

The methods used by Mead et al. [31] and Wilson [53] differ quite significantly from the approaches taken by Frankus and Lee [59], and Fung [46]. These methods involve the development of structural models in which the size, shape, and properties of the alveolar septa and parenchyma are modelled. [59] considered the structure of the lung parenchyma as a cluster of alveoli. This was then modelled as a collection of dodecahedrons, which is described as a regular polygon with twelve pentagonal faces. Frankus and Lee [59] first considered a three-dimensional isotropic material whereby its stress-strain relationship is derived in terms of a strain-energy function W, with respect to the strain invariants I_1, I_2, I_3, as follows

$$\begin{aligned}
\tau_{11} &= 2\left\{\frac{\partial W}{\partial I_1} + \frac{\partial W}{\partial I_2}\left(\lambda_2^2 + \lambda_3^2\right) + \frac{\partial W}{\partial I_3}\frac{I_3}{\lambda_1^2}\right\},\\
\tau_{22} &= 2\left\{\frac{\partial W}{\partial I_1} + \frac{\partial W}{\partial I_2}\left(\lambda_1^2 + \lambda_3^2\right) + \frac{\partial W}{\partial I_3}\frac{I_3}{\lambda_2^2}\right\},\\
\tau_{33} &= 2\left\{\frac{\partial W}{\partial I_1} + \frac{\partial W}{\partial I_2}\left(\lambda_1^2 + \lambda_2^2\right) + \frac{\partial W}{\partial I_3}\frac{I_3}{\lambda_3^2}\right\},
\end{aligned} \tag{4.8}$$

where λ_i, $i = 1, 2, 3$, denotes the stretch ratios and τ_{ii}, $i = 1, 2, 3$ represent the principal components of stress. Frankus and Lee [59] used a numerical finite-element method and pentagonal membrane elements to model the pure homogeneous deformation of the dodecahedrons. They determined that the deformation of a single dodecahedral substructure results

in the displacement of points proportional to the coordinates if the origin of the coordinates is zero. This approximation compared well with experimental data. In this instance, no equation was developed to relate the microscopic distortion properties of the lung to its associated macroscopic deformation. Developing a constitutive equation relating the macroscopic and microscopic stresses and strains of the lung is a subject for future research due to its potential to describe how the microscopic elastic elements of the lung directly influence the macroscopic elements. This study also allowed for pressure-volume curves to be formulated in order to analyse any discontinuities within the parenchyma [59]. Emphysema showed a strong correlation to changes in the pressure-volume response and was linked to structural discontinuities [59]. Frankus and Lee [59] explain that distinguishing between these changes and those that are specific to lung defects requires a theoretical hypothesis to mathematically simulate any irregular lung behaviour arising from internal deformations.

Fung [46] maintained a similar theoretical approach to that of Frankus and Lee [59], whereby the stress-strain relationship of lung parenchyma can be derived by considering different geometries for the alveoli. In this paper [46], the stress-strain relationship is said to be dependent on three factors: The magnitude of stress present in the alveolar walls, the characteristics of surface tension, and the geometry of the alveoli. The above factors are all considered to be a function of the macroscopic strain [46]. Lung parenchyma is considered as a continuum comprised of voids, rather than an individual rubber-like structure or unit [46]. This assumption is useful because it allows for the stresses and strains to be analysed across the whole lung [31, 46]. Fung [46] examined the elasticity of the alveolar sheet. By solving sets of integrals for the macroscopic stress distribution in the lung, the model of the three-dimensional stress-strain relationship for the alveolar tissue is assumed to be similar to that of other soft tissues developed in [54]. However, the physical constants are different [46]. The form of this constitutive equation is derived from the pseudo-strain-energy function W,

$$W = \frac{1}{2} C_{ijhl} e_{ij} e_k \left[\beta + \exp\left(\alpha_{mn} e_{mn} + \gamma_{pq^r} e_{pe} e_{rs}\right)\right], \tag{4.9}$$

such that

$$\sigma_{ij} = \frac{\partial W}{\partial e_{ij}}, \tag{4.10}$$

where the two sets of constants C_{ijkl}, α_{mn}, γ_{pqrs}, and β are fundamental for loading and unloading, respectively [46]. For soft tissues, the stress is defined as an exponential function of the strain [54]. Therefore, the constitutive equations describing the nonlinear relationship between the macroscopic stresses and strains of lung parenchyma is

$$\sigma_1 = \beta\left(c_1 e_1 + c_4 e_2\right) + \left[c_1 e_1 + c_4 e_2 + \frac{a_1}{2}\left(c_1 e_1^2 + c_2 e_2^2 + 2c_4 e_1 e_2 + c_7 e_{12}^2\right)\right] \cdot \exp\left[a_1 e_1 + a_2 e_2\right], \quad \sigma_{12} = \beta c_7 e_{12} + e_{12} c_7 \exp\left[a_1 e_1 + a_2 e_2 + \gamma e_{12}^2\right], \tag{4.11}$$

where σ_{ij} denotes the stress tensor, e_{ij} represents the strain tensor, and β, c_1, c_2, c_4, c_7, a_1, a_2 are the material coefficients [46]. It is important to mention that the formulation of (4.11) is not affected by the specified geometries since these equations correspond to the the elasticity of the alveolar interface as a whole, and not to the geometrical representations of the parenchyma. Fung [46] analysed the deformation of lung parenchyma by defining a geometry for the parenchymal structure, that is, cubic and spherical geometries. These alveolar

geometries correspond to the structure of the lung parenchyma in the reference configuration. However, in its deformed state or current configuration, the alveolar geometries become parallelopiped or ellipsoid in structure, respectively. Fung [46] presents a theoretical analysis of how to obtain the stress tensor for lung parenchyma within these specified geometries, whereby the macroscopic stresses are statistically averaged for random distributions of the polyhedron. This theoretical model is termed the mean alveolus model which uses Ergodic theory [46]. The mean alveolus model was successful in determining the stresses and strain of lung parenchyma defined by a cubic or spherical geometry. However, the downside to this study is that Fung [46] did not account for the stresses resulting from surface tension. Instead, only accounting for the stresses and strains arising as a result of uniform lung deformation [46]. It would be interesting to examine how accurate the mean alveolus model [46] is to modelling the stresses and strains of a diseased lung or whether the mean alveolus model can simulate the elastic behaviour of lung parenchyma through complex geometries. For example, consider the dodecahedra geometry assumed by Frankus and Lee [59].

Fung [40] examined the macroscopic stresses due to surface tension, and its correlation to deformation and atelectasis. Fung [40] provides an extension of the analysis in [46] whereby the stresses due to surface tension are now incorporated into the strain-energy function and stress-strain constitutive equations for the lung parenchyma. Fung [40] accounts for both the surface tension and the elastic stresses in the alveolar septum within a predefined cubic alveolar geometry. He considers a lung consisting of a cluster of alveoli which are cubic in shape in the reference configuration. Upon deformation, the distorted alveoli now assume a rectangular parallelopiped geometry where the boundaries are parallel in relation to the principal axes of strain [40]. The macroscopic stress σ_{11} is obtained by first summing the tensions of every alveoli and then dividing the sum by the cross-sectional area of the membranes. Fung [40] expresses this by the following equation:

$$\sigma_{11} = [2\gamma_{13} + N_{13}(e)]\,\frac{1}{(\lambda_2\Delta)} + \left[2\gamma_{12} + N_{12}^{(e)}\right]\frac{1}{(\lambda_3\Delta)}, \tag{4.12}$$

where $N(e)$ is elastic tension, γ_{ij} the surface tension components, λ_i are the stretch ratios, and Δ is the dimension of the cubic alveoli in the reference configuration. Fung [40] states that knowing how both γ and $N^{(e)}$ changes in relation to λ_1, λ_2, and λ_3, will result in (4.12) being the stress-strain constitutive equation of the parenchyma. Note that σ_{22} and σ_{33} may be derived from (4.12) through a cyclic permutation of subscripts 1, 2, 3. The stress due to surface tension is obtained by separating σ_{11} into its respective components for the elastic tissue stress, $\sigma_{11}^{(e)}$, and the surface tension stress, $\sigma_{11}^{(s)}$, such that

$$\sigma_{11}^{(e)} = \frac{1}{\Delta}\left[N_{13}^{(e)}\frac{1}{\lambda_2} + N_{12}^{(e)}\frac{1}{\lambda_3}\right], \quad \sigma_{11}^{(s)} = \frac{2}{\Delta}\left[\gamma_{13}\frac{1}{\lambda_2} + \gamma_{12}\frac{1}{\lambda_3}\right]. \tag{4.13}$$

Consider the surface tension term given in (4.13). Suppose $\gamma_{12} = \gamma_{13} = \text{constant}$, then (4.13) is not dependent on the stretch λ_1. Furthermore, an increase in transverse stretch, λ_2 or λ_3, results in the stress, $\sigma_{11}^{(s)}$, to decrease [40]. The conceptualised lung described here is composed of rectangular lung parenchyma grouped into a cluster of parallel planes such that the lung undergoes stretch with respect to the direction of the planes [40]. The importance of deriving the lung stress-strain response is emphasised by Fung [40]. He explains that this will allow one to formulate the general equations of lung mechanics as well as provide solutions to three specific problems: (i) uniform lung inflation, (ii) the nonuniform stress distribution in the lung as a result of gravity, and (iii) three potential cases of atelectasis, i.e., planar, axial and focal atelectasis. In order to determine the relationship between the stress and the

strain of the lung, Fung [40] introduces a strain-energy function along with two important assumptions. Firstly, the lung is considered to be preconditioned. In this instance, the lung is actually a pseudo-elastic material. Secondly, the form of the strain-energy function is taken to be similar to the exponential constitutive equation (4.11) due to its affinity with biological tissue [54]. The pseudo-strain-energy function, $\rho_0 W$, incorporates both surface tension and tissue elasticity [40]:

$$\begin{aligned}\rho_o W = \frac{2}{\Delta}(\gamma_{12} - \gamma_{12}) \Bigg\{ & \frac{\lambda_{12}\,\min}{\gamma_{12_{\max}} - \gamma_{12_{\min}}} \lambda_1 \lambda_2 \\ & + \frac{1}{(\lambda_1\lambda_2)_{\max} - (\lambda_1\lambda_2)_{\min}} \left[\frac{{\lambda_1}^2 {\lambda_2}^2}{2} - (\lambda_1\lambda_2)_{\min} \lambda_1 \lambda_2 \right] \\ & - \sum_{n-1}^{\infty} c_n \frac{(\lambda_1\lambda_2)_{\max} - (\lambda_1\lambda_2)_{\min}}{n\pi} \cdot \cos \frac{n\pi \left[\lambda_1\lambda_2 - (\lambda_1\lambda_2)_{\min}\right]}{\left(\underline{\lambda}_1\lambda_2\right)_{\max} - (\lambda_1\lambda_2)_{\min}} \Bigg\} \\ & + C \exp\left[a_1 e_1^2 + a_2 e_2^2 + 2a_4 e_1 e_2\right] + \text{cyclic permutation terms}, \end{aligned} \tag{4.14}$$

where λ_i are the stretch ratios, ρ_0 refers to the reference density, γ_i are components of surface tension, a_1, a_2, a_4, C the material constants, e_i the unit basis vectors. By differentiating $\rho_0 W$ with respect to the stretch ratios λ_i, the Lagrangian stresses can be obtained [40]. Thus, the corresponding Cauchy stress tensor is expressed by

$$\sigma_{ij} = \frac{\rho}{\rho_0} \lambda_i T_{ij} = \frac{\lambda_i}{\lambda_1 \lambda_2 \lambda_3} T_{ij}, \tag{4.15}$$

where ρ defines the density, and $i, j = 1, 2, 3$. [40] explicitly states that the relationship between the stress and the strain of lung parenchyma is nonlinear.

Hoppin et al. [60] investigated the properties of lung parenchymal distortion. Instead of developing a mathematical model to describe the stress-strain relationship of the lung, Hoppin et al. [60] developed an experiment to collect data in order to define the relationship between symmetrical and asymmetrical elastic expansion. For this experiment, lung parenchymal tissue is subjected to triaxial stretch both symmetrically and asymmetrically for a large deformation range. Since lung parenchyma is characterised as a continuum, the assumption was made to model its distortion as a continuum [60]. Microscopically, this characterisation is not applicable as the alveolar walls are discrete elements. Macroscopically, this characterisation is appropriate because the structure of the lung is assumed to be homogeneous to a certain extent, with discrete elements being small enough to be negligible [60]. Hoppin et al. [60] examined cubic parenchymal extracts whereby a tensile force is applied evenly over the entire surface of each side of the extract, with no applied shear stress. A parallel force is further applied at independent points on each parenchymal surface. Under this particular method, the lung became locally distorted in the areas where the forces are applied [60]. Hoppin et al. [60] saw this as a disadvantage as local regional distortions cannot be used to describe the overall distortion of the whole lung. To minimise this disadvantage, they assume that the weight of the whole lung is primarily affected by lung parenchyma, with gravity being negated. According to West [61], regional distortion anomalies occur during lung expansion and the resulting stresses from this distortion is associated with gravity. West and Matthews [62] stated otherwise, claiming that the stresses induced by the weight of the lung are insignificant and are primarily due to lung expansion. Hoppin et al. [60] observed that the distortion due to displacement of an individual alveoli relative to

the surrounding parenchyma did not impact the distortion of the surrounding tissue. Instead, the distribution of the distortion of a cluster of alveoli or lung parenchyma to surrounding parenchyma would be more noticeable in the lung, i.e., mechanical interdependence [31]. The elastic coefficients obtained by Hoppin et al. [60]: the bulk modulus, Young's Modulus and Poisson's Ratio, were directly compared to the model presented in [63]. They described lung parenchyma as a continuum equivalent to an array of interconnected elastic membranes [63]. The bulk modulus and Young's Modulus were observed to increase at high lung volumes, indicating an increase in stiffness of the parenchyma. Poisson's Ratio was measured at ≈ 0.3 in an air-filled lung, whilst this value varied between 0.16–0.24 in a saline-filled lung. However, for this study [60], the lung parenchyma is assumed to undergo small deformations. Whilst this assumption greatly simplifies the elastic analysis of the lung, it does not apply to actual elastic behaviour of the lung. A real lung is said to undergo large nonuniform deformations [8, 64].

Using the distortion data collected by Hoppin et al. [60], Lee and Frankus [65] derived a strain-energy function W for dog lung parenchyma. Firstly, a continuous constitutive relationship is developed to describe the stiffness of parenchyma using Finite Element Methods (FEM) [65]. This is usually expressed in the form of a stiffness matrix, however it is not given in this paper [65]. The strain-energy function for lung parenchyma is derived by considering the strain-energy of an elastic continuum body, expressed as a general function of strain, $W = W\left(e_{ij}\right)$ [65]. Thereafter, the stretch ratios λ_i may be substituted in for the strain e_{ij}. Lee and Frankus [65] consider the elastic continuum body to be a nonlinear material. They approximate the strain-energy function as a polynomial with even powers of the stretch ratios λ_i:

$$W = \Sigma_k \, C_{ijkl} \, \lambda_i^l \, \lambda_j^{k-l}, \tag{4.16}$$

where $i, j = 1, 2, 3$; $k = 2, 4, 6, \ldots, n$; $l = 0, 2, 4, \ldots, k$, and C_{ijk} is a cyclic permutation symbol. Lee and Frankus [65] assume that the material is initially isotropic, implying (4.16) is cyclically symmetric in i, j. The strain-energy function is expressed as

$$\begin{aligned} W = {} & a_1 I_1 + a_2 \left(I_1^2 - 2I_2\right) + a_3 \left(I_1^3 - 3I_1 I_2 + 3I_3\right) \\ & + a_4 \left(I_1^4 - 4I_1^2 I_2 + 2I_2^2 + 4I_1 I_3\right) + b_1 I_2 + b_2 \left(I_2^2 - 2I_1 I_3\right) \\ & + c_1 I_3 + c_2 \left(I_1 I_2 - 3I_3\right) + c_3 \left(I_1^2 I_2 - 2I_2^2 - I_1 I_3\right), \end{aligned} \tag{4.17}$$

where $a_1, a_2, a_3, a_4, b_1, b_2, c_1, c_2, c_3$ are material coefficients [65]. Lee and Frankus [65] evaluated their strain-energy model against the mean alveolus model developed by Fung [40, 46]. Using the experimental distortion data from [60], Lee and Frankus [65] observed that their model captured the nonlinear distortion properties of lung parenchyma more accurately. However, they still considered the mean alveolus model as being a reasonable and efficient method for analysing parenchymal distortion properties. The only difference between the two models is that their model accounted for the pressure-volume relationship of the lung [65], whereas the mean alveolus model did not [40, 46]. Whilst the pressure-volume relationship of the lung does not provide direct information of the stress-strain response of the lung, it can be used to obtain values of the elastic constants such as the bulk modulus, Young's modulus, or Poisson's Ratio [60].

Lee et al. [66] revisited the distortion properties of lung parenchyma from [65]. In this instance, the assumption is made whereby the deformations resulting in any changes to the geometry of the lung parenchyma is considered to be so small that this geometric change is neglected [66]. This assumption is justified by comparing the extent of small deformations

acting on the lung parenchyma to the extent of the overall deformation experienced by the lung [66]. This assumption allowed them to superimpose infinitesimal deformation on finite uniform deformation [66]. Superimposing small deformation onto a large deformation provides a basis for deriving the elastic constants pertaining to each uniform expansion and allows for the lung to be treated as an ideal elastic material [66]. A further assumption is made whereby lung parenchyma is assumed to be a homogeneous compressible continuum [66]. Lee et al. [66] obtained the mechanical elastic properties of lung parenchyma through a strain-energy function W, whereby the parenchyma is subject to small deformations superimposed on large uniform deformation. For an isotropic, homogeneous material, whereby the lung parenchyma undergoes pure homogeneous deformation, the strain-energy function is defined in terms of the stretch ratios λ_i, i.e., $W = W(\lambda_1, \lambda_2, \lambda_3)$. In order to determine the elastic properties of lung parenchyma at different volume levels, Lee et al. [66] assume that the lung undergoes finite uniform expansion to a given volume in the collapsed configuration. The deformation from the reference configuration to the current configuration is infinitesimal pure homogeneous deformation [66]. The Eulerian stresses σ_i given in terms of W are expressed by

$$\sigma_i \lambda_j \lambda_k = \frac{\partial W}{\partial \lambda_i}, \quad \sigma_i^* \eta_j \eta_k = \frac{\partial \hat{W}}{\partial \eta_i}, \tag{4.18}$$

where η_i, η_j, η_k denote the principal stretch ratios of the equal triaxial intermediate state with respect to the reference configuration, $\hat{W}$ is the strain-energy function in terms of η_i, and σ_i^* is the Eulerian stress of the intermediate configuration measured with respect to the reference configuration [66]. By the Taylor series expansion and the stretch ratios λ_i, W is expressed to the first order of smallness in the current configuration. Therefore, the particular form of the strain-energy function for the uniformly expanded lung is derived by taking the derivative with respect to η. This gives an expression for $\hat{W}$ such that the stress-strain relationship is determined by taking the derivative of $\hat{W}$ with respect to η_i:

$$\frac{\partial \hat{W}}{\partial \eta_i}|_\alpha = a(\eta - 1)^n. \tag{4.19}$$

Thus, by integrating (4.19), the strain-energy function is expressed by

$$W(\lambda_1, \lambda_2, \lambda_3) = \frac{3a}{n+1}(\eta - 1)^{n+1} + a(\eta - 1)(\lambda_1 + \lambda_2 + \lambda_3 - 3\eta), \tag{4.20}$$

where a is the coefficient of the equal triaxial stress-strain relationship and n is an integer exponent of equal triaxial stress-strain relationship [66]. This model presents several questions: What is the purpose of describing the above relation as a power-law relation? Has any insight already been provided on the power-law description of lung behaviour? The measured elastic constants were found to be in agreement with the distortion data initially obtained by Hoppin et al. [60]. Lee et al. [66] applied the above model to a particular lung elasticity problem termed the local compliance problem. This problem is concerned with determining the incremental stresses and strains around an internal spherical segment, provided an incremental pressure δP_i is applied to the uniformly deformed configuration [66]. Lee et al. [66] determined that by expressing the lung compliance problem in terms of cylindrical polar coordinates, i.e., a cylindrical domain with a cylindrical internal segment, the stress-strain relationship approximately close to the airways/blood vessels in the lung can be modelled [66]. This problem is explored in more detail in their paper [66].

Nonuniform lung deformation is reliant on respiratory function, which in turn is also dependent on mechanical interdependence [31] and gravity [62]. Therefore, understanding the inhomogeneous behaviour of the lung requires knowledge or insight into the mechanical elastic properties of the lung [67]. Lai-Fook et al. [67] presented their findings from experiments specifically designed to determine some of these properties, whereby lung lobes are subjected to uniaxial loading and indentation tests. Data from pressure-volume curves and these experiments are used to derive the elastic constants of the lung [67]. Under the classical theory of elasticity, the elastic constants were suggested to be capable of describing the lung as an isotropic elastic continuum undergoing small deformations [67]. Lai-Fook et al. [67] describes the elastic behaviour of a theoretical lung model under two assumptions. Firstly, the lung is assumed to be a continuum whereby the stresses and strains are determined as an average over large regions of parenchyma [67]. This assumption satisfies mechanical interdependence. The second assumption neglects the effects of hysteresis as the lung is considered to be an ideal elastic material in this study [67]. Applying this assumption to this theoretical model simplified the nonuniform deformation analysis, although this model becomes inaccurate in describing different loading scenarios where hysteretic behaviour is fundamental [67]. However, assuming the lobes to be uniformly supported when subjected to an applied load provided their most significant source of error [67]. This is because part of the lung lobe which was not loaded by an upper force indirectly participated in supporting the force applied at the lower regions of the lobe [67]. Subsequently, this resulted in Lai-Fook et al. [67] overestimating the area of contact and underestimating the applied stresses. Additionally, they also overestimated the bulk modulus (≈ 0.43) which is much lower at lower inflation pressures [67]. Similarly, Young's Modulus for lung parenchyma at low inflation pressures was two times larger than the actual value at low inflation pressures [67]. These findings did not compare well with the elastic constants derived in [63] and the experimental data in [60]. The reason for this is because the elastic constants of Hoppin et al. [60] and Lambert and Wilson [63] are based on models whereby lung parenchyma is considered to consist of many randomly orientated plane membranes. Lai-Fook et al. [67] suggest that the assumptions made in [60] and [63] may be invalid. However, no particular reason is given to support this statement. Nevertheless, Lai-Fook et al.'s [67] elastic constants agreed with the estimates of Mead et al. [31]. One could argue that mechanical interdependence played a crucial part in this agreement, however the effects of mechanical interdependence are considered to be minor [67]. This consideration stems from their experimental results where lung parenchyma was observed to be easily distorted in shear, rather than in expansion. This was the first mechanical property highlighted by Lai-Fook et al. [67]. Lastly, this property is also functionally significant, i.e., nonuniform deformations result in relatively small ventilation distortions [67].

Vawter et al. [3] examined the elasticity of excised dog lung parenchyma in order to gather data on the elastic properties of lung tissue in distortion. They designed an experimental model to obtain measurements of the stresses and strains on excised rectangular layers of lung parenchyma [3]. This experiment minimised the effects of gravity, surface tension and any boundary conditions associated with the parenchyma. However, the stresses due to surface tension and the effects of gravity on lung deformation play an important role in the overall elastic and physiological response of the lung [21, 40, 61]. This experiment considered biaxial loading [3]. Realistically, the lung undergoes triaxial loading [3]. Further, triaxial loading of the lungs is complex with [60] being one of the few studies to examine the effects of triaxial loading on the lung. Vawter et al. [3] determined that for high levels of stress under biaxial loading, the deformation of lung parenchyma is greater than the deformation observed under uniaxial loading. This is because the parenchymal tissue is

stiffer for high values of stress when loaded in only one direction. For low levels of stress, the parenchymal tissue is less stiff when loaded in only one direction than under biaxial loading [3]. Moreover, Vawter et al. [3] observed no points of intersection between biaxial loading data and triaxial loading data [60]. They also determined that the applied loads in triaxial tests were not large enough to result in compressive strains in the lateral directions [3]. Furthermore, they associated uniaxial parenchymal distortion with low lung volumes, particularly when lung stiffness is low [3]. Vawter et al. [3] emphasise that in order to obtain a complete understanding of the mechanics of lung parenchyma, one must understand the effects of surface tension and consider the viscoelastic properties of the lung. These two properties of the lung must be incorporated into future models in order to describe the exact mechanical behaviour of the lung. Vawter et al. [3] question what the pattern of distortion is like in an intact lung, however, are unable to provide a conclusive answer for this aspect. This is explored in future studies on parenchymal distortion properties [68, 69].

Vawter et al. [3] did not derive a constitutive equation for the stress-strain behaviour of lung parenchyma. This was instead formulated in their subsequent study on lung tissue elasticity in [41]. The constitutive equation is developed under the hypothesis of a simplified alveolar geometry (cubic alveoli) and a pseudo-strain-energy function for the interalveolar septa. By considering the alveolar membranes perpendicular to the z-axis, parallel to the x-and-y-axes, Vawter et al. [41] assumed the following pseudo-strain-energy function W for the alveolar membranes:

$$M_o W = \left(\frac{C'}{2}\right) \exp\left(a_1 E_x^2 + a_2 E_y^2 + 2a_1 E_x E_y\right), \tag{4.21}$$

where M_o is the mass of the interalveolar septa or parenchyma per unit area of the membrane in the reference configuration, C', a_1, a_2, a_4 denote the material coefficients, and E_x, E_y refer to the Green strain tensors in the x and y directions, respectively. The resulting stresses within the interalveolar septa, F_x and F_y, are obtained by differentiating E_x and E_y with respect to λ_x and λ_y, respectively. Note that these stresses relate to the forces in the reference configuration [41]. Using the expressions for E_x and E_y given in [41], $\partial/\partial\lambda_x = \lambda_x(\partial/\partial E_x)$ and $\partial/\partial\lambda_y = \lambda_y(\partial/\partial E_y)$. Thus, the constitutive equation for the interalveolar septa is expressed by

$$F_x = C'\lambda_x \left(a_1 E_x + a_4 E_y\right) \exp\left(a_1 E_x^2 + a_2 E_y^2 + 2a_4 E_x E_y\right), \tag{4.22}$$

where C' is used to obtain the overall level of stress, a_1 and a_2 represent the rate of change of stress with increasing stretch, and a_4 denotes the coupling between two perpendicular directions [41]. Furthermore, Vawter et al. [41] consider the macroscopic stress-strain relationship of lung tissue where T_x denotes the stresses acting on any section perpendicular to the x-axis. The force acting on a unit undeformed area of parenchyma is the resultant of the forces acting within the alveolar septa. Summing all the contributions yields

$$\begin{aligned} T_x = {} & C\lambda_x \left(a_1 E_x + a_4 E_y\right) \exp\left(a_1 E_x^2 + a_2 E_y^2 + 2a_1 E_x E_y\right) \\ & + C\lambda_x \left(a_1 E_x + a_4 E_z\right) \exp\left(a_1 E_x^2 + a_2 E_z^2 + 2a_1 E_x E_z\right), \end{aligned} \tag{4.23}$$

where $C = C'/\Delta$, and Δ is the distance between membranes. The constitutive equation (4.23) is derived by differentiating $\rho_0 W$ with respect to λ_x:

$$\begin{aligned} \rho_0 W = {} & \frac{1}{2} C \exp\left[a_1 E_x^2 + a_2 E_y^2 + 2a_4 E_x E_y\right] \\ & + \text{Cyclic Permutation Terms}, \end{aligned} \tag{4.24}$$

where ρ_0 is the density of the lung in the reference configuration. The second term in (4.24) represents the sum of all terms obtained by cyclic permutation of subscripts x, y of the strain E by x, y, z. Note that (4.24) is a simplified version of the strain-energy function (4.14) derived in [40]. This is because Vawter et al. [41] only considered the elastic stress and not the stresses due to surface tension. Therefore, applying the above constitutive equations to examine the physiological behaviour of an actual lung would require surface tension as an additional term in the equation [41]. Nonetheless, the data gathered from this model matched the experimental data in a satisfactory manner, implying that the model may be used to some extent in analysing the physiological behaviour of an intact lung with suitable boundary conditions [41].

There was still much uncertainty around the magnitude of the elastic constants, largely due to a lack of a well-defined strain-energy function [33]. The need was for a constitutive equation or strain-energy function that could adequately describe the parenchymal elastic properties under the assumption of large deformations. Lai-Fook [33] proposed a different approach towards the formulation of a strain-energy function. Much like the study by Lambert and Wilson [63], they considerd uniform prestressed states [33]. It is assumed that should the prestress of a homogeneous isotropic material be uniform, it would imply that the material is isotropic and the elastic constants are functions of the prestress [33]. Pressure-volume hysteresis was also considered in a certain manner, whereby they assume that the parenchyma is uniformly expanded during both inflation and deflation [33]. This assumption is extremely important as the validity of the elastic moduli estimates depends on this assumption. There are several advantages to this particular approach. Firstly, linear elastic theory could be used to solve problems of small nonhomogeneous deformations superimposed on large deformations. Second, with the superimposed deformations being large, a second-order strain-energy function may be derived with the potential of solving the deformation problems of lung parenchyma [33]. However, the strain-energy function and the constitutive equation for lung parenchyma is not derived in this paper [33]. Instead, Lai-Fook [33] provides measurements of the bulk modulus K, obtained from small pressure-volume perturbations, and the shear modulus μ, measured via indentation tests at a fixed transpulmonary pressure (P_{tp}). The mean value of the bulk modulus varied between 3–6 P_{tp} as the pressure increased from 4–16 cm H_2O [33]. The mean value of the shear modulus is ≈ 0.7 P_{tp} [33]. Lai-Fook [33] determined an estimate of Poisson's Ratio using the mean values of K and μ. Poisson's Ratio varied between 0.37–0.45 as the pressure increased from 4–16 cm H_2O [33]. This result showed consistency with the values for Poisson's Ratio previously reported in [67]. Thus, for small deformations superimposed on reasonably large lung volumes, the lung appears to behave like an ideal elastic material [33]. However, Lai-Fook [33] did not attempt to derive a relationship between the elastic constants and surface tension.

Since the initial discovery of mechanical interdependence by Mead et al. [31], numerous studies focused their attention towards the application of elastic theory to the analysis of lung tissue deformation [40, 46, 65]. Various numerical models were constructed in an attempt to simulate gross lung deformation behaviour [3, 62]. All these studies assume an isotropic, homogeneous lung parenchyma. However, Tai and Lee [70] argue that should lung parenchyma exhibit anisotropic behaviour, major analytical revisions of lung tissue deformation is required. The literature has often presented mixed findings on this subject. Ardila et al. [32] concluded isotropic pleural surface deformation, whilst Hills et al. [29] concluded anisotropic lung expansion. Hoppin et al. [60] used triaxial tension tests on cubical lung tissue specimens, where they observed irregular directional extension behaviour. Note that Hoppin et al. [60] were not concerned with determining the isotropic behaviour of lung parenchyma. Tai and Lee [70] conducted an investigation examining any potential

anisotropic or non-uniform properties of lung tissue. This study makes use of the methodology in [60]. Tai and Lee [70] made no effort to identify the stress-strain behaviour of lung parenchyma. From the results, they observed no clear indication of locational-dependent deformation behaviour, implying uniformity [70]. They noticed arrangements of directional-dependent deformation indicating a general case of mild anisotropic behaviour for young tissue samples [70]. Older tissues samples exhibited less anisotropic features. This study concludes by stating that the assumption of a isotropic homogeneous parenchymal tissue is fairly practical for analysis of regional lung volume deformation studies [70].

Zeng et al. [71] studied human lung tissue to derive its elastic properties. The stresses due to surface tension were neglected by filling the lung with saline-solution [71]. In this paper [71], lung parenchyma is subject to experiments under biaxial loading. They observed evidence of a highly nonlinear stress-strain relationship for the human lung parenchyma from experimental stress-strain curves. Further, they also noticed strong evidence of hysteresis exhibited by the pressure-volume curves. This finding is similar to results produced by [3]. Zeng et al. [71] use preconditioning to derive the unique stress-strain response for loading and unloading, respectively. The formulated pseudo-strain-energy function $\rho_0 W$ for either loading or unloading is a symmetric function of the strain components E_{ij}, expressed in terms of the stretch ratios $\lambda_x, \lambda_y, \lambda_z$. Taking the derivative of $\rho_0 W$ with respect to E_{ij} yields the components of stress S_{ij}:

$$S_{ij} = \rho_0 \frac{\partial W}{\partial E_{ij}}, \tag{4.25}$$

where ρ_0 is the material density with respect to the reference configuration [71]. Taking the derivative of the pseudo-strain-energy function $\rho_0 W$ with respect to the stretch ratio λ_x, gives the corresponding Lagrangian stress T_x:

$$T_x = \frac{\partial \rho_0 W}{\partial \lambda_x} = \frac{\partial \rho_0 W}{\partial E_{xx}} \frac{\partial E_{xx}}{\partial \lambda_x} = \lambda_x S_{xx}. \tag{4.26}$$

Note that the expression for $\rho_0 W$ used in [71] is the general exponential strain-energy function initially proposed by Fung [46], given by (4.9). Zeng et al. [71] present the pseudo-strain-energy function for lung parenchyma as

$$\begin{aligned} \rho_0 W = &\frac{1}{2} c \, \exp\left(a_1 E_x^2 + a_2 E_y^2 + 2a_4 E_x E_y\right) \\ &+ \frac{1}{2} c \, \exp\left(a_1 E_x^2 + a_2 E_z^2 + 2a_4 E_x E_z\right) \\ &+ \frac{1}{2} c \, \exp\left(a_1 E_z^2 + a_2 E_y^2 + 2a_4 E_z E_y\right), \end{aligned} \tag{4.27}$$

where c, a_1, a_2, a_4 denote the material constants, and Ex, E_y, E_z are the corresponding strains in the x, y, z-directions, respectively. Zeng et al. [71] compared their experimental findings on the human lung with that of a dog lung. They determined that both lungs develop similar stresses, however only if the dog lung is stretched more than the human lung. This is because the overall stress distribution for human lungs is three times greater than that of dog lungs, i.e., human lung parenchyma is stiffer than dog lung parenchyma [71]. Zeng et al. [71] did not obtain pressure-volume curves of a saline-filled lung despite multiple attempts. The lung sank with saline and preconditioning was never achieved. The reason for this is unclear, perhaps this occurred as the lungs were experimented on postmortem.

Debes and Fung [72] investigated the influence temperature has on the mechanical properties of lung parenchyma at low lung volumes. They state that the full structural mechanics of the lung must include exploration of how collagen and elastin fibres influence the mechanics of lung parenchyma from within the lung tissue. This is because collagen and elastin fibres are the primary microscopic force-bearing constituents of lung parenchyma [73]. They determined the extent to which lung tissue material undergoes a phase transition between 20 °C–40 °C [72]. This was also done to evaluate whether elastin has a critical temperature between 10 °C–40 °C. Karlinsky et al. [74] provided details on the quasi-static properties of uniaxially deformed lung strips at various temperatures. They found minimal change to the stress-strain relationship between 20 °C–40 °C corresponding to strains between 60%–110%. That is, strains corresponding to high lung volumes with associated forces exhibited by collagen are dominant [74]. Therefore, Debes and Fung [72] directed their study on the mechanical properties of the lung at low lung volumes in order to emphasise the effects of elastin. Note that surface tension is neglected in this study, with particular focus being placed on the mechanics of the structural proteins [72]. Moreover, strains were kept below 30% to emphasise the effects of elastin [72]. From the results, Debes and Fung [72] establish that both collagen and elastin fibres play a fundamental role in the mechanical properties of the lung at low volumes. The stress-strain relationship of collagen is highly nonlinear, whilst elastin exhibits a linear relationship [72]. They conclude that the lung does not have a critical temperature in the 10 °C–40 °C range for mechanical property changes. Instead, these experiments imply that the behaviour of lung tissue at room temperature (25 °C) closely resembles the response at physiological temperatures [72]. The authors did encounter a piece of missing information when examining the mechanical properties of the lung, that may be of potential for future studies to consider. That is, the zero-stress state of these fibres relative to the zero-stress state of parenchyma is unknown, including the material constants of these fibres in the lung [72].

Masksym et al. [75] examined how forces arise in a two-dimensional model of lung tissue elasticity with distributed heterogeneous elements. Each element of the model comprises of generalised collagen and elastin fibres parallel to one another. Note that the fibres stretch and reorient to counter the effects of the applied uniaxial load. Collagen fibres are inelastic at low strains, only contributing to the elasticity of the elements when they become straight [75]. The authors also assume that the straightening lengths of collagen fibres are randomly assigned according to the various distributions. Lastly, a comparison of the force-length curves is made against those measured in a real lung [75]. The model is developed using artificial tissue as a two-dimensional finite element mesh consisting of interconnected line elements. Each line element correlates to a spring-string pair, i.e., springs correspond to elastin fibres and strings correspond to collagen fibres [75]. Each pair has a starting resting length with no applied force. As tension increases for each independent pair, the unit stretches with respect to the elastin stiffness (k_1). The string becomes tightly stretched at knee length (l_k), with the unit now stretching is response to a much stiffer parallel sequence of the spring and string with a combined stiffness (K_2). Therefore, string stiffness $= k_2 - k_1$. Thus, the length-tension relationship of an individual unit is expressed by [75]:

$$\begin{aligned} F &= k_1(l - l_r), \quad l \leq l_k, \\ &= k_1(l_k - l_r) + k_2(l - l_k), \quad l > l_k, \end{aligned} \tag{4.28}$$

where F is the force carried by a respective unit, l is the length of a unit, l_r is the resting length, and k_1 & k_2 represent the stiffness below and above l_k, respectively. Tissue simulation software is used to model the lung tissue, and the solution is achieved via the steepest

descent method [75]. Maksym et al. [75] state that their model is capable of quantitatively accounting for the nonlinear stress-strain behaviour of lung tissue strips, particularly when the knee lengths of the collagen fibres are distributed in accordance with an inverse power-law. The key findings from this model establish that as the macroscopic strain increases as the tissue is stretched, several elements start to support more load than their neighbours [75]. This leads to local distortions with an increased chance of neighbouring elements becoming stressed. As stretch continuously increases, favoured pathways are seen to emerge for force transmission [75]. For large extensions, a continuous network is formed from one end of the tissue to the other, whereby each element of the network is stressed passed its knee length [75]. When the knee length is distributed hyperbolically, Maksym et al. [75] observe that the progressive manner in which this network is created and distributes tension leads to force-length curves similar to physiological lung tissue. This observation could demonstrate the manner in which collagen fibres are recruited with increasing strain to derive smoothly stiffening stress-strain curves of actual lung tissue [75]. Moreover, the morphology of the self-orienting pathways of force transmission express a close resemblance to crack propagation of a solid, however, they behave in a manner opposite to that of cracks. Instead, Maksym et al. [75] acknowledge that these are actually anti-cracks. Cracks tend to form in regions of high stress, where the material begins to yield locally in order to relieve tension. Anti-cracks tend to correspond to areas of force concentration, whereby they self-organise by connecting to neighbouring elements in order to reduce local stresses [75].

Collagen and elastin fibres have been observed to undergo remodelling when affected by stress or disease [73, 75]. Therefore, the re-organised fibre network exhibits altered mechanical properties. This can take the form of a further loss of elastic recoil or a decrease in surface area for gas exchange [73]. The importance of tissue degradation and the remodelling of the tissue network is fundamental for studies involving disease such as emphysema. These aspects can be evaluated by organ-level measurements such as lung resistance and elastance [73]. Lung tissue resistance is a major component of total lung resistance at different breathing frequencies. Brewer et al. [73] hypothesise that during disease progression, the destruction and remodelling of connective tissue results in microscopic alterations of the alveolar walls, which is expressed through lung tissue elastance and hysteresivity. Hysteresivity describes an intensive tissue property defined as the ratio of dissipated energy over a cycle [76]. At the macroscopic level, it is a material property dependent on tissue composition and microstructure. The hypothesis of this study is evaluated using analysis of the mechanical behaviour of the lung parenchyma at both macro-and-microscopic levels in normal and elastance-treated lungs (diseased lungs). Thereafter, the associated changes between the organ-level elastic and hysteresis behaviour and the inflicted mechanical changes across the alveolar wall are examined [73]. From the results of their experiment, the alveolar walls of the treated tissue tended to be more extensible at the microscopic level, i.e., the alveolar walls of diseased tissue is less likely to fold [73]. Brewer et al. [73] observed a strong network effect across the microscopic and macroscopic levels. They state that deformation of an isolated component can have a different response to a component that is included in a network. This effect may highlight that individual alveolar walls may not adhere to the continuum macroscopic strain field [73]. In order to simulate this network effect, the authors calculated expected changes in angles that would take place if deformation of individual alveolar walls adhered to the macroscopic strain field:

$$\Delta\alpha = -\arctan\left[\frac{\varepsilon\,(1+\nu)\sin\alpha_0\cos\alpha_0}{1+\varepsilon\left(\cos^2\alpha_0-\nu\sin^2\alpha_0\right)}\right], \tag{4.29}$$

where ε is the macroscopic strain, α_0 is the original angle of a component with regards to ε, and ν is Poisson's ratio. Their results imply that a continuum analysis cannot be utilised to assess the properties of individual alveolar walls and that a systems model must be implemented to understand the response [73]. To account for the network behaviour, heterogeneous relaxation was enforced into their experimental model. The behaviour of the network elements mimicked the response of the individual alveolar walls in the tissue strips [73]. The reason for this is that the heterogeneous relaxation allows each alveolar wall segment to respond differently to an applied strain [73]. They also agree with the study of Mead et al. [31], where the observed response for each alveolar wall is dependent on the behaviour of its neighbouring walls. Brewer et al. [73] conclude by stating that the alveolar network response is fundamental to the overall mechanical behaviour of individual wall segments. Therefore, they cannot be examined in isolation from their neighbouring parts. Moreover, the degradation of the alveolar walls results in changes to the stress distribution and dissipation of the tissue. If failure is present anywhere throughout the network during cyclic stretching, increased hysteresis could be observed within the microscopic behaviour of the individual components [73]. Thus, failure of the parenchymal walls at high strains could potentially affect elastance at high levels of transpulmonary pressure [73]. Hence, considering emphysema, changes with the structural composition of the tissue, including network failure, could be described in changes to the elasticity and hysteresivity [73]. An interesting avenue to explore could be to examine the mechanics of individual fibres within a single alveolar wall and construct quantitative network models which can associate the scales from fibre constituents to alveolar wall mechanics to the overall lung mechanical behaviour.

Pulmonary distortion cannot be considered small, especially when modelling the nonuniform distortion properties of lung parenchyma. Subsequently, the elastic moduli cannot be deemed as constants when considering large parenchymal distortions. Most importantly, these distortions should not be modelled under the theory of linearised elasticity [64]. Therefore, the elastic moduli should instead be functions of transpulmonary pressure, as well as the magnitude and form of the distortion [64]. The distortion results in reorientation and a corresponding alteration with the strain of the force-bearing components. As a consequence, lung parenchyma becomes a physically inhomogeneous anisotropic material [64]. Recall that Hills [29] considered the lung to exhibit anisotropic behavior without the influence of surface tension and surfactant. Ardila et al. [32] deemed this assumption by Hills [29] to be invalid, showing that the lung is an isotropic homogeneous continuum. Hills' [29] assumption was correct with regards to the lung exhibiting anisotropic behaviour. However, his claim that lung surface tension and surfactant do not contribute to pressure-volume hysteresis and the anisotropic behavior of the lung is invalid. Surface tension and pulmonary surfactant are directly responsible for the observed pressure-volume hysteresis and subsequent anisotropic behaviour of the lung.

Denny and Schroter [64] state that parenchymal elasticity should be described by more than two elastic moduli in order to describe the anisotropic behaviour of the lung. They investigate the degree of anisotropy introduced by nonuniform deformities and examine how applicable the limits of small deformation approximations are to modelling the lung parenchyma in an accurate manner [64]. The elastic response of the large nonuniform deformation on the material properties of lung parenchyma is evaluated using the Finite Element Method (FEM). The elastic moduli are determined for a cuboidal block of parenchyma under the influence of a large nonuniform deformation through uniaxial stretch. The anisotropic parenchymal behaviour is modelled by five elastic moduli, however particular focus is placed on Young's Modulus, Poisson's Ratio and the shear modulus [64]. Several assumptions are made with respect to the model. Firstly, it is assumed that the anisotropic structural

properties of the model can provide the anisotropic elastic properties of the lung parenchyma [64]. This assumption is evaluated by computing the incremental Young's Modulus E_z under uniaxial expansion. They determined that the model has similar elastic properties when deformed in different directions, despite its structure being anisotropic [64]. The deviation from linearity observed in this model has minimal dependence on the chosen direction of the axes [64]. This assumption validates their model as being an ideal simplified representation for a block of actual lung parenchyma. Denny and Schroter [64] also assume that the effects of the alveolar duct to the elasticity of lung parenchyma would have a minor effect on elastic properties. This model is validated against the study by Hoppin et al. [60]. Denny and Schroter [64] observe similar model results to that of the experimental data gathered in [60]. Young's Modulus E_z is observed to increase significantly, while E_x remains approximately constant. That is, the stiffness of the parenchymal fibres increase with stretch, however the component of fibre stiffness perpendicular to the direction of expansion decreases. This indicates the significance of the effect of nonlinear anisotropic material properties whilst undergoing large deformations [64]. The model tends to resist shear by two mechanisms, i.e., reorientation and stretching. The model becomes stiffer with increasing expansion pressures as a consequence of the nonlinear properties of collagen fibres. The shear modulus was slightly higher than Young's Modulus [64]. However, based on the assumptions and the accuracy of the model in trying to replicate actual human lung parenchyma, the computed values are deemed appropriate by Denny and Schroter [64]. Poisson's Ratio is found to vary over a range of values rather than being one constant value. This result is due to the anisotropic behaviour of the parenchymal model [64]. The values of the elastic constants are slightly lower than the results presented in [67]. Denny and Schroter [64] suggest that this is because the elastic constants in [67] are determined from indentation tests, which may have overestimated the values of these constants. Denny and Schroter [64] explain that Young's Modulus does not completely influence the uniform expansion and contraction of lung parenchyma. Similarly, the main determinant of nonuniform parenchymal distortion is not exclusively reliant on only the shear modulus [64]. Instead, all the elastic constants play a role in governing these factors.

Denny and Schroter [64] established the following general elastic theory for modelling the lung. Moreover, it provides a methodical description of the numerous elastic variables and their relation to each other [64]. Most importantly, this theory presents a consistent description for modelling lung parenchyma under the assumption of large nonuniform deformations [64]. The stress σ and the strain ε of lung parenchyma under distortion are decomposed into their respective mean (m) and deviatoric (d) segments [64]. That is, σ_m and σ_d correspond to the mean and deviatoric parts of the stress σ, respectively. Similarly, ε_m and ε_d correspond to the mean and deviatoric parts of the strain ε, respectively. Denny and Schroter [64] express the mean stress σ_m and mean strain ε_m, by

$$\sigma_m = \frac{1}{3}\left(\sigma_{xx} + \sigma_{yy} + \sigma_{zz}\right), \quad \varepsilon_m = \frac{1}{3}\left(\varepsilon_{xx} + \varepsilon_{yy} + \varepsilon_{zz}\right). \tag{4.30}$$

Consider an isotropic body undergoing small displacement gradients such that the stress-strain relationship is described by [64],

$$\sigma_m = 3K\varepsilon_m, \quad \sigma_d = 3G\varepsilon_d. \tag{4.31}$$

Note that the bulk modulus K, and the shear modulus μ, correspond to the Young's modulus E and Poisson's ratio v, by the following equations:

$$K = \frac{E}{3(1-2v)}, \quad \mu = \frac{E}{2(1+v)}. \tag{4.32}$$

Therefore, for any isotropic homogeneous material, the bulk modulus K defines the uniform expansion of the material and the shear modulus μ describes the nonuniform distortion of the material [64]. Denny and Schroter [64] state that two independent material constants can be used to express small displacement gradient material characteristics. Nevertheless, in order to model the nonuniform deformations of the lung, the assumption of small displacement gradients become invalid [64]. The lung experiences large nonuniform deformations. Further, lung parenchyma can no longer be considered an isotropic homogeneous material. Instead, lung parenchyma is actually a nonhomogeneous anisotropic material [64]. However, modelling the stress-strain relationship of a nonhomogeneous anisotropic lung is complex and difficult [64]. Suppose for large deformations, there exists three orthogonal planes of elastic symmetry such that orthogonal anisotropy takes place. Thus, the stress-strain relationship can be obtained by the following components of strain:

$$\varepsilon_x = \frac{1}{E_x}\sigma_x - \frac{v_{yx}}{E_y}\sigma_y - \frac{v_{zx}}{E_z}\sigma_z, \quad \varepsilon_y = \frac{v_{xy}}{E_x}\sigma_x - \frac{1}{E_y}\sigma_y\frac{v_{zy}}{E_z}\sigma_z, \tag{4.33}$$

$$\varepsilon_z = \frac{v_{xz}}{E_x}\sigma_x - \frac{v_{yz}}{E_y}\sigma_y\frac{1}{E_z}\sigma_z, \quad \varepsilon_{yz} = \frac{1}{\mu_{yz}}\sigma_{yz}, \tag{4.34}$$

$$\varepsilon_{xz} = \frac{1}{\mu_{xz}}\sigma_{xz}, \quad \varepsilon_{xy} = \frac{1}{\mu_{xy}}\sigma_{xy}. \tag{4.35}$$

Note that only nine out of the twelve elastic moduli from the above equations are independent [64]. This is because $E_x v_{yx} = E_y v_{xy}$, $E_y v_{zy} = E_z v_{yz}$, and $E_z v_{xz} = E_x v_{zx}$. Moreover, the elastic moduli are not constants, but are dependent variables of the response of the nonuniform deformation and the magnitude of uniform inflation pressure [64]. The elastic variables are further said to be dependent on where they are situated within the lung parenchyma, since the deformation is assumed to be localised [64]. Equations (4.33)–(4.35) represent the stress-strain equations for the general case of lung anisotropic behaviour. Denny and Schroter [64] simplify the case of lung anisotropy by considering transverse anisotropy, where the z-axis is taken as the direction in which the lung parenchyma is stretched from its reference configuration of uniform expansion, perpendicular to the xy-plane of isotropy. Thus, equations (4.33)–(4.35) are expressed as

$$\varepsilon_x = \frac{1}{E_x}\left(\sigma_x - v_{xy}\sigma_y\right) - \frac{v_{xz}}{E_z}\sigma_z, \quad \varepsilon_y = \frac{1}{E_x}\left(-v_{xy}\sigma_y\right) - \frac{v_{xz}}{E_z}\sigma_z, \tag{4.36}$$

$$\varepsilon_z = \frac{v_{xz}}{E_z}\left(\sigma_x + \sigma_y\right) - \frac{1}{E_z}\sigma_z, \quad \varepsilon_{xy} = \frac{1}{\mu_{xz}}\sigma_{yz}, \tag{4.37}$$

$$\varepsilon_{xz} = \frac{1}{\mu_{xz}}\sigma_{xz}, \quad \varepsilon_{xy} = \frac{1}{\mu_{xy}}\sigma_{xy}. \tag{4.38}$$

The full derivation of this three-dimensional lung elastic theory is given in [64].

Majority of studies on the elasticity of the lung, including the ones mentioned in this review, derive constitutive equations where the stress σ is explicitly defined as a function of the strain E. Freed and Einstein [8] proposed an alternate approach for analysing the elastic response of lung parenchyma. They apply the implicit theory of elasticity, developed by Rajagopal [77] from a thermodynamics standpoint. The stress is expressed as an implicit function of the strain, $\mathfrak{h}(\sigma, \mathbf{E}) = 0$. Note that $\mathfrak{h}$ is the response function. Implicit elastic theory incorporates several features that are absent from the classical theory of elasticity. For example, implicit elastic materials can maintain limiting states of either the stress or

the strain, although it is more for the latter. With regards to biological tissue, they exhibit a limiting strain [8]. For the lung in particular, the limiting strain is physiologically expressed in terms of transpulmonary pressure. However, this may also be defined with respect to a limiting volume [8].

A hypo-elastic model for lung parenchyma where the stress rate is defined as an explicit homogeneous function of the strain rate is proposed in a previous paper by Freed and Einstein [78]. That is, $d\sigma = \mathfrak{h}(\mathbf{E})\, d\mathbf{E}$. Freed and Einstein's [78] hypo-elastic theory determines a linear relationship between the pressure P and the bulk modulus K. This finding improves on the classical theory of elasticity where the bulk modulus $K = constant$. However, from the experimental data gathered by Freed and Einstein [78], the lung material should assume a more nonlinear relationship between the pressure P and the bulk modulus K. As a result, this model did not accurately describe the actual behaviour of lung parenchyma. Therefore, Freed and Einstein [8] used implicit constitutive theory to address the need for more accurate and efficient lung parenchymal models. This improved hypo-elastic model expresses the stress rate as an implicit function of the strain rate, $d\sigma = \mathfrak{h}(\sigma, \mathbf{E})\, d\mathbf{E}$. Freed and Einstein [8] develop an implicit framework for strain-energy which displays similar characteristics to the exponential model for biological tissues given in [54]. To support this novel implicit framework, a unique definition of the Lagrangian strain rate is introduced. Contrary to the classic definition of the Lagrangian strain rate, this new definition separates the Lagrangian strain rate into its respective volumetric and deviatoric terms [8]. Freed and Einstein [8] consider this separation to be mathematically and physically justified, as it enables the strain-energy function to be specified in terms of a pair of bulk and shear strain-energy functions for the volumetric strain rate and deviatoric strain rate, respectively. In turn, this allows one to individually distinguish between the bulk modulus and the elastic moduli [8]. The elastic strain-energy function W with respect to the bulk modulus is given by

$$W\left(\ln\Delta, P\right) = \frac{1}{K}\left(\frac{\alpha}{\ln 2}\right)^2 2^{-\frac{P}{\alpha}}, \tag{4.39}$$

where K is the bulk modulus, Δ is the change in pressure, α is the doubling interval of pressure P [8]. The parameters K and α contain units of stress, therefore W also has units of stress [8]. Thus, the respective constitutive equations for the volumetric and deviatoric contributions are expressed by

$$E_V = -2P, \quad E_D = 2\mu + \beta P, \tag{4.40}$$

where P is the pressure, μ the shear modulus, and β is Fung's parameter, a dimensionless constant fundamental for loading and unloading [8, 46]. Combining the two expressions in (4.40) with $E|_{\lambda=1} = E_V + E_D$, yields

$$E|_{\lambda=1} = 2\mu + (\beta - 2)P. \tag{4.41}$$

Equation (4.41) defines the elastic response of lung parenchyma [8]. Note, (4.41) is independent of the tangent bulk modulus and dependent on pressure. The elastic response of the parenchyma is compared against the experimental data gathered by Lai-Fook et al. [67], corresponding well with the data. In particular, the bulk modulus K exhibits a nonlinear response, whilst the remaining elastic moduli are linear. This highlights an improvement in the accuracy of their model, when compared to the hypo-elastic model [78] in describing the actual elastic response of lung parenchyma. Moreover, the resulting models have four parameters for describing the overall elastic behaviour of lung parenchyma. That is, two for

the bulk response and two for the deviatoric response. This satisfies the condition made by [64], i.e., there must be more than two elastic moduli to model the large nonuniform deformations of lung parenchyma. These models are also designed in such a way that they may be implemented and analysed with computational fluid-structure interactions in future studies [8]. Freed and Einstein [8] state that the lung is in fact not an anisotropic material, but rather the pressure dependence of the lung exemplifies an anisotropic response. The lung is considered to be an isotropic hypo-elastic material. Lastly, Freed and Einstein [8] state that understanding the underlying mechanisms and the contribution of this nonlinear elastic behaviour to the overall lung parenchymal response can help in establishing a definitive viscoelastic theory for lung parenchyma in future. Recall that lung parenchyma is not a perfect elastic material. Like all soft biological tissue, it also exhibits identical properties of a viscoelastic material [8, 54, 55].

Predicting the complex respiratory patterns of the lung can be advantageous in managing respiratory motion for physiological therapies and treatments for pathologies such as lung cancer. Eom et al. [79] developed a patient-specific, physiologically applicable respiratory motion model that is able to predict lung tumor motion during cycles of normal breathing. Modern day computational techniques for analysing the geometry of the lung often utilise four-dimensional (4-D) computed tomography (CT) data. However, this data has a tendency to overlook information relating to mesh topology due to excessive surface smoothing [79]. Consequently, the authors make use of an intermediate nonuniform rational basis spline surface representation to evade multiple geometric smoothing procedures used in computational mesh preparations. This is done by relying on measured chest pressure-volume relationships to simulate pressure forces acting on the surface of the model with respect to a particular lung volume [79]. From experimental observations, a hyperelastic model is developed and implemented to model the lung tissue material. This experimental hyperelastic model also accounts for the pleural sliding that takes place inside the rib cage [79]. Eom et al. [79] conclude that the prediction capability of the pressure-volume curve, induced by a nonlinear finite element method, is consistent over the entire cycle of respiration. Furthermore, the biomechanical parameters relating to the model are physiologically measurable [79]. This study can be further applied actual human patients, as well as neighbouring organs affected by respiratory motion and disease.

If we consider the case where lung deformation is the result of cyclic inflation of tidal volume, the strain is completely dynamic [80]. The use of positive end-expiratory pressure (PEEP) allows the lungs to be kept inflated above its functional residual capacity. Therefore, the lung is exposed to further static strain. Protti et al. [80] explain that at any end-inspiration, lung volume can be determined through several combinations of static and dynamic strains resulting in a global strain. Thus, if the lung is inflated to its maximum physiological limit, it will always fail regardless of whether the strain is static or dynamic. However, according to Protti et al. [80], there is data which suggests that for a given global deformation, the static strains are less significant than the dynamic strains. Protti et al. [80] provides clarification on whether different patterns of static and dynamic strains lead to one singular global strain, which in turn produces lung edema. They determined that small dynamic strains and large static strains led to delayed tissue failure, indicating that PEEP tends to protect healthy lungs. However, the extent of this protection is unknown. Moreover, when the lungs are ventilated to their total lung capacity, large static strains are indicative of pulmonary edema [80].

Computational modelling examinations on lung parenchyma illustrate how the geometry of the alveoli and nonuniform stiffness are responsible for deriving the sequence of alveolar expansion [75]. However, Perlman and Bhattacharya [81] identified a lack of data with regards to the direct classification of alveolar segmental distension. They applied real-time

fluorescence imaging with optical sectioning microscopy (RFI-OSM) to an isolated perfused rat lung to determine the micromechanics of alveolar perimeter distension. They hypothesise that alveoli undergo nonuniform expansion. Perlman and Bhattacharya [81] observe much greater distortion due to inflation of type-I epithelial cells when compared to type-II cells. Therefore, when the lung is inflated to near maximum, alveolar expansion exhibits a nonuniform response. Possible reasons for this nonuniform response include heterogeneous septal stiffness or heterogeneous levels of force bearing by the septa, however, an exact cause was not stated in this paper [81]. Perlman and Bhattacharya [81] suggest that the expansion behaviour of a single alveoli is an underlying mechanism of the hysteresis of the whole lung. The observed hysteresis in this paper during alveolar expansion validates previous reports where acinar expansion occurs with hysteresis [81, 82]. Furthermore, they agree with the data from Oldmixon and Hoppin [83], where alveolar recruitment has no affect in physiological lung inflation [81]. Mead et al. [31] determined that subpleural and internal alveoli are subject to similar pressures, whilst Gil et al. [84] showed there is no difference in the alveolar surface area-volume relation between subpleural and parenchymal alveoli. These two findings support the theory that the micromechanics of lung expansion is similar between subpleural and parenchymal alveoli [81]. Perlman and Bhattacharya [81] also found evidence of distention heterogeneity between elements and within within the network. They suggest that these heterogeneities are dependent on the manner in which alveolar expansion activates alveolar secretion. The authors conclude that their finding is indicative of a novel aspect of alveolar micromechanics, where the alveolar perimeter possess considerably different mechanical properties at different locations. These mechanical differences result in at least two unforeseen alveolar predicaments: (i) nonuniform alveolar expansion, and (ii) differences with the degree to which major epithelial cell types in the alveolar perimeter experience distension [81]. The physiological impact of (i) and (ii) are unclear but important to consider. They suggest that uneven alveolar expansion may affect septal and vascular mechanics, while the differences in the micromechanical properties could influence the regulation of surfactant [81].

Bates [57] addresses the confusion around why stress relaxation in lung parenchymal tissue follows a power-law distribution, rather than any other monotonically decreasing function of time. In the literature, it is not clear why this is the case or why a power-law form is preferential in certain complex systems. The common notion amongst theories for the origin of power-laws is sequentiality [57, 85]. That is, the presence of a particular stochastic event may be attributed to a sequence of former necessary events. Each past event is associated with its own likelihood of occurring once the chance presents itself. Thereafter, it has to reach completion before the next event can occur [57]. Therefore, sequentiality could potentially be fundamental in modelling power-law stress adaptation. Bates [57] developed a model of pulmonary lung parenchymal tissue mechanics on the basis of sequential recruitment of Maxwell components. According to Bates [57], all Maxwell elements bear a sum of the overall stress across the model at all times. If sequentiality is the primary component to power-law stress behaviour, then simulating power-law stress adaptation requires a model whereby its elements influence the system dynamics sequentially rather than simultaneously [57]. The model developed in this study is an advancement over general models based on the Maxwell bodies for two reason: (i) It exhibits power-law stress relaxation without the need for a specific distribution of constitutive properties amongst its components (identical components), and (ii) the model already displays quasi-linear viscoelastic behaviour. This model implies that the stress adaption in lung tissue can occur via a sequence of discrete yielding events which result in local stresses being distributed from one stress-bearing region to another. This finding is similar to the data provided in [31, 73, 75]. An advantage of

Maxwell models is that they are useful for describing empirical data, although, they fail to reflect several key aspects of the underlying mechanics which express the progressive relief of stress within lung parenchymal tissue [57].

Al-Mayah et al. [86] examined the influence of the bronchial tree on the accuracy of biomechanical specific image registration of human lungs. The literature often consists of various finite element models which have been established to study the effects of lung weight [62, 64], material properties and boundary conditions [87]. The lung is considered to display homogeneous material behaviour in these investigations. Lung parenchyma comprises of numerous branching tubes within the bronchial tree that have distinct material properties when compared to other tissues [86]. The bronchial tree is the main branch of the lung, therefore, its biomechanical features and geometrical shape should affect the deformation of the lung. Tai and Lee [70] conducted an experiment on the effects of heterogeneous and isotropic behaviour with respect to lung deformation. They included tissue samples from various areas of the lung, particularly the large airway situated at the centre of the parenchyma [70]. Tai and Lee [70] determined that the mean deformation is not affected by the large airway. In the study by Al-Mayah et al. [86], the complete lung is under investigation in order to obtain a more accurate model that is able to simulate the lung's realistic geometry, material properties, and it's interconnecting behavioural response with neighbouring tissue. The lung parenchyma is modelled using hyperelastic material properties initially derived from the experimental data of Zeng et al. [71]. The assumption is made whereby the lungs are allowed to slide relative to the chest cavity via frictionless contact surface [86]. Al-Mayah et al. [86] state that a frictionless surface is effective for improving the accuracy of the final results as it simulates the realistic lubrication of pleural liquid. Three-dimensional finite element models are developed using four-dimensional computed tomography (4DCT) image data. The results of this study show that the bronchial tree has no meaningful influence on the global deformation of the lung. Al-Mayah et al. [86] suggest that this is probably due to the overall response of the lung parenchyma to the applied deformation. This effect is described by its ability to incorporate the applied displacement within a finite distance from the diaphragm, where the largest displacement occurs [86]. Mead [88] describes the mechanics of expanding airways inside the lungs as being highly dependent on geometry and not exclusively dependent on the elastic properties of the lung structure. Thus, the bronchial material properties have minimal influence on the lung mechanical properties [86]. Al-Mayah et al. [86] conclude that the bronchial tree has no global effect on model accuracy, regardless of the modulus of elasticity used for the bronchial tree. Note, the modulus of elasticity does influence the deformation locally, however it's global presence is small enough to be considered negligible. Lastly, the overall estimates of homogeneity in the lungs is sufficient for deformable image registration techniques, although, a more concise local examination at smaller scales is needed [86]. This is due to the fact that heterogeneity could be a significant factor at the local level. That is, modelling the response of the lung as a homogeneous or heterogeneous entity depends on the scale of deformation [86].

The structural deformation of an object can be described by the regional distribution of a strain or stress tensor under classical mechanics [89]. Strains have the capability of detailing the entire deformation of a material, however, the utilisation of strain components or principal strains to describe the behaviour of lung deformation is said to not be the best approach [89]. This is because strain components are not physiologically intuitive with regards to lung deformation. Furthermore, the lungs are not subject to a definitive coordinate system, making interpretation of the individual strain components difficult. Amelon et al. [89] explain that regional lung deformation can best be described through indices capable of reflecting the independent aspects of lung deformation. Three indices for lung deformation are proposed in this study. These indices are determined from the displacement field

and uniquely represent the change in volume and the subsequent preferred orientation that occur with respect to volume change [89]. The first index of lung deformation is taken as the Jacobian (J), which gives a measure of volume change. This is expressed in terms of the stretch ratios λ [89]:

$$J = \lambda_1 \lambda_2 \lambda_3, \tag{4.42}$$

where J is the ratio between the current volume and the reference volume of a particular region and varies from zero to infinity. Note: $J = 1$ implies no change in volume, $J < 1$ implies a reduction in volume or net contraction, and $J > 1$ implies an increase in volume or net expansion. The second and third indices are derived from a shape-change spectrum graph, where the origin relates to areas that have experienced perfectly isotropic volume change ($\lambda_1 = \lambda_2 = \lambda_3$). The x and y axes are independent of changes in volume. Amelon et al. [89] state that the further a point is from the origin, the deformation is more anisotropic. Therefore, the distance between a data point and the origin represents the magnitude of anisotropy and is defined as the anisotropic deformation index (ADI) [89]:

$$ADI = \sqrt{\left(\frac{\lambda_1 - \lambda_2}{\lambda_2}\right)^2 + \left(\frac{\lambda_2 - \lambda_3}{\lambda_3}\right)^2}, \tag{4.43}$$

where λ represents the stretch ratios. ADI ranges from $0 - \infty$, where 0 implies perfectly isotropic deformation. Additionally, the degree and behaviour of anisotropic deformation is reflected by the angular position of the spectrum graph. That is, points closer to the y-axis describe stretching in one direction (regions where a cube deforms into rod-like cuboid), while points closer to the x-axis describe stretching in two directions (regions where a cube transforms into a slab-like cuboid) [89]. Thus, the angular position is reflective of where a particular region is characterised within the spectrum of shapes between these two boundaries. The angular position of a data point, normalised between $0 - 1$, describes the behaviour of anisotropy [89]. This is termed the slab-rod index (SRI) [89]:

$$SRI = \frac{\arctan\left(\lambda_3\left(\lambda_1 - \lambda_2\right)/\lambda_2\left(\lambda_2 - \lambda_3\right)\right)}{\pi/2}. \tag{4.44}$$

J, ADI, and SRI are indices with independent physical interpretations capable of describing both the change in volume and directional preferences to it [89]. Amelon et al. [89] elevated the change in volume within the inferior-dorsal region. The ADI was increased in this region due to its relative position to the diaphragm and due to lobar fissures whilst sliding. Vessel areas of the lung experienced significant rod-like deformation compared to the rest of the lung, indicating a high SRI [89]. Amelon et al. [89] suggest that these indices can enable future research on regional lung deformation, both experimentally and computationally, to determine efficient physiological descriptions of lung displacement fields through image processing or numerical analysis.

Roan and Waters [90] explain that image processing capabilities are greatly hindered by the limitations and complex features of lung mechanics. Consequently, this limits the understanding of the micromechanics of an individual alveolus. Investigating the mechanical environment of the alveolus usually accounts for the properties at the level of the entire organ (macroscopic) or at the level of the alveolus (microscopic). The microscopic properties of the lung are very important as they influence the overall macroscopic behaviour of the lung. Therefore, the lung must be considered as a prestressed interconnected network whereby its global response to a mechanical force is reliant on both the properties of its

network components and how those components influence their neighbouring counterparts [31, 90]. Thus, the mechanical properties, composition, geometry, mechanical forces, and boundary conditions are all crucial features which can directly or indirectly impact the mechanical behaviour of the alveolus [90]. The alveolar strain field has always been challenging to describe due to its complex structure and the limited imaging techniques that are capable of measuring the deformation as a function of volume at the alveolar scale [90]. Roan and Waters [90] describe the extent of mechanical deformation in the alveolus and how it affects it through controlling surfactant release, permeability, inflammation, and cell injury and repair. Lung injury and disease are considered to arise from substantial changes to the alveolar mechanical network, directly affecting the cells through changes in the strain field [90]. However, there still exists many gaps in the understanding of the alveolar network due to the complexities of lung parenchymal tissue. Moreover, the use of computational mechanics to attempt to characterise lung function in health and disease is important in determining certain features that cannot be expressed through imaging methods. However, the authors explain that these models cannot describe, to full extent, the complex physiological mechanical instances that take place within the lung [90]. Accordingly, these issues can only be addressed by determining the relevant mechanical properties, boundary conditions, and mechanical loads. Roan and Waters [90] disclose that complicated experimental, computational, and theoretical techniques are which also combine biology, chemistry, mechanics, and image processing techniques are required to fully understand the alveolar mechanical network and its influence on neighbouring alveolar cells.

Suki and Bates [58] delve deeper into the complexities of lung parenchymal tissue. They explain how this complexity is a result of the mechanical behaviour of lung tissue which reflects the properties of its components, however, it displays contrasting differences to behaviour of its individual microscopic elements. Therefore, understanding the overall mechanical tissue response is fundamental because of the way in which the various components are arranged and how they interact with respect to one another [58]. Similarly, Suki and Bates [58] agree that lung tissue mechanical properties must be understood as one singular interconnected system [31, 90], as opposed to understanding these properties on the basis of individual components independent of each other. They suggest that a systems methodology is required to describe how the macroscopic properties of lung tissue emerge from the behaviour of its associated microscopic properties. This must involve mathematical and computational modelling for the various relationships and nonlinear responses [58]. The mechanical properties of lung parenchyma are elastic, dissipative, and highly nonlinear. The bulk elastic response of parenchymal tissue is described by the relationship between inflation pressure and volume [1]. However, lung tissue is viscoelastic, implying that the observed elastic properties are actually dependent on the change in volume over a period of time. Additionally, it is not possible to determine perfectly static elastic properties as this requires changing volume at an infinitesimal rate [58]. Therefore, it is more efficient to measure the quasi-static properties that tend to occur during cyclic rates, although, these are slower than normal rates of respiration [58]. Thus, the quasi-static compliance of the lung (C) is defined by the ratio of change in volume to the change in pressure under these conditions. The microscopic elements (collagen and elastin) are interconnected within the complex tissue network, accordingly, the quasi-static compliance is not representative of the properties of any fundamental components. That is, the bulk pressure-volume behaviour of the parenchyma does not reflect the stress-strain behaviour of either elastin or collagen [58]. Instead, it exemplifies the manner in which collagen gradually overtakes the stress-bearing function from elastin as volume increases. This emergent behaviour is known as percolation [58], as network strain increases there is an increase in the number of network constituents

that distribute to the stiffer portions of the tissue. Percolation provides a general mechanism whereby changes at the microscopic scale can largely impact the overall response at the macroscopic level [58]. Suki and Bates [58] note that this is not the only mechanism responsible for this effect. Percolation can be useful toward understanding how pathological alterations at the microscopic level and macroscopic level are connected, however, it is important to first determine whether percolation actually has any medical significance. On the other hand, this highlights the important role of lung imaging techniques as they have the potential to discover early stages of parenchymal tissue failure using the concept of percolation [58].

Suki and Bates [58] also touch on the power-law behaviour of lung parenchyma. They explain that power-law behaviour should not correspond to a single element to reflect any emergent responses. Furthermore, they argue that a complete understanding of power-law theory cannot be based on standard Maxwell (spring and dashpot) models described by ordinary differential equations. Instead, it is more appropriate to derive partial differential equations describing these continuous parameter models [58]. The authors also suggest that fractional calculus may be useful due to its natural ability to support the behaviour of power-law phenomena [58, 91]. Additionally, lung tissue is not only dynamic, but highly nonlinear. Suki and Bates [58] highlight that the nonlinear and dynamic properties are separable to an appropriate approximation, implying quasi-linear viscoelasticity. This suggests that the relaxation of stress in lung tissue following sudden increments of strain, x, is expressed by [58]:

$$S(t) = A(x)t^{-k}, \tag{4.45}$$

where S is the stress dependent on time t, A is a constant, and k is a positive exponent less than one. Equation (4.45) maintains this form regardless of where the strain values are taken along the nonlinear static stress-strain [58]. That is, all nonlinear behaviour in (4.45) is represented by $A(x)$, while the time-dependent segment (t^k) remains linear [58]. The dynamical mechanical behaviour exhibited by lung tissue is considered to be an emergent phenomenon that requires further evaluation with respect to the underlying behaviour of its microscopic elements [58]. Lastly, Suki and Bates [58] provide an explanation as to why lung tissue is so complicated. They state that lung tissue has to be a complex material as it has to satisfy a large number of biological and mechanical processes. Furthermore, the underlying mechanisms of this complex tissue network, such as sequential fibre recruitment and percolation, result in subsequent emergent behaviours disregarding any crucial details of individual parenchymal tissue elements [58]. Gaining a comprehensive understanding of how these emergent responses arise and function is highlighted as a possible avenue for future research in lung mechanics [58].

It is globally accepted that the elastic properties of soft tissues within the lung are in fact heterogeneous and vary depending on each person. Although, current finite element models are described with regards to the assumption that lung parenchymal tissue is homogeneous [62, 86, 87]. This is primarily due to the fact that the elastic material constants of human lung parenchyma are difficult to measure. Furthermore, the literature does not provide accurate numerical approximations of these constants. Li et al. [92] use a deformable image registration (DIR) modelling approach to derive a more physically accurate assumption of the lung under heterogeneity. Deformable image registration is used to establish a spatial correlation between time-varying volumetric images, under four-dimensional computed tomography, in order to produce efficient ventilation images [92]. The information reflected by deformable image registration also describes complex respiratory motion and physiological details that modern radiotherapy techniques can utilise to treat lung tumors [92].

The objective of their study is to determine how efficient the deformable image registration method can overcome two fundamental challenges of previous biomechanical lung deformation models, the need for accurate boundary conditions and the lack of information on the elastic distribution within the lung. The authors assume lung tissue to be heterogeneous. The proposed deformable image registration technique combines a varying intensity flow block-matching algorithm along with a finite element model for lung deformation [92]. The primary properties of an elastic material are described through Young's modulus and Poisson's ratio. Therefore, Li et al. [92] assume Poisson's ratio to be constant during lung deformation, and Young's modulus is taken to vary spatially in order to characterise the unknown elasticity distribution. Specifically, lung deformation is considered to be a stress-strain problem, whereby the associated boundary conditions are determined from the algorithm and the element-specific Young's modulus distribution is estimated by solving an optimisation problem via the quasi-Newton method [92]. The results show that the algorithm provided vastly improved accuracy when describing lung deformation. This model is capable of simulating patient-specific and position-accurate lung deformation by spatially varying estimates of Young's modulus [92]. It further improves on the registration accuracy when compared to a standard uniform model, implying that the model in [92] is more applicable for characterising lung deformation. Li et al. [92] were not able to determine whether the sizes of different tumors play a role in affecting the accuracy of image registration. However, they hypothesise that large tumors have more influence on the elasticity of the lungs when compared to smaller abnormalities. Recall that Li et al. [92] assume Poisson's ratio is constant, however, lung tissue naturally comprises of different structures each associated with unique values of Poisson's ratio. Therefore, one can attempt to include this behaviour into the deformation model, which will have an effect on accuracy of image registration. Lastly, the significance of estimating tissue elasticity for patient-specific and position-accurate cases is important in clinical application. For example, Young's modulus is advantageous for detecting the area or region of a lung tumor since tissue abnormalities have different elastic properties when compared to normal healthy lung tissue [92].

Mechanical models employing techniques involving spring and dashpot components have been used to reflect the parenchymal tissue viscoelastic properties [57]. The parameters of these components can be estimated by least squares fitting the temporal response of the material's Young's modulus or shear modulus to the approximations of the various mechanical models [93]. Dai et al. [93] measure the stress relaxation on excised lungs during inflation and apply these measurements to three models, namely, the standard linear solid model (SLS), the generalised Maxwell model (GM), and the fractional standard linear solid model (FSLS). The SLS model is the simplest model capable of estimating the stress relaxation and creep with a parallel sequence of a Maxwell model and a spring [94]. The temporal response to a step strain described by this model is expressed by a decaying exponential function [93]. However, the SLS model is limited in its ability to provide an accurate representation of dynamic phenomena over numerous time periods and within expansive material content such as biological tissue [94]. This limitation can be overcome, although, often at the expense of obscuring the physical significance of viscoelasticity [93]. The FSLS model is based on the theory of fractional order derivatives extended to biological tissue viscoelasticity [94]. Fractional order derivatives explore the behaviour of materials that seem to coexist between pure elastic and viscous material [93]. The temporal and frequency response follow power-law functions [58, 91]. These power-law functions seem to occur naturally in soft tissue viscoelasticity. Moreover, they have shown potential to introduce new disease and medical treatment specific parameters, as well as being effective in describing underlying tissue alterations associated with pathology [58, 93]. In this study by Dai et al. [93], lung

viscoelasticity is characterised by determining lung stress relaxation behaviour using the above mentioned models. Note that the relaxed Young's modulus was measured separately via an indentation test [93]. They determined that the FSLS model provides the best fit from all the models. It characterises stress relaxation phenomena including an initial steep decay and the corresponding slow asymptotic decay toward stability [93]. This finding indicates that stress relaxation simulates a power-law decay rather than an exponential decay [93]. Quantitatively, this is expressed by the equation:

$$G(t) = at^{-\beta} + b, \tag{4.46}$$

where G is the stress dependent on time t, a and b are constants, and $\beta \approx 0.07$ is a positive experimental parameter less than one [58, 93]. The GM model identified one parameter in a more efficient manner than the FSLS model, although, the FSLS model still provided the best overall description of stress relaxation in lung parenchymal tissue [93]. The authors conclude that the fractional order viscoelastic model is superior due to its ability to reflect a power-law stress decay. In this study, the reported measurements were observed at only a single transpulmonary pressure due to time constraints and the number of airways that were examined [93]. Future studies could examine the effects of different airway pressures and attempt to identify how airway pressure influences the stress relaxation behaviour of lung parenchyma. Additionally, Dai et al. [93] pointed out that indentation tests and stress relaxation tests have only been applied with regards to static transpulmonary pressure and small parenchymal deformation. Another potential avenue for future research includes investigating the dynamic viscoelastic behaviour of the lung during breathing and provide a more descriptive understanding of breathing mechanics which could improve the current understanding of lung pathology and disease [93].

The lung parenchyma is often assumed to exhibit an isotropic response [8, 33, 40, 46, 66], however, verification of this assumption is lacking within the literature [95]. Comparative methods usually provide some insight into the isotropy of an elastic material, although, they fail to compare the entire stress-strain relationship at different directions of loading to quantitative histological data [95]. Weed et al. [95] evaluated lung parenchymal tissue under compression attributed to three experimental groups comprising of tissue specimens oriented against three anatomical planes. Each group is subject to uniaxial compression and correspond to a particular anatomical plane. The main objective of this study is to characterise whether the assumption of lung isotropic behaviour is valid in lung mechanics [95]. Weed et al. [95] present data which strongly supports the concept of lung parenchyma being an isotropic material. The methods and techniques documented in this paper establish an effective system for assessing the isotropic response for other biological tissues [95]. This verification of isotropy enables further analysis of more complex properties such as viscoelasticity, strain-rate dependency, and stress-rate dependency.

During respiration, the global deformation of lung tissue is uniform. However, the internal strains expressed by the lung during respiration are locally nonuniform as a result of its interconnected network [58, 81]. Subsequently, this causes local binding strains that increase the stiffness in the parenchyma [64, 75, 81]. Andrikakou et al. [96] explain that during any external mechanical loading, the response of the tissue structure is nonuniform. This phenomenon correlates to the micromechanics of the lung parenchymal structure, the lung constituents, the associated pre-strain exhibited by the parenchyma and the rate of strain differentials apparent during deformation [96]. Andrikakou et al. [96] identify the strain-rate sensitivity of lung parenchymal tissue under quasi-static tension and compression. The objective of this study is to characterise the bulk deformation response. Compression and

tension experiments were performed at three different rates of strain, i.e., 0.25, 2.5, and 25 min^{-1}. A nonlinear viscoelastic model is used to describe the tissue behaviour using experimental data. They assume a separable time-dependent and strain-dependent material response, whereby the relaxation stress with respect to a step-strain loading history is expressed by:

$$\sigma(\varepsilon, t) = \sigma_0(\varepsilon) g(t), \tag{4.47}$$

where the functions $g(t)$ and $\sigma_0(\varepsilon)$ are dependent on time and strain, respectively [96, 97]. The time function obtains its form through the Prony series [97], such that:

$$g(t) = c_5 + \sum_{i=1}^{4} c_i \exp^{(-t/\phi_i)}, \tag{4.48}$$

where t and ϕ_i represent time and the time constants, respectively. Further, c_i is the dimensionless constants associated with c_5 through $\sum_{i=1}^{4} c_i + c_5 = 1$. Therefore, for an arbitrary strain history, the stress is measured via the Leaderman form of the superposition integral [98], given by:

$$\sigma(\varepsilon, t) = \int_0^t g(t-s) \frac{d\sigma_0(\varepsilon)}{ds} ds, \tag{4.49}$$

such that $\sigma_0(\varepsilon)$ defines the instantaneous stress at strain ε. Substituting (4.48) into (4.49), and solving the subsequent integral via finite time increments leads to the following expression:

$$\sigma\left(t_{n+1}\right) = c_5 \sigma_0\left(t_{n+1}\right) + \sum_{i=1}^{N} \left(\exp^{-\Delta t/\phi_i} \sigma_i\left(t_n\right) + c_i \frac{1 - e^{-\Delta t/\phi_i}}{\Delta t/\phi_i} \left[\sigma_0\left(t_{n+1}\right) - \sigma_0\left(t_n\right)\right] \right). \tag{4.50}$$

On the basis that the stress at the previous time increment (t_n) is known, then (4.50) can characterise the stress at any time (t_{n+1}) [96]. The full derivation of this model can be found in [96] and [97]. Suki and Bates [58] previously stated that lung parenchymal tissue exhibits both elastic and dissipative mechanical properties, along with highly nonlinear phenomena. The compression and tension tests at the different rates of strain coincided with a nonlinear elastic and viscoelastic mechanical behaviour for the rat lung tissue [96]. Moreover, a highly nonlinear stress-strain relationship was observed for the tissue. Andrikakou et al. [96] accurately characterised the parenchymal tissue behaviour using a hyper-viscoelastic model, commonly utilised in soft tissue mechanical studies.

Al-Mayah et al. [99] presented evidence highlighting that a simple linear material model is satisfactory for describing lung deformation as an alternative to a hyper-elastic model. This particular study determined that if a large diaphragm motion occurs, the deformation is concentrated towards the lower lobes of the lung. This finding is similar to the observation made by Maksym et al. [75]. Additionally, they also determined that this concentrated deformation dissipates rapidly within a short distance from the diaphragm-lung interface. Al-Mayah et al. [99] conclude that when a large deformation is applied to the lung tissue, most of the lung actually experiences minimal deformation. This implies that linear isotropic material properties can provide results analogous to nonlinear anisotropic material properties [99].

There have been numerous dynamic lung tissue studies [11, 87, 100], however, a systematic validation of these experiment's modelling results from patient image data has not

been carried out. This is addressed by Seyfi et al. [101] by validating human lung deformation estimates against the results of image registration. Image registration can accurately represent lung motion based on four-dimensional computed tomography imaging [86, 87]. This study makes use of geometrical and spatially-dependent elastic properties derived from two human patients [101]. Lung tissue is assumed to be a linear isotropic elastic material in this study [101], based on the findings in [99]. Their results show that this assumption is satisfactory for the majority of the lung, except near the diaphragm [101]. Seyfi et al. [101] explain that this assumption acts as a compromise between complexity and computational cost. Furthermore, the effects of any errors are a direct consequence of this assumption, which are already accounted for due to the overbearing influence of diaphragm pressure [101]. The findings reported in this study indicate that the absolute displacement tends to increase from the interior surface to the exterior surface, also from the top to the bottom of the lung. That is, the distribution of intrapleural pressure reduces towards the top and interior parts of the lung lobe [101]. This is a consistent observation with regards to the distribution of the intrapleural pressure, which originates from the rib-cage and diaphragm [101]. Regions close to the rib-cage and heart exhibited relatively larger displacement errors than the interior portion of the lung, approximately less than or equal to 3 mm [101]. Errors of this magnitude are not a major issue and are considered to be clinically acceptable. However, these discrepancies imply that the contact between the lung and the chest wall, including the motion of the heart, should be considerable areas of further examination for potential model accuracy improvement in lung deformation research. Seyfi et al. [101] also observed a significant improvement in the approximated displacement values when considering the heterogeneous behaviour of lung parenchyma, however, they state this does not correlate to the isotropic homogeneous linear behaviour of the whole lung.

Advancements in the field of image processing and registration have made it possible to examine regional lung deformation through noninvasive techniques. These methods have the ability to describe the complex spatial patterns that occur during volumetric deformation in healthy lungs [68]. Additionally, they can provide information about whether these deformations are patient-specific and whether the deformation is isotropic or anisotropic [68]. Hurtado et al. [68] investigate spatial geometries and frequency distribution of appropriate lung deformation values corresponding to regional deformation in healthy human subjects. They utilised image-based finite element biomechanical analysis, which previously resulted in significant accuracy improvements of regional lung deformation estimates [102]. The corresponding regional deformation images were used to determine potential spatial arrangements and frequency distribution from various estimates of deformation [68]. This study also utilises the anisotropic deformation index (4.43) and the slab-rod index (4.44), initially explored in [89]. Hurtado et al. [68] assume hyperelastic constitutive behaviour for the parenchymal tissue, implying that the biomechanical response may be derived through a deformation energy density $W(\mathbf{F})$. If the deformation is considered to be isotropic, then

$$W(\mathbf{F}) = \bar{W}(I_1, I_2, I_3), \tag{4.51}$$

where I_1, I_2, I_3, are the strain invariants. That is, the deformation energy density is only dependent on the strain invariants of the right Cauchy-Green deformation tensor $\mathbf{U}$, expressed by

$$I_1 = \frac{1}{3} tr(\mathbf{U}) = \frac{1}{3}(\lambda_1 + \lambda_2 + \lambda_3), \tag{4.52}$$

$$I_2 = \frac{1}{6}\left((tr\,(\mathbf{U}))^2 - tr\,(\mathbf{U})^2\right)$$
$$= \frac{1}{3}\left(\lambda_1\lambda_2 + \lambda_2\lambda_3 + \lambda_3\lambda_1\right), \tag{4.53}$$
$$I_3 = det\,(\mathbf{U}) = \lambda_1\lambda_2\lambda_3, \tag{4.54}$$

where λ defines the stretch ratios. Note that the definition of invariants differs by a constant of $1/3$, in this study, when compared to the definitions of the first and second invariants. This is done for with respect to normalisation, i.e., all invariants will assume a unitary value when deformation does not occur ($\mathbf{F} = \mathbf{I}$) [68]. Hurtado et al. [68] determined from histograms of the individual lungs that log-normal distributions adequately represent the frequency distributions of deformation invariants in the lung. This finding is said to commonly support the normalisation of the invariants [68]. At the regional level, the local volumetric deformation within the lung parenchyma demonstrates unique spatial variations in healthy human subjects [68]. This study is limited by several factors, including the consideration of a small population sample of eleven subjects whereby age, gender, and fitness are all neglected. In general, this would limit the conclusions made around frequency distributions and spatial arrangements [68]. Moreover, small regions of highly localised deformation were seen to occur close to lung fissures in some subjects, however, this was not accounted for by the authors. Fissure sliding can induce irregularly high shear strain values, directly affecting the accuracy of approximating the minimum and maximum values of the stretch ratios [68]. Instead, Hurtado et al. [68] attributed this effect to the high cases of regional deformation due to lobar sliding. These deformations are considered to be negligible due to them occurring within localised regions with finite volumes [68]. Future research could use deformable image registration methods to account for shear strains due to sliding and make a distinction between them and actual shear deformation.

Eskandari et al. [103] address the lack of knowledge surrounding functionally relevant data for lung parenchyma through experimental characterisation of the heterogeneous, anisotropic material properties of porcine extraparenchymal and intraparenchymal airways. Their objective is achieved through uniaxial tension tests applied to lung specimens at three different airway levels (trachea, large bronchi, and small bronchi) and with respect to two orientations (axial and circumferential) [103]. The data revealed significant anisotropy and regional differences in sampled pseudo-elastic and viscoelastic tissue behaviours of proximal and distal brochial airways [103]. The findings presented in this study are similar to the responses of other biological tissues. Specifically, lung tissue is sensitive to preconditioning, although, not to the extent of some other organ tissues [103]. Circumferential airway tissue was observed to be more compliant than axial airway tissue. That is, axial airway tissue reaches stress relaxation at a faster rate than the circumferential airway tissue [103]. Eskandari et al. [103] state that it is appropriate to assume uniform behaviour for the the bronchial tree's intraparenchymal regions, during the modelling process. However, the same cannot be implied for pseudo-elastic and fractional stress relaxation responses, because anisotropy and heterogeneity must be taken into consideration [103]. They also suggest that due to the time-dependent behaviours of lung parenchyma, a potential metric for disease characterisation and progression can be developed through research on airway viscoelasticity [103]. This suggestion is based on this study's anisotropic and heterogeneous observations regarding pertinent stress relaxation and time constants [103].

The lung is complex due to it being mechanically and structurally heterogeneous [104]. Vast amounts of investigations have attempted to understand the mechanics of the lung

in order to grasp this complexity. These studies have tried to define a consistent relationship between lung structure and compliance in relation to the organ, tissue, and cellular constituents [93, 105, 106]. Polio et al. [104] explain that this complexity cannot be fully comprehended, because the literature comprises of numerous techniques and methodologies attempting to determine lung tissue compliance. This includes indentation tests on small excised parenchymal tissue samples and elastography performed on whole lungs. Polio et al. [104] analyse these different techniques, and provide a direct comparison on various evaluation procedures in order to characterise how the reported modulus of lung tissue varies across each method, along with their associated constraints. The limited knowledge on nonlinear, viscoelastic, heterogeneous and anisotropic materials is also addressed in this study. Polio et al. [104] utilised techniques commonly applied in tissue mechanics to approximate the linear and nonlinear responses of lung parenchyma. The authors also present a new method for measuring the modulus of lung tissue at similar length scales to that of microstructure heterogeneities within the tissue [104]. This technique is called cavitation rheology, a method for focal examination of the mechanical properties of material. Cavitation rheology involves creating an air cavity at the tip of a needle which is then inserted into a material and pressurised until the material fails due to the rapid elastic deformation or irreversible fracture. Their findings indicate that cavitation rheology exhibits significantly higher measurements when compared to indentation, uniaxial expansion, and small amplitude oscillatory shear (SAOS) tests. Additionally, cavitation rheology is considered to be the least destructive applied technique as it does not require any excised lung tissue to perform testing [104]. The reported bulk modulus of lung parenchyma is very similar to the bulk modulus obtained using micro-indentation. However, the stiffness values derived through cavitation rheology were much higher and similar to the reported bulk modulus of pulmonary vessels [104]. They explain that cavitation rheology may be more sensitive to the stiffness contributions of vessels and the constituents of the extracellular matrix (ECM). They also consider that it could be sensitive to local heterogeneities within the tissue [104]. Polio et al. [104] conclude that cavitation rheology gives a consistent measurement of the mechanical properties of the lung on a tens-of-microns scale, and is unaffected by tissue damage induced by other testing methods. Furthermore, it provides a suitable technique for characterising localised heterogeneities within lung parenchyma. This attribute is meaningful since the tens-of-microns scale could be more pertinent to how cells interact with their local regions [104]. Therefore, future studies could look at determining the modulus of materials and biological tissues via cavitation rheology to not only describe the mechanical properties of the lung, but to also potentially identify and develop materials which can accurately represent lung parenchymal tissue [104].

Biaxial tension tests have been used often in the literature to examine the different states of deformation and the stress-strain relationship of lung parenchyma [3]. However, biaxial tension tests fail to provide accurate representations of the three-dimensional volumetric deformation states within the lung, i.e., large stretches in three dimensions [107]. As a consequence of this fact, physiologically superior compressible material properties are not precisely reported in these studies. Hoppin et al. [60] provided the only triaxial tension experiment examining the compressibility of lung parenchyma, following the same methodology in [70]. However, this particular study had several limitations [60]. Firstly, lung tissue was kept frozen which is known to alter its mechanical behaviour [74]. Secondly, lung tissue was kept fixed by fish hooks during the experimental procedure, with these hooks causing local distortions resulting in large boundary effects. Third, the corresponding volumes of the reference state and current state was measured through approximations using lines drawn manually on photographs. This affected the accuracy of the calculations of the

stresses [107]. Lastly, only three specimens were experimented on. Therefore, according to Birzle et al. [107], there exists no experimental procedures or subsequent data to adequately describe the compressible material behaviour of viable lung parenchyma at high volume changes. Birzle et al. [107] address this lack of knowledge by presenting a unique experiment to accurately capture the compressible lung tissue properties. Using the results of the experiment, a suitable hyperelastic strain-energy function describing the nonlinear compressible behaviour of lung parenchyma is derived, along with its corresponding material constants. Lung parenchyma is assumed to be a an isotropic material [107]. The subsequent hyperelastic strain-energy function

$$\boldsymbol{\Psi}\left(I_1, I_2, I_3\right), \tag{4.55}$$

with invariants $\mathbf{I}$ corresponding to the right Cauchy-Green deformation tensor is utilised to describe the elasticity of lung parenchyma [107]. During the pressure-volume-change experiment, a purely volumetric deformation occurs. Therefore, the deformation gradient, $\mathbf{F}_{vol}$, is simplified [107]. Accordingly, the volume change

$$J = \lambda^3 = V_b / V_e, \tag{4.56}$$

where λ represents the stretch ratios, is equal to the measured change in volume, with invariants

$$I_1^{Vol} = 3J^{2/3}, \quad I_2^{Vol} = 3J^{4/3}, \quad I_3^{Vol} = J^2, \tag{4.57}$$

are formulated as a function dependent on the volume change J. As a consequence, the strain-energy function can be reformulated to include purely volumetric deformation [107]. In this instance, the stress-strain relationship can be defined in terms of a pressure-volume-change expression [107]. Thus, the hydrostatic pressure can be derived from the strain-energy function [108]. Hence, the strain-energy function,

$$\Psi\left(I_1, I_3\right) = c\left(I_1 - 3\right) + \frac{c}{\beta}\left(I_3^{-\beta} - 1\right) + c_d\left(I_1 - d\right)^d, \tag{4.58}$$

is defined in terms of the following pressure-volume-change expression:

$$P = 2c\left(J^{-1/3} - J^{-2\beta-1}\right) + 2c_d d J^{-1/3}\left(3J^{2/3} - 3\right)^{d-1}. \tag{4.59}$$

Birzle et al. state that (4.59) is appropriate for characterising the experimental results, and is applicable to determine the volumetric material behaviour. According to the authors, this study is the first to establish accurate experimental data on the volumetric material behaviour of lung parenchyma over the entire physiological range. The resulting data is used to optimise the material parameters through the above hyperelastic strain-energy function (4.58), which describes the nonlinear compressible material behaviour of lung parenchyma, particularly at high pressure changes [107]. Even though an elastic model is presented here, it is important to remember that lung parenchyma is viscoelastic [8]. In this pressure-volume-change experiment, the viscoelastic properties cannot be determined, because it compares static pressure levels. That is, the formation and influence of internal pressures are immeasurable through this experiment. However, uniaxial tension tests can derive the viscoelastic features of lung parenchyma [107]. One could look at extending this nonlinear hyperelastic model in [107] to include viscoelastic data from uniaxial tests to characterise the viscoelastic behaviour of lung parenchyma.

Lung parenchymal tissue is mainly exposed to high volumetric deformations [107]. During respiration and mechanical ventilation, isochroic deformations are more likely to occur, especially in diseased lungs [89]. Birzle et al. [109] identify the volumetric and isochoric tissue behaviour of lung parenchyma. Various compression experiments have been performed in order to capture the compressible material behaviour of lung parenchyma under large volumetric deformations [93, 95, 96], however, compression is not a physiological feature of lung tissue [109]. Birzle et al. [107] proposed a novel experiment to accurately examine the volumetric material behaviour of lung tissue at high volume rates. Although, their experiment was only capable of describing the dominant volumetric behaviour, the isochoric deformation was not determined [109]. Accordingly, this study [109] extends on the pressure-volume change experiment conducted in [107], with the addition of isochoric and small volumetric deformations. Therefore, two sets of experiments are performed, specifically, pressure-volume-change experiments and uniaxial tension tests. Consequently, Birzle et al. [109] utilised a coupled inverse analysis allowing them to combine the data from both experiments and determine the material constants of their hyperelastic model. The associated strain-energy function with subsequent material constants is expressed by:

$$\begin{aligned}\boldsymbol{\Psi} = {} & 356.7\,Pa\,(I_1 - 3) + 331.7\,Pa\left(I_3^{-1.075} - 1\right) \\ & + 278.2\,Pa\left(I_3^{-1/3} I_1 - 3\right)^3 + 5.766\,Pa\left(I_3^{1/3} - 1\right)^6,\end{aligned} \tag{4.60}$$

where I_1, I_3 are the strain invariants. Note that (4.60) is derived in a similar manner to the model presented in [107]. Further, (4.60) is recognised to efficiently model both sets of experiments. Thus, the above constitutive relation is capable of describing the nonlinear volumetric and isochoric response of lung parenchyma [109]. According to Birzle et al. [109], this is the first study to successfully model the principal volumetric behaviour, along with the nonlinear isochoric deformation of lung parenchyma via experimental measurements and numerical analysis. The above constitutive equation can be used to assist in improving more advanced computational lung models [109]. This would be best applied to the stresses and strains that take place within the lung parenchyma during normal and artificial breathing, enabling the efficient identification, diagnosis and simulation of diseased lung tissue.

Throughout the literature, it is commonly suggested that describing the actual viscoelastic behaviour of lung parenchyma can improve continuum and computational models, and contribute to a better comprehensive understanding of lung functionality in health and disease [8, 95, 96, 107]. Additionally, an accurate and efficient viscoelastic constitutive equation is fundamental for describing the stress-strain relationship of lung parenchyma during normal and artificial respiration. Birzle and Wall [110] present a small extension to their studies in [107, 109], whereby they determine the viscoelastic constitutive response of lung parenchyma, with particular emphasis on the nonlinear, compressible, frequency-dependent material properties. The constitutive model developed in this study corresponds to a three-dimensional nonlinear viscoelastic material response at large three-dimensional lung parenchymal deformations [110]. From their experimental observations, Birzle and Wall [110] determined the material constants of two viscoelastic material models suitable for three-dimensional deformations. That is, the standard linear solid model (SLS) and the fractional standard linear solid model (FSLS), previously applied in [93]. In order to characterise the viscoelastic behaviour of rat lung parenchyma, uniaxial tension tests were conducted at different frequencies. One of their other objectives was to determine a set of material constants capable that represent the whole physiological range of frequencies. Therefore, they

used a coupled inverse analysis, which equally includes all the different tension tests performed on one sample [109, 110]. The constitutive model deemed appropriate for the description of the viscoelastic, nonlinear, compressible material response of lung parenchyma is given as [110]:

$$\begin{aligned}\Psi = {} & 356.7Pa\,(I_1 - 3) + 331.7Pa\left(I_3^{-1.075} - 1\right) \\ & + 71.05Pa\left(J^{-2/3}I_1 - 3\right)^3 + 5.766Pa\left(I_3^{1/3} - 1\right)^6,\end{aligned} \tag{4.61}$$

where I_1, I_3 are the strain invariants. Note that (4.61) is modelled in tandem with the model of fractional viscoelasticity [110]. Birzle and Wall [110] determined that (4.61) is appropriate for describing the complex nonlinear, compressible, viscoelastic material response of lung parenchyma. Moreover, it can be utilised with finite element models in order to characterise the whole range of physiological frequencies [110]. The authors explain that this model enables one to quantify the stresses and strains of lung parenchymal tissue during natural and artificial breathing more accurately. An important area for consideration would be to understand how this model can be utilised to determine the stress-strain relationship of human lung parenchyma, or apply this technique to examine diseased tissue to further improve on models describing the mechanics of healthy and diseased lungs.

Birzle et al. [111] presented a method to experimentally quantify the mechanical behaviour of the major load-bearing components of lung parenchyma and their associated interactions. They also numerically determine individual material models for each constituent. Having intricate material descriptions of the contributions of the load-bearing constituents is uncommon within the context of the literature, with many models inaccurately characterising the response of an individual constituent [111]. This is mainly because these models correspond to experimental data of the whole lung, rather than a single force-bearing constituent [13, 67, 112]. The objective of this study is to provide a clear explanation of the individual contributions towards maintaining the major load-bearing mechanisms of the lung parenchyma and their interactions through a constitutive law [111]. Therefore, Birzle et al. [111] adopt an additive split of a suitable strain-energy function to describe each component independently. These strain-energy models are formulated within the context of nonlinear continuum mechanics viewpoint, and are further applied to finite element method simulations. The material response of an individual component is nonlinear and the corresponding fibre orientation is assumed to be isotropic in their inverse analysis [111]. Therefore, a hyperelastic strain-energy function, $\Psi\,(I_1, I_2, I_3)$, with invariants of the right Cauchy-Green deformation tensor are utilised in this study. Each constituent is modelled with respect to an associated strain-energy function, that is, Ψ^{CF}, Ψ^{EF}, Ψ^{FI}, Ψ^{GS} represent the effects of collagen fibres, elastin fibres, collagen-elastin fibre interaction, and ground substance respectively. These constituents, as a network, describe the behaviour of homogeneous lung parenchyma, expressed by:

$$\Psi^{Parenchyma} = \Psi^{CF} + \Psi^{EF} + \Psi^{FI} + \Psi^{GS}. \tag{4.62}$$

To establish each constituent response, Birzle et al. [111] examine combinations of preselected hyperelastic constitutive relations capable of describing the behaviour of lung tissue. The authors chose the neo-Hookean strain-energy function,

$$\Psi = c_E\,(I_1 - 3) + \frac{c_E}{\beta}\left(I_3^{-\beta} - 1\right), \tag{4.63}$$

along with the strain-energy function,

$$\Psi_{c_x} = c\,(I_1 - 3)^d\,, \tag{4.64}$$

where x in Ψ_{c_x} is the value of exponent d [111]. In order to identify the material constant x, the error between experimental and computational displacement values must be minimised in the inverse analysis and optimisation procedure. The optimal combination of strain-energy functions for each constituents is obtained with respect to (4.63) and (4.64). For ground substance, the best relation is $\Psi_{NH} + \Psi_{c_6}$, collagen fibres best correspond to $\Psi_{NH} + \Psi_{c_{11}}$, elastin fibres correlate to Ψ_{NH}, and the collagen-elastin fibre interaction best agrees with $\Psi_{NH} + \Psi_{c_3}$ [111]. Birzle et al. [111] briefly summarise the identified constituent-specific material relations of lung parenchyma:

$$\Psi^{Parenchyma} = \Psi^{CF} + \Psi^{EF} + \Psi^{FI} + \Psi^{GS}, \tag{4.65}$$

where

$$\Psi^{GS} = 52.42Pa\,(I_1 - 3) + 48.75Pa\left(I_3^{-1.075} - 1\right) + 0.473Pa\,(I_1 - 3)^6\,, \tag{4.66}$$

$$\Psi^{CF} = 59.64Pa\,(I_1 - 3) + 55.46Pa\left(I_3^{-1.075} - 1\right) + 0.00003337Pa\,(I_1 - 3)^6\,, \tag{4.67}$$

$$\Psi^{EF} = 84.78Pa\,(I_1 - 3) + 78.84Pa\left(I_3^{-1.075} - 1\right), \tag{4.68}$$

$$\Psi^{FI} = 219.1Pa\,(I_1 - 3) + 203.8Pa\left(I_3^{-1.075} - 1\right) + 1.115Pa\,(I_1 - 3)^6\,. \tag{4.69}$$

From their observations, at small strain ranges, ground substance experiences the lowest mechanical effect. However, the collagen-elastin fibre interaction has the most dominant effect over the tissue behavior [111]. At larger strain ranges, the mechanical influence of collagen fibres increase. Moreover, upon comparing the effects of collagen fibres to elastin fibres, elastin exhibited a slightly stiffer response at small strain ranges. Although, at higher strain ranges, collagen was observed to have the most influence on the tissue response [111]. This model has the ability to provide a more efficient description of the effects of various lung diseases that significantly alter the underlying mechanisms of lung tissue. One can consider incorporating this proposed constituent-specific constitutive relation into computational models of the respiratory system in order to simulate the behaviour of the individual components. Furthermore, one could predict the behaviour of any alterations to these constituents and their resulting effects on the whole respiratory system during normal and artificial breathing, particularly in the case of pathogens that alter the fibres of lung parenchyma, such as emphysema or fibrosis [111].

Breathing involves interaction between fluid and solid mechanical phenomena within the lung, however, there is a considerable lack of experimental data describing the effects of air flow to deformation. Additionally, the relationship between pulmonary structure and lung function is vague [113]. As a consequence, this makes it difficult to capture how the underlying constituents affect the global parenchymal tissue response and limits the potential for medical advancements and clinical translation [113]. Therefore, Eskandari et al. [113] developed a structure-based constitutive model that describes uniaxial mechanical behaviour of the proximal and distal airways [103, 113]. Furthermore, the bio-composition pertaining to each tissue area is assessed to understand how the individual constituents impact bulk tissue behaviour [113]. That is, structurally augmented constitutive relations are derived which include the influence of collagen and elastin fibres within the parenchymal tissue network. Specifically, the corresponding strain-energy functions incorporate a matrix description of six models; namely, the compressible Neo-Hookean, incompressible Neo-Hookean,

unconstrained Ogden, incompressible Ogden, uncoupled Mooney-Rivlin, and the incompressible Demiray; superimposed with nonlinear fibre constituents [113]. However, only a brief derivation of the first Piola-Kirchoff stress (P) for the Neo-Hookean strain-energy function is provided in [113]. Thus, Eskandari et al. [113] determined that the structural tissue architecture and collagen composition are the main determinants for the reported airway anisotropy and heterogeneous mechanical behaviour. The subsequent constitutive theory for the bronchi presented in this paper can be implemented into finite element models. This will enable further examination of pathological airway obstruction, a possible deeper understanding of fluid-structure interaction during respiration, and the development of potential numerical approximations that can be applied in clinical diagnosis and treatment [113].

The interconnecting behaviour of the whole lung is based on the mechanical interactions of its tissue elastic and resistive properties across all scales [7, 31, 58]. However, the structural mechanical properties of the lung has not been fully characterised. Classical pressure-volume experiments involving the inflation of air- or saline-filled lungs to describe the elasticity and compliance of the lung, although, these studies describe the overall mechanical behaviour of the whole lung without accounting for the effects of local stresses and strains that occur within the lung parenchyma [13, 32, 60]. This lack of information has lead to scientists indirectly omitting useful physiological details, particularly in the case of respiratory disease [114]. Recent studies have since provided fundamental insights into the material description of the airways [103, 113], and lung parenchyma at the tissue and microscopic levels [107, 109–111, 115]. Mariano et al. [114] further addresses this lack of knowledge by providing the first detailed description of lung mechanical deformation throughout the whole lung. They introduce a method of relating pulmonary scales and values of local strain and deformation behaviour to global pressure-volume response of the entire lung. Specifically, they utilise digital image correlation (DIC) which can yield novel insights regarding how the lung continuously stretches and expands during virtual breathing in real-time [114]. From their observation, Mariano et al. [114] describe various lung phenomena pertaining to surface heterogeneity, lung anisotropy, and changes in tissue compliance. Firstly, the surface strain images show that the lung exhibits significant heterogeneous behaviour during regional expansion across the lung surface [114]. This response varies with the size and orientation of the main airways [103]. Furthermore, the lower and central regions were noticed to exhibit greater strains, however, this is species-dependent. Rat lung were used in this study, therefore human lungs will display different responses [114]. Secondly, strain anisotropy was seen to differ across the parenchyma with some locations being more isotropic than their neighbouring regions [114]. Additionally, the degree of anisotropy altered with each location. That is, changes to the flow rate resulted in various degrees of anisotropy regardless of the maximum inflation levels being identical [114]. Lastly, they observed a nonlinear relationship with varying degrees of decreased lung compliance. This decreased shift in strain is suggested to be a consequence of the lung reaching maximum expansion, indicating a potential physiological limit whereby strain hardening occurs [114]. This study also had a limitation, whereby changes in the manner in which the lung inflates the pleural cavity changes the negative pressures during breathing. Mariano et al. [114] explain that this can greatly alter local parenchymal tissue dynamics during inflation which may result in possible implications to the regional aeration of lung tissue. The observations reported in this study can be used to reinforce the application of surface strains to characterise the subsequent strain in bulk tissue [114]. Moreover, one can use the measured surface strains from this paper to develop new comparative studies on lung deformation for healthy and pathological lungs [114]. For example, anisotropy can act as a bio-indicator in the early diagnosis and treatment of several lung diseases, where the degree of anisotropy becomes significantly altered.

The use and effectiveness of image processing techniques has become important throughout the field of biomechanics [116]. Arora et al. [69] establish the use of digital volume correlation (DVC) analysis in lung parenchymal tissue to evaluate the three-dimensional strain field at the alveolar level from the time sequence of reconstructed tomograms (images taken from within a subject). They present an improvement on their methodology for image acquisition within an intact thorax [69, 116]. This computational model aims to deliver more physiologically relevant strain values, considering the lungs remain intact within the rib cage, that is, with bounded expansions during respiration [69]. Arora et al. [69] observe that regions with particularly low deformation, when compared to neighbouring regions, tend to deform more uniformly at later stages of the experiment. This heterogeneous behaviour is a common feature of normal breathing [69]. Additionally, digital volume correlation showed distinct patterns of heterogeneous deformations which further highlighted the contrasting degree of tensile strains between tangential regions of lung tissue when compared to central areas [69]. Therefore, regions close to the boundary were observed to expand more significantly than the central regions, corresponding to the subsequent effect of an airway such as the trachea [69]. The authors also determined that the intact thorax provides a form of protection from premature beam damage, enabling more strain states to be captured within the same region [69]. Future application of digital volume correlation analysis can include correlating local deformations to the total volumetric changes of different species and evaluating how closely they correspond to global pressure-volume measurements. Moreover, this can assist in analysing varying degrees of lung compressibility or expansion within the parenchyma in order to describe the absolute volumetric deformation across the whole lung [69]. Arora et al. [69] state that current studies should involve research into smaller lung volumes and larger fields of optical views, where the entire lung can be imaged across all instances of lung inflation. This requires a direct comparison of volume measurements and its relation to global lung compliance, including a comparison of the distributions of volumetric deformation from region to region [69].

Investigations into the physiological and mechanical functions of the lung have since been rejuvenated due to the recent global Covid-19 pandemic. Computational mechanical models have the ability to enhance the predictive capabilities and determine more precise physiological estimates of lung properties, however, most of these studies are impeded by the lung's complex mechanical responses and structural networks [117]. There is also an absence of mechanical experiments linking the load-bearing organ-level response to regional tissue behaviours. Maghsoudi-Ganjeh et al. [117] address these shortcomings by introducing a novel reduced-order surface model of the lung, which incorporates the mechanical response of the bronchial network, parenchymal tissue, and the visceral pleura. Specifically, they provide the first inverse finite element analysis to computationally characterise the entire lung, supported through digital image correlation (DIC) analysis, resulting from applied pressure-volume loading [117]. Inverse finite element analysis yields specimen-specific mechanical properties by minimising the error between displacement values approximated through general finite element methods and those determined through experimental techniques [111, 117]. Maghsoudi-Ganjeh et al. [117] explore three different constitutive equations for their multiple finite element model. First, the homogeneous isotropic hyperelastic model is used, based on the compressible Mooney-Rivlin hyperelastic model [118], with strain-energy function:

$$W = C_{10}\left(\bar{I}_1 - 3\right) + C_{01}\left(\bar{I}_2 - 3\right) + \frac{1}{D_1}(J-1)^2, \tag{4.70}$$

where $\bar{I}_1$, $\bar{I}_2$ are the first and second invariants of the deviatoric deformation tensor, J the Jacobian of the deformation gradient $\mathbf{F}$, with C_{10}, C_{01}, and D_1 the three unknown material constants [117]. The second model is the homogeneous anisotropic hyperelastic relation, established from the Holzapfel-Gasser-Ogden (HGO) derivation [56], whereby:

$$W = W_{iso} + W_{ani}, \tag{4.71}$$

with associated equations for the isotropic and anisotropic response, respectively:

$$\begin{aligned} W_{iso} &= C_{10}\left(\bar{I}_1 - 3\right) + \frac{1}{D}\left(\frac{J^2 - 1}{2} - \ln\left(J\right)\right), \\ W_{ani} &= \frac{k_1}{2k_2}\left\{\exp k_2\left[k\left(\bar{I}_1 - 3\right) + (1 - 3k)\left(\bar{I}_4 - 1\right)\right]^2 - 1\right\}, \end{aligned} \tag{4.72}$$

where k, k_1, k_2, C_{10}, and D are five unknown material constants, and $\bar{I}_4$ is the pseudo-invariant of the deformation tensor $\mathbf{C}$ [117]. Lastly, they consider the heterogeneous isotropic linear-elastic model, initially presented in [119], with Young's modulus E and Poisson's ratio ν. Maghsoudi-Ganjeh et al. [117] observed that the value of the shear modulus is much greater when accounting for the parenchyma and it's underlying constituents together, rather than only considering isolated lung parenchyma. The ratio between the bulk modulus and shear modulus was approximately 5.5 in the homogeneous isotropic hyperelastic model and 0.5 for the heterogeneous isotropic linear-elastic model, i.e., it is significantly less than incompressible materials [117]. This finding justifies the assumption of lung parenchyma being a compressible material [110]. Furthermore, their computational model implies that lung elasticity is not evenly distributed across the various regions of the lung [117]. Although, the shear moduli is at its minimum in the anterior which corresponds to the location of maximum deformation [117]. The optimisation algorithm applied in this study suggests that an isotropic description of lung parenchyma is capable of capturing the experimental displacement to a precise degree [117], subsequently, the anisotropic characterisation could be simplified with a predefined isotropic tissue response, similar to the behaviour mentioned in [120]. Maghsoudi-Ganjeh et al. [117] also found that major strains tended to predominantly align with the medial-lateral direction, whereas minor strains preferred to align with the anterior-posterior direction. This observation could imply that the spatial patterns and strain orientations are a result of the geometrical and force loading properties, rather than the anisotropic behaviour of lung tissue [117]. The authors establish a suitable foundation which can be extended to future studies to attribute the effects of various macroscopic ventilation solutions on regional pulmonary stress and strain distributions. Furthermore, this framework can be used to examine how lung pathogens modify the stress-bearing constituents and the overall response of the lung [117].

Mechanical ventilation is regularly used to assist with breathing in patients suffering from respiratory diseases and disabilities. It has many advantages, however, it is also known to cause ventilator-induced lung injuries and death. This has resulted in more refined investigations attempting to improve on the techniques currently implemented in mechanical ventilation. These include multi-oscillatory and high-frequency ventilation [121]. Although, there exist few studies which have analysed lung mechanical deformations under variable loading. Therefore, Mariano et al. [121] addresses this gap through the use digital image correlation (DIC) to characterise ventilation strains more effectively. Digital volume correlation (DVC), optical computed tomography (OCT), and elastography have commonly been used to provide strain measurement values [69, 104], however, these techniques are time

sensitive which significantly affects the reported lung behaviour [121]. On the other hand, digital image correlation analysis is a novel method for analysing topological deformations during porcine lung inflation [121]. Mariano et al. [121] employ DIC as a real-time continuous imaging approach to examine lung deformations in pigs and provide insight into regional pulmonary behaviours. Particularly, lung tissue strain heterogeneity and isotropy. They also further investigate volume and rate ventilation effects on lung behaviour [121]. From the results of this study, they determined that the upper regions of the lung experience greater strains than lower regions. This is attributed to the bronchial network which is heterogeneous geometrically, and in terms of its material constants [103, 114]. However, human alveolar sizes are four times greater in the upper regions when compared to lower regions, implying that human lungs are more capable of undergoing greater stretches [121]. Additionally, the larger regional surface strains were observed to alter the deformation behaviour of surrounding parenchymal tissue, most likely due to the underlying bronchial network [103, 113]. Furthermore, lung surface strains and pressures were observed to depend on volume. That is, lung surface strains and pressure increases with increasing inflation volume [121]. Mariano et al. [121] also determined that the greatest concentration of strains are located towards the upper surface of the parenchymal tissue. However, this finding could be due to the nature in which this experiment was carried out. The authors noticed that the breathing rate did not significantly affect local strains, however, significance is seen in the rate variables where peak pressure increases and peak lung volume decreases with greater respiratory frequency [121]. This is suggested to be a result of the viscoelasticity of lung parenchymal tissue which is known to cause pressure drops at slow rates of breathing [11]. Furthermore, faster breathing rates may hinder the permeation of air through the airways and tissue leading to increased pressures and lower volumes in an inflated lung [121]. Further research into breathing frequencies is required as the lung inspiratory rate is one of the primary factors responsible for ventilator-induced lung injuries [121]. Lastly, lung tissue strain is determined to exhibit an anisotropic response [121], although, this observed anisotropic behaviour is assumed to be attributed to the underlying airway network, which has demonstrated to be twice as stiff along the main bronchial tree [114, 122]. Mariano et al. [121] conclude that this study provides novel characterizations for computational models and it facilitates a fundamental foundation for future investigations to assess the mechanical functions of healthy and diseased lungs to establish more effective techniques for mechanical ventilation.

5 Lung Blast Mechanics

Using wave propagation to probe the interior of the lung allowed for scientists to examine changes to the lung structure and potential areas of disease. Yen et al. [123] investigate why the lung, compared to all other organs, is more susceptible to injury or deformity when subjected to a blast force. It also remains unknown as to why the speed of a stress wave is much smaller in all other organs when compared to the lung [123]. In the lung, edema or injury is a result of trauma to the lung parenchyma after exposure to a blast wave at a region of high stress. Yen et al. [123] consider it necessary to determine the stress wave speeds that cause this trauma, in particular, the speed of shock waves. In their experiments on rabbit and goat lungs, the wave speed is expressed by

$$c = \left(\frac{B}{\rho}\right)^{\frac{1}{2}}, \tag{5.1}$$

where c is the wave speed, B an elastic constant, and ρ the density [123]. Yen et al. [123] utilize the first arrival time of the stress wave in order to calculate the wave speed. The wave is established as a shock/compression wave using (5.1) such that

$$B = \lambda + 2\mu, \tag{5.2}$$

where λ and μ denote the Lame constants. Note that $\lambda = K - (2/3)\mu$, where K and μ denote the bulk modulus and the shear modulus, respectively. The expression for λ is substituted into (5.2), which is subsequently substituted into the expression for λ [123]. This yields the resulting equation for the elastic moduli of the parenchyma, given by

$$B = K + \frac{4}{3}\mu. \tag{5.3}$$

Yen et al. [123] used experimental values of the bulk modulus K and the shear modulus μ, along with the wave speed equation (5.1) to determine theoretical values of the wave speed c. For rabbit lungs, they calculated a wave speed of 16.5–36.9 m/s as transpulmonary pressure varies between 0–16 cm H_2O. For goat lungs, the wave speed is 31.4–64.7 m/s as transpulmonary pressure varies between 0–20 cm H_2O. These findings indicate that the wave speed is dependent on the size of the lungs as well as transpulmonary pressure [123]. The bulk modulus, shear modulus, and parenchymal density also show significant agreement with theoretical and experimental wave speeds [123]. Yen et al. [123] conclude that weak supersonic shock is followed by bulk flow within the lungs. In turn, this results in the trauma associated with the shock wave [123].

Fung et al. [124] describes the mechanism of impact injury on the lung. Lung tissue has great strength under compression, i.e., it is capable of supporting large deformation. However, under a rapidly applied compressive load, the lung becomes increasingly susceptible to edema following impact and injury through hemorrhage [124]. In general, the lung is dominated by stress waves under rapid applied loading. This compressive load may result via car accidents or bomb explosions. The first wave from either of these two instances is known as a shock wave. Fung et al. [124] considered the following question: Why does a compression wave cause edema or hemorrhage in the lung? Fung et al. [124] hypothesise that this damage is caused by the tensile principal strains induced in the alveolar walls during expansion [124]. As a result, small airways may collapse and trap gas within the alveoli at a critical strain, leading to traumatic atelectasis [124]. Subsequently, upon completion of the wave propagation, the collapsed airways will reopen at a higher values of strain. Thus, this expansion will result in the trapped gas adding further tension to alveolar wall. Note that tensile and shear stresses develop in the alveolar walls as a consequence of compression [124]. The results of this experiment agreed with the above hypothesis. Fung et al. [124] determined that overstretching the lung parenchyma increased the rate of edema fluid formation and the critical strain for airway opening is much higher than it is for closing. Yen et al. [123] reported similar observations based on his findings on the effects of shock wave propagation to lung deformation and pulmonary edema. Fung et al. [124] also highlight that the hysteresis of compressed lungs which are forced to collapse is much larger than the hysteresis of normal uncompressed lungs. Fung et al. [124] made an important identification whereby tension and compressive stress waves result in highly nonuniform stress distributions throughout the lung parenchymal tissue network. From this observation, Fung et al. [124] provide a theoretical analysis examining the elastic response of a cluster of alveoli with trapped gas subject to a compression or tension stress wave. For this analysis, the cluster of alveoli is assumed to attribute a similar behaviour to that of an elastic shell enclosed by

a continuum [124, 125]. The alveoli are modelled as a cylindrical tube with spherical ends, and the lung is considered to be a homogeneous compressible material in order to analyse the dynamic elastic response of the whole lung with respect to the shock wave [124]. The theoretical analysis confirms that the maximum principal tensile stress is of the same order of magnitude as the maximum initial compressive stress at certain positions of the lung tissue [124]. Thus, the greater the initial transpulmonary pressure, the membrane clusters of alveoli will experience a greater maximum tensile stress [124]. Fung et al. [124] did not derive constitutive equations for the stress-strain relationship of lung parenchyma, instead using pressure-volume curves to indirectly approximate this relationship. They also did not identify the precise locations of any collapsed airways.

Blast waves can be extremely severe, especially at the surfaces of differing tissue densities and organs. In particular, the lung is most susceptible. This damage or injury is the result of coupled energy into human tissues due to blast over-pressure [126, 127]. This injury is known as Primary Blast Lung Injury (PBLI) [127]. Blast injuries are drastically influenced by the environment in which they occur. Complex blast waves generate when an explosion occurs within the confines of reflecting surfaces (within buildings or vehicles) [127]. These closed-air blast waves are the product of reflected waves continuously enhancing each other along with the effects of the original shock wave. This has a additive effect which results in a greater positive pressure phase which leads to more severe injury. Blast waves also have a complex form which differs in both magnitude and time. According to Eftaxiopoulou et al. [126], research on biological systems subjected to blast forces tend to lean in too heavily on shock over-pressure, neglecting the effect of wave duration. Wave duration is said to be misunderstood and requires further research to allow for more accurate information on blast mechanics [126]. Eftaxiopoulou et al. [126] developed an experimental model in order to examine the inflammatory response of primary blast wave application on the lung limb. This includes investigating the effect of changing the magnitude and duration of the blast wave. This study permits a controlled delivery of primary blast to depict the duration's associated with the a range of open-field and enclosed environments. Their model assess primary blast limb trauma by utilising a compression driven shock tube to distribute an isolated and controlled blast wave [126]. A shock tube is a piece of equipment that allows one to generate well-defined pressure oscillations of different magnitudes over varying periods of time [128]. From the results of their experiment, Eftaxiopoulou et al. [126] observed no significant differences in heart rate after lung injury. This finding supports their hypothesis whereby the thorax is not exposed to blast loading in the experiments, i.e., it is a true isolated blast model. Moreover, the results imply that the immune system is highly sensitive to damage caused by blast overpressures during a prolonged period of time. This study mainly focuses on the application of blast waves to the respiratory limb, which is found to exhibit a systematic inflammatory response [126]. The inflammatory response observed here is an immediate autonomic response which may result in haemorrhage and parenchymal injury [126, 127]. The underlying mechanisms responsible for haemorrhage remain unknown. However, Scott et al. [127] states that a blast wave will dissipate its kinetic energy within the lung through subsequent generation of shear and stress waves. Low velocity shear waves result from the deformation of the thoracic wall which leads to the observed surface haemorrhage [127]. Shear waves are also responsible for random distribution of tissues of differing densities around fixed points, resulting in injury of the parenchymal tissue [127]. The associated changes observed were dependent on a characteristic of the blast wave, i.e., duration. However, these changes are brief and can take place in the absence of alternative blast injury mechanisms [126].

Arora et al. [116] examined the microstructural mechanical changes that take place within the lung when subjected to blast waves and how these changes influence the strain

distributions of the tissue. The alterations and deformations to the lung tissue was explored using digital volume correlation (DVC). DVC is a powerful method for investigating three-dimensional strain fields within a certain deforming subject [116]. This technique is achieved through a variety of efficient volumetric image processing methods. Using DVC, Arora et al. [116] showed how contrasting levels of blast loading can affect the response of lung tissue during breathing. They also determined whether the observed loss of lung function correlates to time mechanical effects. That is, can local defects develop into major sites of damage over a certain duration. This study also considered the interdependence of healthy tissue with neighbouring injured tissue units [116]. They conducted shock tube experiments in order to create blast injured specimens, with blast over-pressures between 100–180 kPa. Synctron tomography imaging was utilised on blast injured lung specimens to record the volumetric image data of the lungs. Thereafter, DVC was implemented and quantative analysis was used to describe the damaged architecture of the lungs [116]. Arora et al. [116] did not observe any significant microstructural changes to the parenchymal tissue morphology when exposed to a controlled low-to-moderate-level of blast waves. Areas which influenced focal zones of hyperstraining were captured through DVC. These findings were supported through morphological analysis, whereby the focal injury caused by a blast tends to diffuse significance throughout the tissue [116]. Arora et al. [116] studied the effect of non-instantly fatal blast waves and determined that the mechanical response of the lung had been majorly distorted in these instances. Clinically, with regards to PBLI, the information presented in [116] provides new reasons for why patients may experience delayed symptoms of blast lung injury and inflammation, or experience issues associated with delayed injury during treatment. This study is deemed successful by Arora et al. [116]. This is because the data supports the applicability of the DVC technique to explore more blast conditions to further characterise the nature of PBLI. Furthermore, further studies can attempt to identify potential high risk diffuse injury processes through this novel applied imaging analysis technique.

6 Concluding Remarks

Global and continuum lung models have been developed to better understand the mechanical functioning of the lung in health and disease. Global models include the analysis of pressure-volume curves on whole lungs. However, the pressure-volume behaviour of the lung is not capable of describing the underlying mechanical functions, for example, the stress-strain relationship of lung parenchymal tissue [7, 107]. Continuum models prioritise the individual effects and associated interactions of lung parenchyma, surfactant, airways, and airflow [129, 130]. Roth et al. [130] states that by separately analysing the different lung mechanical phenomena, one can reproduce and approximate the response of various lung pathogens, and the effects of different treatments. However, continuum models require improvement in order to better understand the mechanical behaviour of lung tissue. That is, a more accurate description of the constitutive mechanics is necessary to model the lung parenchyma. Lung parenchyma has often been assumed to be homogeneous and isotropic, including its underlying constituents and structures [60, 70]. However, the lung has also been known to exhibit anisotropic behaviour [29]. Recent studies suggest that lung parenchyma exhibits homogeneous or heterogeneous behaviour depending on the scale of deformation experienced by the surface of the lung [86, 99, 101]. Moreover, examination of the linear isotropic material properties were seen to closely resemble the results of nonlinear anisotropic material properties [99]. Weed et al. [95] presented evidence supporting the fact that lung parenchyma is

isotropic, where the underlying mechanisms and constituents of lung tissue at the micro-scale had a global impact on the lung macroscopically. In particular, the heterogeneous behaviour of the microscopic elements of the parenchymal interconnected tissue network allow the whole lung to behave as a homogeneous system. It has since been established that lung tissue deformations exhibit an anisotropic response [121]. Although, Maghsoudi-Ganjeh et al. [117] explains that the anisotropic deformations of the lung parenchyma can be simplified with an isotropic description, as it can approximate the elastic deformations of lung tissue to an acceptable degree.

The more recent studies in lung mechanics have concerned themselves with research into soft biological tissues and analysing the lung at a microscopic level (cellular and molecular). However, there are still some challenging aspects in lung mechanics that have yet to be dealt with. One of these challenges relates to understanding the microscopic elastic components relative to the macroscopic nonlinear elastic response of the lung parenchyma. This could assist in establishing a definite viscoelastic theory for lung parenchyma in future [8]. Furthermore, the potential capabilities of computational systems and multi-scale modelling should not be underestimated. They have the ability to enable the development of more significant and efficient lung models that incorporate both macroscopic and microscopic mechanical lung properties. Determining an accurate and descriptive geometry in computational models of physiological structures is fundamental for providing potentially meaningful results from numerical analysis. The lungs are comprised of various mechanical and functional coupled systems and subsystems. Therefore, computational models must vary in structure over a range of different scales of interest [100]. High-quality image processing and medical imaging is capable of providing efficient resolution data whereby subject-specific interdependent models of the lung can be built upon as computational domains. Thereafter, sets of governing equations would need to be solved to simulate and understand certain lung phenomena. Additionally, computational modelling and simulation of breathing motion is important as it provides fundamental insight into the respiratory dynamics of the human lung. The development of four-dimensional computed tomography (4DCT) image processing has allowed for the measurement and characterisation of respiratory motion within the lung. This technique has also made it possible to quantify the breathing motion of lung tumors more accurately than standard radiation therapy. Radiation therapy provides insufficient details around organ and tumour mobility during respiration [87]. Additionally, enhancements in biologically-concentrated digital image correlation (DIC) analysis has facilitated the effective quantification of interdependent mechanical processes between organ-level and local tissue responses for rapidly occurring large nonlinear deformations [117, 121]. DIC has since been advanced and extended to examine the behaviour of sensitive soft biological tissues, particularly the lung [121]. These techniques could possibly introduce new, efficient and accurate methods of examining how the mechanical functions of the lung are impacted due to changes from healthy to diseased states. This will enable researchers to engineer systems to improve assessment and early detection of lung health and disease. The primary work and theoretical foundations of lung mechanics are already set in place.

All future research into lung mechanics must involve the specific examination of the mechanical elastic and resistive properties of the lung and their associated physiological significance. Examples include determining a potential consistent constitutive equation that describes the nonlinear stress-strain relationship of lung parenchyma, obtaining accurate approximations of the elastic moduli of the lung, determining how pathogens affect the elastic and mechanical properties of the lung, and defining a consistent theory for the deformation behaviour of lung parenchyma. A potential area of future research in lung mechanics regards implicit constitutive theory, which has the potential to describe the nonlinear stress-strain response of a material in more consistent manner. This theory could allow one to analyse the

deformations and distortions experienced by the lung more accurately. Furthermore, future investigations could build upon the studies of Wall et al. [129] and Roth et al. [130], in attempting to develop an extensive computational model for the entire respiratory system that combines all properties of fluid and solid mechanics at both macroscopic and microscopic states. This model must consider the individual effects and mutual mechanical interactions of lung parenchyma, surfactant, the airways, and air flow; with each interaction allowed to be modelled separately. Future studies could also attempt to apply fractional derivative theory to better understand the stress-strain relationship of lung parenchyma or attempt to derive a more concise viscoelastic constitutive equation for the lung parenchyma. Additionally, developing an improved understanding of lung parenchyma viscoelastic tissue may possibly lead to more realistic analytical models. This would result in improved pulmonary diagnosis, treatment and knowledge within the field of lung mechanics.

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Declarations

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