



PONTIFICIA UNIVERSIDAD CATÓLICA DE CHILE
ESCUELA DE INGENIERÍA

MICROMECHANICAL MODEL OF THE LUNG PARENCHYMA FOR MULTI-SCALE SIMULATIONS

FELIPE CONCHA ROJAS

Thesis submitted to the Office of Research and Graduate Studies
in partial fulfillment of the requirements for the degree of
Master of Science in Engineering

Advisor:

DANIEL HURTADO SEPÚLVEDA

Santiago de Chile, June 2017

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*To my mom Carmen Gloria,
my fiancée Camila
and my unconditional friend W.P.*

ACKNOWLEDGEMENTS

I would like to sincerely thank to all the people that, in one way or another, have been part of my learning process. I decided to study engineering because I wanted to know how bridges were built. Now, seven years later, I am proud of not only having fulfilled my purpose, but also about having understood the logic behind, that kind of thought where several elements can be assembled and add their properties to create a complex system. I really think that this scheme of interactions go far beyond mathematics and physics.

Fist of all, I want to thank my family, since they were who motivated me to study and learn and to be always trying to use the full of my capabilities. That has led me to pursue a long list of goals that would probably make, more than someone in my family, regret motivating me so hardly. In particular, I want to thank my mom, Carmen Gloria, because she was who supported me in the most difficult times and because she has shared with me most of my special moments. She has been really present at every time and I hope she continues doing it.

I also want to thank all my professors who have taught me all that I know now. In particular, professors from the department of Structural and Geotechnical Engineering. I will be always grateful for all your answers to my persistent questions and for motivating me to always go further. Special mention to my advisor, Daniel Hurtado, whom I had the good fortune to meet in my first years in the university and whom I have followed in several classes to learn the most possible about mathematics and mechanics. He encouraged me to propose myself various challenges that made me a better student.

In terms of this work, I want to thank all the professors that have been part of my thesis committee. I am really grateful for having read my work and for taking the time to make corrections. I hope that my research has been to your liking.

I can not forget all my classmates and friends that I have met during my years of study. They have supported me a lot of times beside of spending really good times during study as well as during breaks. In this line, I want to also thank Francisco and Ellen, who supported me during my internship in Stanford University. That was a really good experience that made me grow in terms of social skills, contact networks and mainly to consolidate my knowledge. Our work there had a happy ending with the publishing of mi first paper.

I also have to really thank Camila, my fiancée. I met her during my first steps in this work and she was always a really special support, particularly when things went wrong during first months of my thesis. What a patience she has had with me!

Finally I want to thank to the National Commission of Scientific and Technological Research (CONICYT) for having financially supported this work through the grant CONICYT-PCHA/MagsterNacional/2016-22161492.

TABLE OF CONTENTS

ACKNOWLEDGEMENTS	iv
LIST OF FIGURES	viii
LIST OF TABLES	xi
ABSTRACT	xii
RESUMEN	xiii
1. INTRODUCTION	1
1.1. Motivation	1
1.2. Objective	2
2. STATE OF THE ARTE	5
2.1. Lung anatomy	5
2.2. Lung modeling	8
2.3. Homogenization	13
3. THEORETICAL FRAMEWORK	23
3.1. Continuum Mechanics Theory	23
3.2. Nonlinear Homogenization Theory	29
4. THE HYPERELASTIC TETRAKAIDECAHEDRON MODEL	35
5. REPRESENTATIVE VOLUME ELEMENT COMPUTATIONAL MODELS	47
5.1. Lung microstructure acquisition	47
5.2. Representative volume element modeling	48
6. MODEL VALIDATION	53
7. DISCUSSION AND FUTURE WORKS	65
7.1. Model parameters: physiological and physical basis	65

7.2. Accuracy of the TKD model	68
7.3. Computing advantages	70
7.4. Uncertainty and disadvantages	71
7.5. Limitations and future works	75
8. TKD MODEL IMPLEMENTATION ON A COARSE-SCALE MODEL	78
9. CONCLUDING REMARKS	84
REFERENCES	85
APPENDIX	94
A. Nodal Coordinates	95
B. Lattice Vectors	95
C. Element Vectors	96
D. Pairs for Rotational Springs	97
E. Example of Macro-Micro condition	98
F. Nodal Displacements	99
G. Sensitivity Analysis	100

LIST OF FIGURES

1.1	Multiple lung scales	3
1.2	Multi-scale idealization	4
4.1	Microstructure of the lung	36
4.2	Kelvin's tetrakaidecahedron	37
4.3	TKDr and unit cell	38
4.4	Collagen fibers in the lung microstructure	44
5.1	3D reconstruction of alveolar walls	48
5.2	RVE at the reference configuration	49
5.3	RVE and lung tissue domains	50
6.1	Hydrostatic pressure field on RVE at the current configuration for isotropic deformation pattern	53
6.2	Von Misses stress field on RVE at the current configuration for isotropic deformation pattern	54
6.3	Von Misses stress field on RVE at the current configuration for anisotropic deformation pattern	54
6.4	TKD - RVE average stress-stretch comparison under isotropic volumetric expansion and inflation pressure p_A	56
6.5	TKD - RVE average stress-stretch comparison under isotropic volumetric expansion and inflation pressure p_B	57
6.6	TKD - RVE average stress-stretch comparison under anisotropic volumetric expansion and inflation pressure p_A	57

6.7	TKD - RVE average stress-stretch comparison under anisotropic volumetric expansion and inflation pressure p_B	58
6.8	TKD - RVE average stress-stretch comparison under biaxial elongation and inflation pressure p_A	58
6.9	TKD - RVE average stress-stretch comparison under biaxial elongation and inflation pressure p_B	59
6.10	TKD - RVE average stress-stretch comparison under uniaxial elongation and inflation pressure p_A	59
6.11	TKD - RVE average stress-stretch comparison under uniaxial elongation and inflation pressure p_B	60
6.12	TKD model: current configurations under each displacement pattern and inflation	61
6.13	Stress-free uniaxial elongation comparison: Cavalcante - TKD model	62
6.14	Poisson effect comparison for the TKD model at stress-free uniaxial elongation	62
6.15	RVE average anisotropic stresses under isotropic volumetric expansion and inflation pressure p_A	63
6.16	RVE average anisotropic stresses under isotropic volumetric expansion and inflation pressure p_B	63
6.17	Mesh size comparison for RVEs	64
7.1	Deformed TKD: views	67
7.2	Comparison of mesh quality	74
G.1	Sensitivity analysis: TKD - RVE comparison under isotropic volumetric expansion and inflation pressure p_A	100

G.2	Sensitivity analysis: TKD - RVE comparison under anisotropic volumetric expansion and inflation pressure p_A	101
G.3	Sensitivity analysis: TKD - RVE comparison under equibiaxial elongation and inflation pressure p_A	102
G.4	Sensitivity analysis: TKD - RVE comparison under uniaxial elongation and inflation pressure p_A	103
G.5	Sensitivity analysis: TKD - RVE comparison under isotropic volumetric expansion and inflation pressure p_B	104
G.6	Sensitivity analysis: TKD - RVE comparison under anisotropic volumetric expansion and inflation pressure p_B	105
G.7	Sensitivity analysis: TKD - RVE comparison under equibiaxial elongation and inflation pressure p_B	106
G.8	Sensitivity analysis: TKD - RVE comparison under uniaxial elongation and inflation pressure p_B	107

LIST OF TABLES

5.1	RVEs data for lung inflated at p_A	50
5.2	RVEs data for lung inflated at p_B	50
5.3	RVE data for lung inflated at p_B . Data for large RVE mesh	51
5.4	Displacement patterns for RVE simulations	52
6.1	Sensitivity analysis for inflation pressure p_A	55
6.2	Sensitivity analysis for inflation pressure p_B	55
6.3	Optimal TKD model parameters	56

ABSTRACT

The lung is the main organ of the respiratory system and is the responsible of accomplishing breathing through the gas exchange at the alveolar walls level. However, the lung tissue can be damaged by several reasons such as atelectasis, emphysema, edema, etc. In these cases it is often applied artificial ventilation to assist breathing, nevertheless, heterogeneous responses of the tissue are obtained including stiffening, strain hotspots, or collapse of alveolar sacs, which makes difficult the correct choice of procedures to heal the lung. This has motivated an increasing collaboration between medicine and engineering, leading to the development of several research to simulate the mechanical behavior of the lung. First attempts were focused on the mechanical response of the macroscopic structure of the lung, followed by studies on its microstructural behavior given by the alveolar walls. Strictly, multi-scale approaches capable of considering simultaneously macro and micromechanical behavior should be developed, nevertheless, a wide span of mathematical and computational limitations have complicated this issue. To overcome this, and motivated by its ability to represent the alveolar geometry, this work proposes a micromechanical model of the lung tissue based on the tetrakaidecahedron geometry, that is suitable to be implemented for multi-scale simulations. This model is capable of including incompressibility, hyperelasticity, representing medium porosity domains and, as demonstrated against direct numerical simulations of the lung microstructure, to predict, through an homogenization approach and with high accuracy, the overall mechanical response of representative volume elements of the lung with a very low computational cost. This model is also suitable to be extended in future works with the purpose of including higher level of details, establishing an important starting point for the development of more complex models both for the lung parenchyma as for porous materials in general.

Keywords: Multi-scale material modeling, Homogenization, Lung mechanics, Alveolar wall, Tetrakaidecahedron.

RESUMEN

El pulmón es el principal órgano del sistema respiratorio y es el responsable de llevar a cabo la respiración a través del intercambio gaseoso a nivel alveolar. Ahora bien, el tejido pulmonar puede ser dañado por diversos factores tales como atelectasia, enfisema, edema, etc. En dichos casos la ventilación artificial suele ser usada para asistir la respiración, sin embargo, respuestas heterogéneas del tejido pueden ser obtenidas incluyendo rigidización, concentración de deformaciones o colapso de los sacos alveolares, dificultando los procedimientos para sanar el pulmón. Esto ha motivado una creciente colaboración entre medicina e ingeniería, llevando al desarrollo de diversas investigaciones para simular el comportamiento mecánico del pulmón. Los primeros trabajos se centraron en su respuesta macromecánica, los que luego llevaron a estudios acerca de su comportamiento microestructural dado por las paredes alveolares. En rigor, enfoques multi-escala que consideren simultáneamente el comportamiento macro y micromecánico deberían ser desarrollados, sin embargo, una serie de limitaciones matemáticas y computacionales han dificultado esta labor. Ante esto, este trabajo propone un modelo micromecánico del tejido pulmonar, basado en la estructura del tetrakaidecaedro debido a su idoneidad para representar la geometría alveolar, y que es apto para ser implementado en simulaciones multi-escala. Este modelo es capaz de incluir incompresibilidad, hiperelasticidad y, como se demostró para simulaciones numéricas, es capaz de predecir, mediante un enfoque de homogenización y con alta precisión, la respuesta mecánica total de volúmenes elementales representativos del pulmón con un bajo costo computacional. Este modelo puede ser extendido para futuros trabajos con el propósito de incluir mayores niveles de detalle, estableciendo un importante punto de partida para el desarrollo de modelos más complejos tanto del parénquima pulmonar como de materiales porosos en general.

Palabras Claves: Modelación multi-escala de materiales, Homogenización, Mecánica pulmonar, Paredes alveolares, Tetrakaidecaedro.

1. INTRODUCTION

1.1. Motivation

The lung, main and largest organ of the respiratory system, is essential for the process of respiration, i.e. the transport of oxygen and carbon dioxide through the blood-air barrier. To accomplish such a vital function, the lung must cyclically deform to accommodate and discharge considerable volumes of air during ventilation, a life-long process that fundamentally depends on the mechanics of the lung tissue, understood as its ability to deform and bear stresses within physiological limits (West, 2012).

Mechanics also plays a key role in the development of respiratory diseases, as excessive stretching of the alveolar tissue may result in inflammation and ultimately lung injury in patients undergoing mechanical ventilation, where large air volumes or high airway pressures may be necessary in order to recruit alveolar units (ARDSnet, 2000). The importance of mechanics in lung physiology has led clinicians and physiologists to develop mathematical models of the mechanical behavior of the lung, since they allow for in-silico experimentation with a fine-level resolution that is otherwise extremely difficult or impossible to perform in the wet laboratory.

Despite these advances, to date, the majority of current modeling efforts are aimed either at the tissue scale (macrostructure) using a phenomenological approach for constitutive modeling without considering the underlying microstructure (S. Rausch et al., 2011), or at the alveolar scale (microstructure) limited to understand mechanisms at the micrometer range (Wiechert et al., 2009). Thus, a multi-scale approach that connects alveolar microstructure with tissue-level behavior of the lung remains an outstanding field of research in lung biomechanics. According to this, the main objective of this work is to develop and widely validate, for the first time, an analytical micromechanical model of the lung parenchyma suitable for multi-scale simulations, capable of considering the shape and the mechanical behavior of lung at the alveolar walls level, as well as to compute the tissue level constitutive relation through the use of homogenization theory.

1.2. Objective

Nowadays, engineering problems have reached a wide span of areas. Studies go from the classical civil engineering that concerns about buildings and environment to biomechanical and biomedical issues, going through by computer science, electronics and all kind of technology developments. Furthermore, since simulations are a key concept in engineering due to their hability to predict the response of complex systems, they have been strongly enhanced during last time. To this end, the typical approach of including only main details has been replaced by approaches including “the three multis”, understood as multi-processor, multi-physics and multi-scale. The first one has increased the velocity when running simulations, while the second one has considered the simultaneous interaction among several classes of phenomena that are present in nature and that formerly where simply neglected. The third, that it is the focus of this work, has the main purpose of considering the different size scales that interact inside a material when a certain stimulus has been applied.

The present thesis concerns about the mechanics of the lung parenchyma in terms of how the porous structure of the tissue rules deformations on the whole organ and thus how this influences the overall mechanical response, unlike the classical approach of considering a continuum homogeneous structure for the lung. Then, in terms of modeling, one can think about different size scales with the purpose of taking into account porous structure interacting with the whole organ. Lung tissue can usually be split into three scales: macro-scale, that corresponds to the lung which is observable to the naked eye, meso-scale, corresponding to the porous structure formed by the alveolar walls and finally micro-scale, corresponding to the components of alveolar walls such as fibers or cells. For more clarity, Figure 1.1 shows different scales. Nevertheless, for the sake of simplicity and because the focus of this work will be in the alveolar walls, meso-scale will be considered as the micro-scale and components of the alveolar walls will be simply neglected.

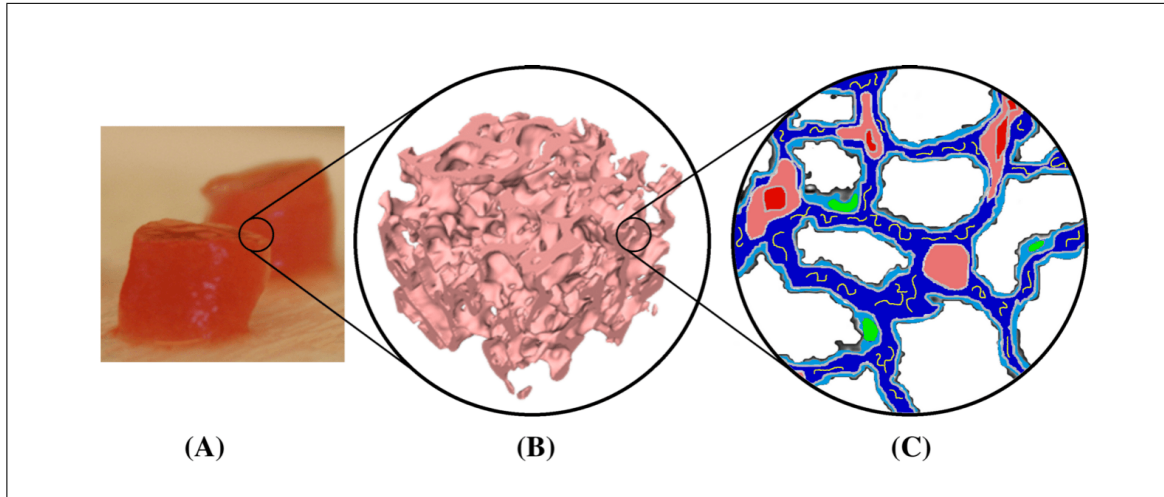


Figure 1.1. Multiple lung scales. (A) macro-scale, corresponding to the lung tissue observable to the naked eye. (B) meso-scale, corresponding to the alveolar walls. (C) micro-scale, corresponding to the components of alveolar walls. In yellow, collagen and elastin fibers; in light blue, endothelial cells with green nucleus; in dark blue, interstitium; in light red, blood plasma; in dark red, blood cells; in light gray, the basement membrane. Figure taken from (S. Rausch et al., 2012)

To make possible the interaction between the porous structure with the whole lung (or in other words the micro-macro interaction) from a computational and mathematical point of view, in this work a micromechanical model of the lung parenchyma suitable for multi-scale simulations has been developed with the purpose of establishing an useful tool for researchers that are focus on the study of the mechanical behavior of the lung at the organ and at the alveolar level with a low computational cost. Using an homogenization approach, this model is capable of returning the macroscopic stress state when a macroscopic deformation has been imposed, by means of representing the same average mechanical behavior as the porous structure of the lung. A simplified scheme of what has been explained above can be seen in Figure 1.2, where the lung microstructure has been idealized by a polyhedral structure that is mechanically equivalent in terms of its energetical contribution to the whole lung. This model has been compared with direct numerical simulations of the lung microstructure obtaining a very good agreement. I hope

this model contributes to the development of more sophisticated and accurate models both for biomechanical ends as any other about the modeling of composite materials.

This work has been organized as follows: in Chapter 2 an extensive description about the lung modeling and homogenization approaches developed to represent composite materials will be reviewed to have a global vision of current efforts in lung modeling and what is still remaining to be done. Chapter 3 will cover the basics that have been used to develop this work, both in terms of continuum mechanics and nonlinear homogenization theoretical frameworks. Then, in Chapter 4 an homogenized material model to represent the lung microstructure will be detailed, which will be later compared with the representative volume elements of lung microstructure presented in Chapter 5. Results for comparison will be shown in Chapter 6 for several deformation patterns. Chapter 7 will discuss about the more relevant aspects of this work, highlighting the advantages and disadvantages of the developed model and proposing future works and challenges. In the light of future works, Chapter 8 will detail the implementation of the proposed model for multi-scale approaches. Finally, concluding remarks will be presented in Chapter 9.

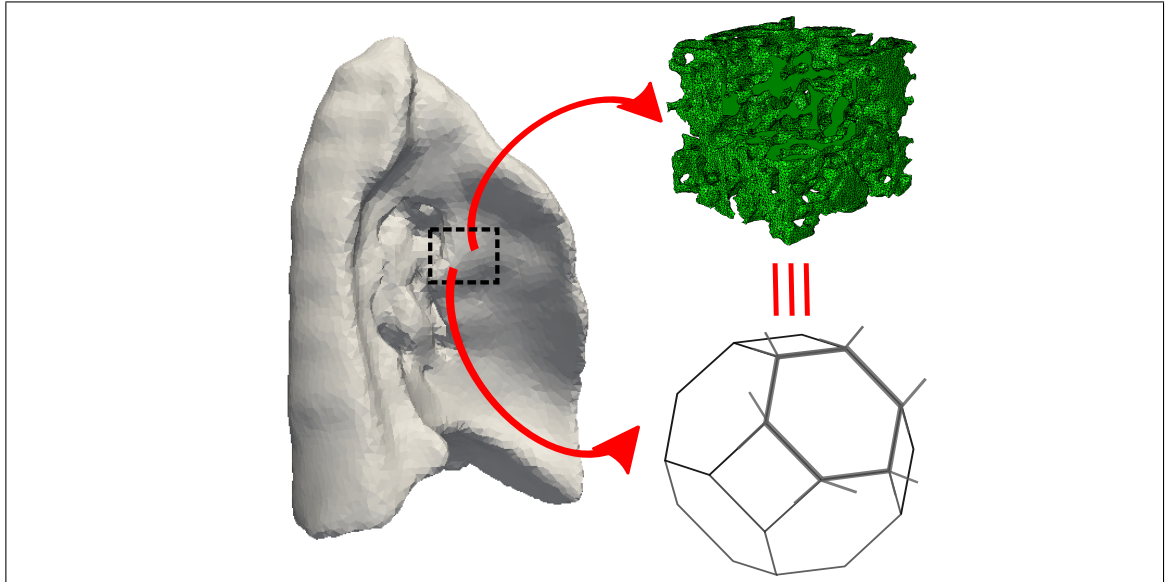


Figure 1.2. Idealization of multi-scale approach. Green geometry corresponds to the microstructure of lung tissue. Polyhedral structure represents the idealized geometry used to represent the lung microstructure.

2. STATE OF THE ART

Since in this work, microstructure of the lung will be modeled by using homogenization for the sake of a multi-scale approach, works about both lung modeling and homogenization will be reviewed to understand what kind of models have been already developed and mainly what kind of analysis have not been covered yet. Nevertheless, for studying a system, it is completely necessary to understand how that system works. So, in this chapter it will be firstly explained, as simple as possible, lung anatomy, to later review lung models that have been proposed and their scopes. Finally, works about linear and non-linear homogenization will be reviewed, putting special attention on the proposed models per se.

2.1. Lung anatomy

The respiratory system is the biological system in charge of the intake and transport of oxygen and its exchange with the carbon dioxide to later transport and expulsion of it. According to (Ethier & Simmons, 2007), this system is composed by the conducting airways and the associated structures. The conducting airways have the purpose of the air transport from the mouth or nose into the alveoli, the basic unit where the gas exchange occurs. To accomplish that function, they are formed by several structures that can be classified in conducting zone and respiration zone.

Conducting zone has a purely transport function. They begin in the pharynx, and continue through the larynx and trachea, where it splits into two bronchi, each one addressed to one lung. Then, bronchi split into bronchioles which in turn also split and so on until reaching, after sixteen branching, the terminal bronchioles, the last zone belonging to the conducting zone. Note that, even when the cross sectional area of each branching decreases, the total area of all branching increases, which decrease the airway resistance and the airflow velocity (S. Rausch et al., 2012). After the terminal bronchioles, branching continues until reaching twenty three levels from bronchi, establishing this the start of

the respiratory zone, where the gas exchange takes place. There, respiratory bronchioles, alveolar ducts and alveolar sacs can be found, with alveoli budding from the walls forming the so called alveolar acinus.

Alveoli are the elemental structure for the gas exchanging through the blood-air barrier. They constitute the basic unit of the lung tissue, forming a foam-like tissue known as the lung parenchyma. There are around 480 million alveoli with an average diameter of $100\ \mu\text{m}$ (Ochs et al., 2004), whose tissue is composed by cells such as endothelial and epithelial, and an extracellular matrix which includes water and macromolecules of elastin, collagen and proteoglycans, among others. In general terms, epithelial cells line the alveolar wall with the supporting basement membrane as long as endothelial cells line capillaries also supported by the basement membrane (S. Rausch et al., 2012). Collagen and elastin fibers are embedded in a hydrated gel called the ground substance (Suki et al., 2005), which is also composed by proteoglycans. According to (Toshima et al., 2004) elastin and collagen act as parallel mechanisms to bear lung stresses and strains, each one fulfilling a function at a certain level of deformation. Elastin constitutes easily extensible fibers (Suki et al., 2005) that can resist small deformations (Setnikar, 1955) with a linear stress-strain relationship (Y. Fung, 2013), so that it dominates the lung elasticity at normal breathing (Suki et al., 2005). Collagen corresponds to helical structures with a rigid rodlike structure (Suki et al., 2005) able to resist larger deformations (Setnikar, 1955) and that have a nonlinear constitutive behavior (Y. Fung, 2013) increasing its stiffness to limit excessive distention, so that, it is the main load bearing element within the alveolar wall (Suki et al., 2005). Collagen and elastin fibers can be considered with a certain orientation in individual alveoli structures, but when a large number of alveoli are considered, orientations become heterogeneous and then, there is not a preferred orientation in human or rat samples (Mercer & Crapo, 1990).

Besides elasticity, there is a viscous behavior on alveoli due to a thin liquid film which line them and works as a surface tension to limit volume expansion and that makes the lung tend to collapse. As mentioned in (S. Rausch et al., 2012), this surface tension is

responsible, among other phenomena, for the hysteretic behavior of the lung about the pressure-volume relation at inflation and deflation. To allow for the lung expansion, the role of epithelial cells II is key because they produce surfactant, which reduces surface tensions making necessary a lower work to expand the lung (Rosen & Kunjappu, 2012). Then, surfactant influences the lung macroscopic behavior by ensuring lung stability and then avoiding collapse for compressive deformations (Avery & Mead, 1959).

To make the gas exchange possible, the vascular system plays a crucial role in providing the blood needed for mass transfer. Pulmonary arteries supply the deoxygenated blood to the lung as well as pulmonary veins discharge the oxygenated blood from it. For this purpose, pulmonary capillaries are attached to the alveolar walls which results, between the blood and air, in a thin layer of around $2.22 \mu\text{m}$ composed by capillary endothelial and airway epithelial cells, and the basement membrane, establishing the so called “blood-air barrier” where the gas exchange takes place.

Nevertheless, even when the gas exchange has been explained at the microscopic level, it still remains to detail how air filling in the lungs occurs for subsequent gas exchange. Lungs are surrounded by the thoracic cage, which is like a deformable container formed mainly by the vertebral column, ribs, and sternum. Among the thoracic cage and the lungs, the pleural membrane can be found which contains inside of it an essentially incompressible fluid called the intrapleural fluid. Structures mentioned above constitute part of the associated structures previously mentioned because they also make possible breathing. To accomplish breathing, lungs are passively deformed, it means, there are no muscles producing any force directly on them, but this process is driven by the the intrapleural pressure changes due to the relative displacement of surrounding structures such as the thoracic cage and the diaphragm (Eom et al., 2010). Thus, the inflation process is carried out without high stresses or deformations (Ethier & Simmons, 2007). For example, when inspiring, thoracic cage and diaphragm moves producing a negative intrapleural pressure P_{ip} which in turn produces a tensile stress on the lungs. If this negative pressure is large enough to counter the alveolar pressure P_{alv} , that is a slightly different value than the

atmospherical pressure due to the several branching of the airways, the resulting transpulmonary pressure $P_{tp} = P_{alv} - P_{ip}$ will be positive and a diffusion process will produce the air income to the lungs. In this line, and due to the same phenomena, it is well known the natural tendency of the lung to collapse due to its elastic recoil and surface stress. Then if $P_{tp} = 0$, the lung collapses, so to avoid this, the intrapleural pressure has to be slightly negative at rest (-3 to -4 mmHg (Ethier & Simmons, 2007)), which means that the lung is under prestress.

2.2. Lung modeling

Several attempts to understand the mechanical behavior of lung parenchyma and the alveolar walls have been carried out. First works were focused on pressure-volume curves to study the stress-strain relation of the lung tissue. Later, more accurate information about elastic, viscoelastic and thermal behavior among others, has been obtained from uniaxial, biaxial and triaxial experiments on cats, dogs, rabbits and humans. Hildebrandt (Hildebrandt, 1970) studied the viscoelastic behavior of cat lungs. Motivated by his findings that hysteresis was a mix of viscoelasticity and rate-independent plastic hysteresis, he proposed a nonlinear model that includes linear viscoelasticity and plastoelasticity, by means of Prandtl bodies. Zeng et al. (Zeng et al., 1987) studied human lung mechanical properties without considering surface tension or viscous behavior. They performed biaxial experiments and they fitted a hyperelastic model. Sugihara et al (Sugihara et al., 1971) experimentally studied the elastic uniaxial behavior of lung strips by means of force-length curves. They found that the maximum stretch was an important tissue property that decreases with increasing age. Furthermore, according to (Sugihara et al., 1972), viscoelastic properties of the lung are expressed through stress relaxation, creep and the hysteretic behavior, so they measured experimentally the hysteresis ratio and the stress relaxation. Mijailovich et al. (Mijailovich et al., 1994) investigated the load transfer friction between the slipping fibers in the connective tissue network by proving several hypothesis about elastance and hysteresivity.

In general terms, experiments show an important exponential stiffening in stress-strain relation that could be explained by the overall properties of collagen fibers (Suki et al., 2005), which highlights the importance of considering the micromechanical response when modeling the macroscopic one.

The importance of mechanics in lung physiology, as well as the high costs and ethical issues of animal experimentation, has led clinicians and physiologists to develop mathematical models of lung biomechanics, since they allow for computational experiments with a fine-level resolution that may be otherwise extremely difficult or impossible to perform in the wet laboratory. Thus, all kind of linear and non linear models have been studied for both the microscale and macroscale.

One of the first works about lung modeling was the one proposed by Fung (Y.-C. Fung, 1975). He proposed an analytical expression, based on several constants to be determined by *in-vivo* or *in-vitro* experiments, for the stress-strain constitutive relation of the lung understood from a macroscopic overview, i.e., without detailing the effect of the microstructure. Then, he tried to explain three kinds of applied problems such as uniform inflation of the lung, stress distribution on the lung due to the own weight and atelectasis. Despite of only representing effective properties from a porous structure without paying attention on it, this kind of approach was taken for a number of studies due to the simplicity of fitting analytical expressions to experimental data and its easy implementation on finite element software, even when those experiments were referred to certain loading conditions and biological issues. Al-Mayah et al. (Al-Mayah et al., 2007) studied the behavior of the whole lung by means of tracking the lung and tumor displacements. They used a hyperelastic material model fitted to the experimental data measured by (Zeng et al., 1987), in addition to modeling the interaction between the lung and the thoracic cavity around by using a frictionless surface-based contact condition. However, they applied displacement boundary conditions which did not constitute a truly physiological condition. In the same line of tumor tracking, Eom et al. (Eom et al., 2010) also used an hyperelastic material model for the lung, with data obtained from (Zeng et al., 1987). However, to

be more physiologically accurate, they applied pressure on the surface of thoracic cavity rather than displacements, such that pressure followed the pressure-volume curves proposed in literature. Rausch et al. (S. Rausch et al., 2011) created a lung power law by an inverse analysis between experimental data and several energy density function contributions among which are Neo-Hookean, Mooney-Rivlin, Blatz and Ko (Blatz & Ko, 1962), Ogden (Ogden, 1974), Yeoh (Yeoh, 1993), etc. Nevertheless, despite of good agreement in their results, their constitutive model do not have a physiological basis given by the microstructure which would be expected for more realistic modeling, specially when dealing with simulation of specific conditions.

To develop more accurate models of the lung mechanics, several studies about modeling the lung microstructure have been conducted, mainly based on the lung microstructural geometry given by the alveoli. Dale et al. (Dale et al., 1980) proposed an elastic single alveolar model formed by a truncated octahedron (also known as tetrakaidecahedron) that was similar to the alveolar geometry and that was capable of filling the space, leaving no voids. Since the distribution of fibers inside the alveolar walls was not well known, this model was assumed to be composed by pin-jointed bar elements, lying both on the borders as inside of faces (which represented alveolar walls). With this model, which has the difficulty of being solved by a finite element approach, they obtained pressure-volume curves for saline-filled lung cases that were qualitatively in good agreement with experiments. Then, Kowe et al. (Kowe et al., 1986) continued the work of (Dale et al., 1980) using the same single alveolar model but they did not include only elastic stresses, but also the surface tension effects given by the surfactant. Later, Denny and Schroter (Schroter, 1995), motivated by the single alveolar model, proposed an alveolar duct model composed by thirty six truncated octahedras, with the four central ones having their faces removed to generate a longitudinal duct. Same as (Dale et al., 1980), truncated octahedras were composed by septal border line elements lying on the perimeter of faces and cross linked elements lying on the faces to represent a network of elastin and collagen fibers. Also, they included septal border line elements lying on the perimeter of faces open to the central duct, representing alveolar mouths. They included the elastic behavior of fibers, given

by experimental data, in addition to the surface tension contributed by the alveolar walls. They obtained pressure-volume curves for the case of air-filled and saline-filled lungs and they found that the alveolar duct model was closer to the experimental data than a single alveolar model. Yuan et al. (Yuan et al., 1997) researched about the role of fiber network and interstitial cells to the macroscopic mechanics of the lung by using a linear viscoelastic model. They found that the fiber network determinate the mechanical properties of the lung parenchyma which could be influenced by interstitial cells. To understand the viscoelastic behavior of the lung, Denny and Schroter (Denny & Schroter, 2000) conducted studies on three cases of lungs: air-filled (normal case), saline-filled (null surface tensions) and a lavaged case (known constant surface tension). For this purpose they used their alveolar duct model proposed in (Schroter, 1995) to later model the viscoelastic behavior by means of the quasi-linear approach proposed by Fung (Y. Fung, 2013), that includes elastic stresses and stress relaxation, and the surface-tension model developed by Otis et al. (Otis et al., 1994). They evaluated the elastance and tissue resistance and they found good agreement with the experimental published data for the air-filled case but not so good for the lavaged-case.

As part of the study of specific conditions, some kind of lung damages have been analyzed such as emphysema, atelectasis or edema. Gefen et al. (Gefen et al., 1999) studied the stress distribution in a two-dimensional alveolar septa obtained from electron micrograph for normal and emphysematous conditions. For the same conditions, de Ryk et al. (de Ryk et al., 2007) researched about the stress distribution in a three-dimensional idealized alveolar geometry, given by a dodecahedron-based acinar model. Both works caused an alteration of the mechanical properties of the tissue to simulate emphysema and investigated effects in a range of pressures and lung volumes. Both found stress concentration on certain zones for the normal cases and significant increased stresses for the abnormal one. Furthermore, (de Ryk et al., 2007) found an important change on the stress distribution when a slightly varying of pressure was applied in addition to the emphysema. Makiyama et al. (Makiyama et al., 2014) analyzed the stress distribution around an atelectatic region inside a two-dimensional domain by using regular hexagonal and Voronoi honeycombs,

beside of nonlinear elasticity for material model. For the unregular mesh, they obtained local stresses up to sixteen times the ones obtained for the regular one, supporting results obtained by (S. M. Rausch et al., 2011).

Some works went further with the purpose of not studying isolated effects only at the micro-scale or at the macro-scale, but make them interact as part of a more physiologically correct approach. With the purpose of investigating about the macroscopic elastic constants necessities to model the lung under large non-uniform deformation (uniaxial), Denny and Schroter (Denny & Schroter, 2006) proposed a multi-scale approach by using the single alveolar model proposed in (Schroter, 1995) to simulate a cubic block composed by ninety one assembled ones, neglecting alveolar ducts. They found that anisotropic properties for large deformations can not be neglected. Furthermore, as mentioned by (Denny & Schroter, 2006), they demonstrated the fact that the lung microstructure can rule the macrostructure response and then, it can be used for proposing a macroscopic material law. Later, Rausch et al. (S. M. Rausch et al., 2011) generated real three-dimensional alveolar geometries to understand and quantify the strain distribution at the alveolar walls when an external strain was imposed on the boundary. They found hotspots of local deformation that could be up to four times the global one imposed, independent of the loading type. A detailed model to capture micro and macro interactions was established by Wiechert et al. (Wiechert et al., 2011) who employed for the first time a square finite element approach (FE2) to consider, when modeling the whole lung, its microstructure by using real alveolar geometries. However, this method involves a very high computational cost which even requires that only certain regions can be simulated with this method.

Despite of some approaches for multi-scale simulations have been performed, there is no agreement with respect to the material model of the lung tissue. Although it should be probably highly nonlinear, several attempts to find linear elastic parameters for the alveolar walls have been carried out. Brewer et al. (Brewer et al., 2003) used an *in-vivo* elastase-treated rat lung model to study the relation between the mechanical behavior of alveolar walls, in terms of elastance and hysteresivity, and the whole lung, when it was cyclically

and uniaxially stretched. To this end, they used immunofluorescence microscopy to measure angular changes and stretches of alveolar walls in terms of macroscopic stretch. By means of a linear network model, they concluded that the whole network was the key to understand the relation between alveolar walls and the whole lung, since individual fibers had heterogeneity, remodeling, possible failure, contributing all of them to the macroscopic response. Cavalcante et al. (Cavalcante et al., 2005) obtained stress-strain curves for lung tissue strips and generated hexagonal fiber network geometries from images of immunofluorescently labeled collagen networks. They modeled these geometries as one-dimensional pin-jointed elements with a nonlinear stress-strain relationship. They realized that, under uniaxial or shear deformation and without prestress, this geometry was unstable since elements were pin-jointed. Thus, they included a rotational stiffness between the springs to make them not free to rotate. They calibrated their model to obtain a stress-strain curve similar to the experimental ones and they were able to predict the Young's module of a single alveolar wall as $E \approx 5\text{KPa}$. Since their work was limited to a two-dimensional analysis, the elastic module obtained constitutes just an approximation, but the only one to that date. Luque et al. (Luque et al., 2013) investigated decellularized lung scaffolds by using atomic force microscopy and indentation tests on alveolar walls. By means of a frequency domain analysis, they found that, for the alveolar extracellular matrix, the storage modulus was around 6 KPa. Furthermore, Young modulus at the alveolar walls kept constant at different levels of indentation, which according to them implies a linear mechanical response of the matrix when subject to small deformations, which was opposite to the general consideration of nonlinear constitutive relation for the whole lung, meaning that the overall response was controlled by the microstructure.

2.3. Homogenization

To make multi-scale simulations numerically tractable, a suitable modeling tool is homogenization. The term “Homogenization” has been coined by Suquet to denote the process of calculating overall properties in heterogeneous domains (Suquet, 1987) where

the composite material is replaced by an homogeneous material with effective properties. With this approach microstructure can be directly considered in the macroscopic model with a low computational cost. In general terms composite materials can be classified according to inclusion models or foam (open or closed) models depending on their volume fraction of solid material.

In linear homogenization, the classical approach consists on finding theoretical bounds for the overall mechanical properties of composite domains. Hashin and Shtrikman (Hashin & Shtrikman, 1961) obtained bounds for the bulk and shear modulus as function of the elastic modules and volume fraction of each phase. Nevertheless, statistics about the phase configuration has been shown to be significant (Brown Jr, 1955) and it was not accounted in this work. Later, and considering porous materials as composite materials where one phase is the own material and the other is void, Hashin (Hashin, 1985) proposed the known “composite spheres assemblage model”, which was a composite domain given by a porous and incompressible hyperelastic matrix composed by hollow spheres (or cylinders for two-dimensional approaches). These spheres had different radii, being considered as perfectly distributed to fill the space. With this model, Hashin obtained an exact solution for the overall stresses under a state of isotropic large deformation.

As part of the study of inclusion models, Danielsson et al. (Danielsson et al., 2004) proposed a hyperelastic constitutive model to the represent porous materials based on a hollow sphere. Under a macroscopic deformation state given by the three principal stretches, the deformation field was analytically obtained to later average the local energy density function to obtain the overall one. Thus, macroscopic stresses were analytically obtained and compared with direct numerical simulation of multi-voids domains. Although a good agreement was obtained, a drawback of this model is that the void evolution was expected to be ellipsoidal, an idealized case generally not found. An important approach to obtain overall mechanical properties in composite domains with relatively low voids volume fraction was the one proposed by Ponte Castañeda and later extended by Lopez-Pamies, which unlike (Danielsson et al., 2004), did not use an specific geometry.

Ponte Castañeda (Castañeda, 2002) proposed a second-order homogenization approach that considers field-fluctuation. Later, Lopez-Pamies and Ponte Castañeda (Lopez-Pamies & Ponte Castañeda, 2004) extended the previous work (Castañeda, 2002) to finite elasticity, by choosing an optimal linear comparison composite. Then, Lopez-Pamies and Ponte Castañeda (Lopez-Pamies & Castañeda, 2007) performed another extension of their work and they proposed a second-order homogenization model capable of including statistics about the microstructure evolution for porous elastomers, which is known to be quite significant to induce phenomena as hardening, softening and unstabilities. Nevertheless, as mentioned, this model has been tested for low voids volume fractions, which is clearly opposite to the case of the lung.

With the purpose of assessing the accuracy of different models of homogenization, Moraleda et al (Moraleda et al., 2007) studied an incompressible hyperelastic two dimensional porous domain under uniaxial elongation, biaxial elongation and uniaxial traction. To this end, they performed direct numerical simulation and compared it with two different homogenization models: the one proposed by Hashin (Hashin, 1985) and the second-order homogenization developed by Lopez-Pamies and Ponte Castañeda (Lopez-Pamies & Ponte Castañeda, 2004) found to be more accurate the second one. The model of Hashin was the less accurate because it assumed cylinders perfectly distributed which maintained their shapes after deformation, however, in the tested model by (Moraleda et al., 2007) under uniaxial or biaxial elongation, circular voids did not remain circular, but they evolved to polygonal shapes, leaving the tissue almost as interconnected strips. Furthermore, among the deformation states evaluated, uniaxial traction was the better predicted by the model of (Lopez-Pamies & Ponte Castañeda, 2004), since circular voids evolved to ellipsoidal voids, which corresponds to the shape expected by the method. In particular, it establishes a very interesting issue for researching about modeling the lung microstructure, due to this tissue, rather than being thought as several spherical voids distributed in the domain, should be considered as strips of tissue representing the alveolar

walls that make up voids of all kind of polyhedral geometries, that is exactly the less favorable case studied by (Moraleda et al., 2007). This last one suggest that the alveolar structure should be studied from a foam point of view instead of an inclusion one.

Several works about obtaining analytical or numerical properties of open and closed cell foams have been proposed. Using linear elasticity, Gibson and Ashby (Gibson & Ashby, 1982) found analytical expressions for the overall mechanical properties of foam materials. For this purpose, they used dimensional analysis, it means, they did not consider any specific geometry. Considering only bending deformation, they calculated the elastic moduli and collapse strength, either for elastic buckling or plastic hinges, which were expressed as function of the relative density and constants as follows:

$$\frac{\text{foam property}}{\text{cell wall property}} = C \left(\frac{\rho}{\rho_s} \right)^n \quad (2.1)$$

where C and n are the constants, ρ is the overall density and ρ_s is the solid material density. Nevertheless, this procedure had two deficiencies: this kind of analysis had a good agreement with testing for low density materials such that $\frac{\rho}{\rho_s} \leq 0.1$ and it did not consider the effect of axial and shear forces. To solve this problem, they did consider a specific cell shape and they took into account the deformation driven by axial and shear forces, in addition to a better estimation of relative density. However, problems arose again when $\frac{\rho}{\rho_s} \geq 0.3$ due to the validity of the assumptions taken about geometry. A summary about the mechanical properties can be found in Table 2 of (Gibson & Ashby, 1982). In general terms they found that similar to open cell foams where cell edges carry all the load, for closed cell foams edges also carry the main part of the load.

According to Christensen (Christensen, 1979), when having a composite material, there are three basics idealized geometries that inclusion phase can assume: spherical, cylindrical or lamellar which give rise to particles, fibers and platelets respectively. Using linear elasticity and the concept of transversely isotropic material, Christensen and Waals (Christensen & Waals, 1972) obtained analytical expressions for five independent elastic material constants for the case of a single composite cylindrical fiber. Then, they obtained

exact solutions for the overall Young modulus and the Poisson coefficient for a composite material constituted by an isotropic matrix and three-dimensional randomly oriented fibers. In the same line, Christensen (Christensen, 1979) found exact solutions for the overall bulk, shear and Young modulus of a composite material formed by a matrix and a distribution of randomly oriented platelets inside it. Later, Christensen (Christensen, 1986) took the approaches of (Christensen & Waals, 1972) and (Christensen, 1979) to study the mechanical behavior of low density isotropic foam materials with open and closed cells respectively, considering the matrix phase with vanishing properties. He found that the overall Young modulus for the closed cell model was until three times the Young modulus for the open cell. Furthermore, they found the open cell to have a better response under compression loads that induce buckling.

One of the most popular foam models is the well known tetrakaidecahedron (Thomson, 1887), hereinafter also referred as TKD, a space-filling cell which almost minimizes surface area per unit volume (Gibson & Ashby, 1999). In this line, Fung (Y. Fung, 1988) have proposed a model composed by an assemblage of tetrakaidecahedrons, where the central one have been removed to simulate alveolar mouths and ducts. Thus, he found that a combination of TKD was a suitable model to describe the geometry of the acinar structures in the lung in terms of shapes, angles, lengths, etc, due to the regularity of the alveolar structure according to histological photographs and distribution pattern of collagen and elastin.

Several authors have studied the linear elastic mechanical behavior of the tetrakaidecahedron unit cell. Zhu et al. (Zhu et al., 1997), Warren and Kraynik (Warren & Kraynik, 1997), Li et al. (Li et al., 2003) and Sullivan et al. (Sullivan et al., 2008) have found analytical expressions for its overall elastic constants, as Young, shear or bulk moduli. For this purpose, they have covered different levels of details on their analysis according to the inclusion of axial, shear, bending and twisting effects on the struts of the unit cell. Of particular interest was the work of Warren and Kraynik (Warren & Kraynik, 1997). In their approach, they considered the tetrakaidecahedron as an open cell unit structure composed

by joints and struts elements with identical shapes. They also considered it as a periodic arrangement, so they used lattice vectors to describe the struts directions. Furthermore, motivated by the symmetric geometry in addition to the application of homogeneous deformation, only a certain region composed by eighteen nodes and struts was considered. In their analysis they included both axial and shear deformations, beside of bending and twisting rotations and they expressed force-displacement relation for each strut by means of their respective compliances. Thus, using kinematic compatibilities and equilibrium equations they obtained analytical expressions for the internal efforts and local stresses on the struts which then led, through an averaging process, to the calculation of overall mechanical properties as the bulk and shear moduli. Although this analysis has been limited to linear analysis, it constitutes a starting point to the study of more complex geometries with more complex constitutive relations.

In addition to the tetrakaidecahedron, many other unit cells have been proposed to represent the overall mechanics of foam materials. Zhang (Zhang, 2008) developed a linear elastic unit cell constituted by three struts forming the one eighth of a cube. By means of an average field approach, he obtained the macroscopic deformation field generated under a macroscopic load applied. Thus, he found the elastic compliance terms necessities to characterize the mechanical behavior of the foam material as a function of the relative density, relative sizes of the unit cell and applied load. As only axial and bending effects have been considered in the calculation of deformation fields, according to Zhang, his model was applicable to low and medium density materials due to shear deformation were significant when relative density increase.

Beside of analytical works, there are also some numerical approaches. By one hand, overall linear elastic properties have been investigated, using the finite element method, in closed foams by using a tetrakaidecahedron model built from plates (Venkatachalam, 2013). By the other hand, linear elastic properties in open cell foams have been found in (Li et al., 2005) and (Hedayati et al., 2016). Li et al. (Li et al., 2005) used a one-dimensional finite element approach of assembled frame elements to study different load

cases on a tetrakaidecahedron structure, solving the degrees of freedom and then calculating the overall Young, shear and Poisson moduli to later comparison with literature. Heyadati et al. (Heyadati et al., 2016) proposed a unit cell given by a truncated hexahedron. Same than (Li et al., 2005), they used a one-dimensional finite element approach to analytically obtain the stiffness matrix of their unit cell in addition to expressions for several overall mechanical properties. They also performed numerical simulations to assess the accuracy of their method. An issue of interest when modeling foam materials is their response to compression loads and instability. The majority of the works previously presented were focused on elongation deformations since, as mentioned by (Warren & Kraynik, 1991), when a unit cell is loaded under compression, struts will buckle for sufficiently large strains. Since by the moment buckling is a quite hard topic, its study has been neglected for the sake of the good understanding of foam materials. Nevertheless, some works about it have been published as the one of Laroussi et al. (Laroussi et al., 2002) who proposed a tetrakaidecahedron-assembled model to analyze buckling and failure surface.

Although most of the works about homogenization focus on finding overall properties in linear elastic unit cells, there are some nonlinear approaches too. Warren and Kraynik (Warren & Kraynik, 1991) studied isotropic low-density foam material by means of a pin-jointed tetrahedral unit cell composed by four half struts subjected only to axial deformation. Although in their analysis they used linear elasticity, they included finite displacements arguing that it was enough to represent the overall nonlinear behavior of a foam material. By means of nodal force equilibrium, kinematic compatibilities and an average process, they related local strains with a macroscopic imposed deformation state and they found expressions for microscopic and macroscopic stress states. Thus, they proposed a polynomial, based on invariants, energy density function, whose coefficients were obtained from the overall stress states obtained for uniaxial and biaxial deformation. According to Warren and Kraynik, in spite of axial deformations were considered as dominant with respect to bending as long as foam material was subject to large deformations, real open cell foams were not pin-jointed and then shear modulus was not negligible. Thus, to better estimate the mechanical behavior of open cell foams, they included an extra

term to their proposed energy density function to account for the global rotational energy involved.

A little further went the work of Wang and Cuitiño (Wang & Cuitiño, 2000). They also studied low density materials but they were capable of including simultaneously geometric and material nonlinear behavior. They proposed several two- or three-dimensional unit cells composed by different number of members working as lattice in order to represent a periodic structure. They classified unit cells according to the number of members used to represent the unit cells, given by the number of elements that share the same vertex. According to Wang and Cuitiño, members can be treated as beams allowing the use of axial, bending and shear deformation energies. Nevertheless, as large deformations have been considered, shear energy can be neglected and bending energy can be assumed as localized in the member joints, leaving the axial strain energy lying on the member geometry. Hence, for each member, an energy density function is calculated as the sum of an axial strain energy and a bending energy. Then, the overall energy density function for the whole unit cell is obtained by averaging all member energies into the unit cell volume. In practice, energy is given by the deformation that each member suffers, which is computed by means of the force equilibrium and kinematic compatibilities among the members and the macroscopic deformation field imposed. According to Wang and Cuitiño, their approach explicitly incorporates the geometry of foam microstructure and its connectivity. Nevertheless, contrary to what they point out, they do not consider explicitly the foam geometry, since they just take into account the lattice vectors necessary to represent it, but it is done independent of the real shape of the unit cell. Thus, even when this work is quite similar to the one which will be discussed in the present thesis, here real geometry will be explicitly considered and the nonlinear material and geometric behavior will be focus on real geometry rather than into the lattice vectors used to describe it.

In the same line of nonlinear homogenization approaches, Feng and Christensen (Feng & Christensen, 1982) developed a Neo-Hookean model to simulate foam compression, similar approach as the one proposed by Guo et al. (Guo et al., 2008), who proposed a

constitutive relation for large deformations for a Neo-Hookean hollow cilindre. Demiray et al. (Demiray et al., 2006) obtained numerical stress-strain relationship for nonlinear material behavior at large deformations for a tetrakaidecahedron structure using Timoshenko beams. Nevertheless, as can be understood, there are no analytical approaches for tetrakaidecahedron models including both material and geometrical nonlinearity beside of being addressed to medium porosity materials.

From the previous review some conclusions can be extracted: (1) the mechanical behavior of the lung tissue, given by the alveolar walls, is to the date unknown and it constitutes a research field. (2) Macroscopic and microscopic material models have been developed for the lung parenchyma, but by one hand, macroscopic approaches are restricted to the experimental conditions which they arise from and by the other hand, microscopic approaches have not been widely validated. (3) In most works, lung microstructure and macrostructure have not been simultaneously considered and when it has been done, through multi-scale approaches, they have had important limitations with respect to computational and mathematical resources. (4) Several studies about composite and porous materials have been carried out and the inclusion of nonlinearity has also been considered. Moreover, in terms of the lung, a certain unit cell as been considered as quite suitable. Therefore, in this thesis, the objective will be to develop and to validate a nonlinear elastic material model of the lung that incorporates the information of its microstructure given by its volume fraction and that can be easily included into multi-scale simulations through an homogenization approach, such that the model receives a macroscopic deformation state and returns a macroscopic stress state. As a drawback, the model proposed will not incorporate the viscous behavior of the lung tissue and surface tension in addition to only use a simplified model to represent the elasticity of alveolar walls. Furthermore, even when the model can stand for compressive deformations and buckle if load is significant, that is quite similar to the reality of foam materials, only elongation deformation states will be analyzed leaving the study of compression to future works. Even so, to the author's knowledge, the present approach would constitute the first one to include lung microstructural effects for macroscopic simulations of the lung mechanics, being widely validated against

in-silico experiments and following a rigorous approach of nonlinear homogenization. So it should establish a significant contribution in terms of less computational cost and more accurate analysis, making possible a better understanding of the lung mechanics.

3. THEORETICAL FRAMEWORK

In this section continuum mechanics and homogenization theoretical frameworks will be formulated with the main purpose to later study a porous material as the lung, with a multi-scale approach where different scales are considered by separately but whose responses are linked.

3.1. Continuum Mechanics Theory

Let's consider a body in the reference or undeformed configuration $\mathcal{B}_o$ and in the current or deformed configuration $\mathcal{B}$. A certain point on the reference domain is defined as $\mathbf{X}$, as well a certain point on the current domain is defined as $\mathbf{x}$. It defines the map $\varphi(\mathbf{X})$ as the one-to-one correspondence between the undeformed and deformed states such that $\varphi(\mathbf{X})$ on $\mathcal{B}_o \rightarrow \mathbf{x}$ on $\mathcal{B}$. Then, the deformation gradient tensor $\mathbf{F}$ is defined as

$$\mathbf{F} = \frac{\partial \varphi(\mathbf{X})}{\partial \mathbf{X}} = \mathbf{I} + \frac{\partial \mathbf{u}}{\partial \mathbf{X}} \quad (3.1)$$

where $\mathbf{I}$ is the unit tensor and $\mathbf{u}$ is the displacement field corresponding to $\mathbf{u} = \mathbf{x} - \mathbf{X}$. Moreover, it is usually defined the jacobian of transformation as the determinant of tensor $\mathbf{F}$ as

$$J = \det \mathbf{F} \quad (3.2)$$

In practical terms, jacobian J can be understood as the volumetric change ratio of an infinitesimal particle idealized as a cube located at $\mathbf{X}$ when it is deformed to $\mathbf{x}$. Thus,

$$J = \frac{V}{V_o} \quad (3.3)$$

where V_o is the volume of the idealized cube at the reference configuration as well as V is the volume of the idealized cube at the current configuration.

Depending on the kind of issue being studied, finite deformation problems can usually be studied from a lagrangian (material) or an eulerian (spatial) approach. Thus, there

are deformation and stress tensors related to each kind of formulation. In this line, two classical tensors for measuring deformations are used: the right Cauchy Green strain tensor $\mathbf{C}$ for lagrangian approaches and the left Cauchy Green strain tensor $\mathbf{b}$ for eulerian approaches. Both tensors are defined as

$$\mathbf{C} = \mathbf{F}^T \mathbf{F} \quad (3.4)$$

$$\mathbf{b} = \mathbf{F} \mathbf{F}^T \quad (3.5)$$

Under a certain deformation state that accounts for axial and angular deformations, a principal deformation state can be found through an eigenvalues analysis as follows

$$\det(\mathbf{b} - \lambda_i^2 \mathbf{I}) = 0 \quad \forall i \in \{1, 2, 3\} \quad (3.6)$$

where $\lambda_i, i \in \{1, 2, 3\}$ are the principal stretches acting on the principal directions which correspond to the square roots of the eigenvectors of $\mathbf{b}$. Principal stretches can be easily understood for the case of a cube as the final length over the initial length of the deformed dimension. From principal stretches, invariants for tensor $\mathbf{b}$ can be calculated as:

$$I_1(\mathbf{b}) = \lambda_1^2 + \lambda_2^2 + \lambda_3^2 \quad (3.7)$$

$$I_2(\mathbf{b}) = \lambda_1^2 \lambda_2^2 + \lambda_1^2 \lambda_3^2 + \lambda_2^2 \lambda_3^2 \quad (3.8)$$

$$I_3(\mathbf{b}) = \lambda_1^2 \lambda_2^2 \lambda_3^2 \quad (3.9)$$

Furthermore, invariant I_3 is related to J according to $\sqrt{I_3} = J = \lambda_1 \lambda_2 \lambda_3$.

A very important issue for finite deformations is the polar decomposition. Under a certain deformation state given by a tensor $\mathbf{F}$, it can always be separated into a purely stretch tensor and a purely rotation tensor. Rotation tensor is always defined as $\mathbf{R}$, whereas depending on the kind of formulation, it is used the right stretch tensor $\mathbf{U}$ for lagrangian approaches or the left stretch tensor $\mathbf{v}$ for eulerian approaches. They are related to $\mathbf{F}$ according to

$$\mathbf{F} = \mathbf{R} \mathbf{U} = \mathbf{v} \mathbf{R} \quad (3.10)$$

Rotation tensor is calculated by means of the director cosines as long as stretch tensors are obtained from Cauchy Green strain tensors as

$$\mathbf{U}^2 = \mathbf{C} \quad (3.11)$$

$$\mathbf{v}^2 = \mathbf{b} \quad (3.12)$$

In practice, the calculus of stretch tensors is carried out by spectral decomposition as follows

$$\mathbf{U} = \sum_{a=1}^3 \lambda_a \mathbf{N}_a \otimes \mathbf{N}_a \quad (3.13)$$

$$\mathbf{v} = \sum_{a=1}^3 \lambda_a \mathbf{n}_a \otimes \mathbf{n}_a \quad (3.14)$$

where $\mathbf{N}_a$ and $\mathbf{n}_a$ are respectively the principal directions of tensors $\mathbf{C}$ and $\mathbf{b}$ related to the principal value λ_a .

Now that kinematics has been widely explained, obtention of stress tensors will be detailed. Let W be the energy density function associated to a solid. In this work, it will be assumed that for each infinitesimal point, W will be only a function of the deformation state existent on that point, such that $W = W(\mathbf{F})$. Moreover, due to the assumption about that only isotropic materials will be discussed, W will be only a function of the three previously defined invariants I_1, I_2, I_3 or, the same, a function of the three principal stretches, such that $W = W(\lambda_1, \lambda_2, \lambda_3)$. Furthermore, W will be assumed to fulfill requirements of objectivity and material symmetry (Holzapfel, 2000). Several stress tensors can be defined, as the first Piola-Kirchhoff stress tensor $\mathbf{P}$, second Piola-Kirchhoff stress tensor $\mathbf{S}$, and Cauchy stress tensor $\boldsymbol{\sigma}$, which are computed according to

$$\mathbf{P} = \frac{\partial W}{\partial \mathbf{F}} \quad (3.15)$$

$$\mathbf{S} = \mathbf{F}^{-1} \mathbf{P} \quad (3.16)$$

$$\boldsymbol{\sigma} = J^{-1} \mathbf{P} \mathbf{F}^T \quad (3.17)$$

Tensor $\boldsymbol{\sigma}$ corresponds to the forces per unit of current area plotted in the current configuration whereas $\boldsymbol{P}$ corresponds to the forces per unit of current area plotted in the reference configuration. $\boldsymbol{S}$ has not a physical meaning, but it is useful for certain formulations as defining elasticity tensors. In this line, it is important to define expressions for the material and spatial elasticity tensors $\mathbb{C}_m$ and $\mathbb{C}_s$ respectively, since, for example, they are required when implementing material models in finite element software. In simple terms, the material elasticity tensor can be computed according to

$$\mathbb{C}_m = 2 \frac{\partial \boldsymbol{S}}{\partial \boldsymbol{C}} \quad (3.18)$$

which in indicial notation corresponds to

$$\mathbb{C}_{mABCD} = 2 \frac{\partial S_{AB}}{\partial C_{CD}} \quad (3.19)$$

Spatial elasticity tensor can be calculated in a more difficult way and details can be found in (Holzapfel, 2000). Nevertheless, a direct expression obtained from the material elasticity tensor is usually used. It is as follows

$$\mathbb{C}_{sabcd} = J^{-1} F_{aA} F_{bB} F_{cC} F_{dD} \mathbb{C}_{mABCD} \quad (3.20)$$

where indicial notation has been used to define expression for spatial elasticity tensor because tensorial notation is too cumbersome. Nevertheless, in this thesis $\mathbb{C}_s$ will be required, but for the sake of simplicity, a different expression will be used based on principal stresses and stretches. Following the demonstration from (Holzapfel, 2000), it yields

$$\begin{aligned} \mathbb{C}_s = & \sum_{a,b=1}^3 J^{-1} \lambda_a^2 \lambda_b \frac{\partial S_a}{\partial \lambda_b} \boldsymbol{n}_a \otimes \boldsymbol{n}_a \otimes \boldsymbol{n}_b \otimes \boldsymbol{n}_b + \\ & \sum_{a,b=1, a \neq b}^3 \frac{\sigma_b \lambda_a^2 - \sigma_a \lambda_b^2}{\lambda_b^2 - \lambda_a^2} (\boldsymbol{n}_a \otimes \boldsymbol{n}_b \otimes \boldsymbol{n}_a \otimes \boldsymbol{n}_b + \boldsymbol{n}_a \otimes \boldsymbol{n}_b \otimes \boldsymbol{n}_b \otimes \boldsymbol{n}_a) \end{aligned} \quad (3.21)$$

where only one index has been used for stress tensors $\boldsymbol{S}, \boldsymbol{\sigma}$ referred to principal coordinates.

Now that stresses and strains have been defined, it is finally necessary to define equations to solve the mechanical equilibrium. The static equilibrium configuration at the reference configuration for a body $\mathcal{B}_o$ subject to body forces $\mathbf{B}$ on the whole domain with external tractions $\bar{\mathbf{T}}$ and displacements $\bar{\mathbf{u}}$ on its boundary $\partial\mathcal{B}_o$ is obtained by solving the following strong formulation of the equilibrium problem: given $\bar{\mathbf{T}}$ on $\partial\mathcal{B}_o^t$ and $\bar{\mathbf{u}}$ on $\partial\mathcal{B}_o^u$, find $\mathbf{u}$ on $\mathcal{B}_o$ such that

$$\operatorname{div} \mathbf{P} + \mathbf{B} = \mathbf{0} \quad \text{in } \mathcal{B}_o \quad (3.22)$$

$$\mathbf{P} = \frac{\partial W(\mathbf{F})}{\partial \mathbf{F}} \quad \text{in } \mathcal{B}_o \quad (3.23)$$

$$\mathbf{F} = \mathbf{I} + \frac{\partial \mathbf{u}}{\partial \mathbf{X}} \quad \text{in } \mathcal{B}_o \quad (3.24)$$

$$\mathbf{u} = \bar{\mathbf{u}} \quad \text{on } \partial\mathcal{B}_o^u \quad (3.25)$$

$$\mathbf{P}\mathbf{N} = \bar{\mathbf{T}} \quad \text{on } \partial\mathcal{B}_o^t \quad (3.26)$$

$$\partial\mathcal{B}_o^u \cup \partial\mathcal{B}_o^t = \partial\mathcal{B}_o \quad \text{and} \quad \partial\mathcal{B}_o^u \cap \partial\mathcal{B}_o^t = \emptyset \quad (3.27)$$

where $\mathbf{N}$ is the unit normal of $\partial\mathcal{B}_o$ pointing outwards.

Now, since the lung tissue will be assumed to work as an incompressible material, incompressibility formulation will be explained. The classical approach in which this constraint is included in the material energy density function is through the use of parameters of Lagrange to penalize volumetric deformations. In this section, the symbol $(\hat{\cdot})$ will be used to denote incompressible conditions for a variable $(\cdot)$, nevertheless other chapters and sections will not use this terminology since the complete work concerns to incompressible materials. So, including this constraint, the new energy density function $\hat{W}$, the first Piola-Kirchhoff stress tensor $\hat{\mathbf{P}}$ and the Cauchy stress tensor $\hat{\boldsymbol{\sigma}}$ are expressed as follows:

$$\hat{W} = W - p(J - 1) \quad (3.28)$$

$$\hat{\mathbf{P}} = \mathbf{P} - pJ\mathbf{F}^{-T} \quad (3.29)$$

$$\hat{\boldsymbol{\sigma}} = J^{-1}\mathbf{P}\mathbf{F}^T - p\mathbf{I} \quad (3.30)$$

where p is the parameter of Lagrange, also referred to the pressure field needed to enforce incompressibility.

Thus, the static equilibrium configuration at the reference configuration for an incompressible body $\mathcal{B}_o$, with body forces $\mathbf{B}$ on the whole domain with external tractions $\bar{\mathbf{T}}$ and displacements $\bar{\mathbf{u}}$ on its boundary $\partial\mathcal{B}_o$ is obtained by solving the following strong formulation problem: given $\bar{\mathbf{T}}$ on $\partial\mathcal{B}_o^t$ and $\bar{\mathbf{u}}$ on $\partial\mathcal{B}_o^u$, find $\mathbf{u}$ and p on $\mathcal{B}_o$ such that

$$\operatorname{div} \hat{\mathbf{P}} + \mathbf{B} = \mathbf{0} \quad \text{in } \mathcal{B}_o \quad (3.31)$$

$$\hat{\mathbf{P}} = \frac{\partial W(\mathbf{F})}{\partial \mathbf{F}} - pJ\mathbf{F}^{-T} \quad \text{in } \mathcal{B}_o \quad (3.32)$$

$$\mathbf{F} = \mathbf{I} + \frac{\partial \mathbf{u}}{\partial \mathbf{X}} \quad \text{in } \mathcal{B}_o \quad (3.33)$$

$$\det \mathbf{F} - 1 = 0 \quad \text{in } \mathcal{B}_o \quad (3.34)$$

$$\mathbf{u} = \bar{\mathbf{u}} \quad \text{on } \partial\mathcal{B}_o^u \quad (3.35)$$

$$\hat{\mathbf{P}}\mathbf{N} = \bar{\mathbf{T}} \quad \text{on } \partial\mathcal{B}_o^t \quad (3.36)$$

$$\partial\mathcal{B}_o^u \cup \partial\mathcal{B}_o^t = \partial\mathcal{B}_o \quad \text{and} \quad \partial\mathcal{B}_o^u \cap \partial\mathcal{B}_o^t = \emptyset \quad (3.37)$$

As expected, all tensor fields described are functions of $\mathbf{X}$, however, for the sake of clarity, their dependences have been omitted.

Finally, for the specific case of an incompressible Neo-Hookean material model, $\hat{W}$, $\hat{\mathbf{P}}$ and $\hat{\boldsymbol{\sigma}}$ are computed as follows

$$\hat{W} = \frac{\mu}{2}(\operatorname{tr}(\mathbf{F}\mathbf{F}^T) - 3) - p(\det \mathbf{F} - 1) \quad (3.38)$$

$$\hat{\mathbf{P}} = \mu\mathbf{F} - pJ\mathbf{F}^{-T} \quad (3.39)$$

$$\hat{\boldsymbol{\sigma}} = J^{-1}\mu\mathbf{F}\mathbf{F}^T - p\mathbf{I} \quad (3.40)$$

$$J = 1 \quad (3.41)$$

where μ is the shear modulus.

3.2. Nonlinear Homogenization Theory

In this subsection notation and equations will follow those used by Fish (Fish, 2013) to describe multi-scale modeling of composite materials formed by a macrostructure (coarse-scale) and a microstructure (fine-scale). Let Ω_X^ξ be the composite domain in the reference configuration with coordinates $\mathbf{X}$, boundary $\partial\Omega_X^\xi$ and unit normal $\mathbf{N}^\xi$ pointing outwards. Moreover, let Ω_x^ξ be the composite domain in the current configuration with coordinates $\mathbf{x}$, boundary $\partial\Omega_x^\xi$ and unit normal $\mathbf{n}^\xi$ pointing outwards. As seen, subscript X will refer to the reference configuration, whereas x will refer to the current one. Furthermore, superscript ξ will denote the existence of fine-scale features. Then, the strong formulation of the boundary value problem for the composite domain at the reference configuration can be formulated as: given $\bar{\mathbf{T}}^\xi$ on $\partial\Omega_X^{t,\xi}$ and $\bar{\mathbf{u}}^\xi$ on $\partial\Omega_X^{u,\xi}$, find $\mathbf{u}^\xi$ on Ω_X^ξ such that

$$\operatorname{div} \mathbf{P}^\xi + \mathbf{B}^\xi = \mathbf{0} \quad \text{in } \Omega_X^\xi \quad (3.42)$$

$$\mathbf{F}^\xi = \mathbf{I} + \frac{\partial \mathbf{u}^\xi}{\partial \mathbf{X}} \quad \text{in } \Omega_X^\xi \quad (3.43)$$

$$\mathbf{u}^\xi = \bar{\mathbf{u}}^\xi \quad \text{on } \partial\Omega_X^{u,\xi} \quad (3.44)$$

$$\mathbf{P}^\xi \mathbf{N}^\xi = \bar{\mathbf{T}}^\xi \quad \text{on } \partial\Omega_X^{t,\xi} \quad (3.45)$$

$$\partial\Omega_X^{t,\xi} \cup \partial\Omega_X^{u,\xi} = \partial\Omega_X^\xi \quad \text{and} \quad \partial\Omega_X^{t,\xi} \cap \partial\Omega_X^{u,\xi} = \emptyset \quad (3.46)$$

where vectors and tensors are the same as those defined in section 3.1 but referred to a composite domain due to the use of superscript ξ .

Now, the composite domain will be explained in terms of the two separated scales: coarse and fine. Let Ω_X be the coarse-scale domain in the reference configuration with boundary $\partial\Omega_X$. Now, vectors $\mathbf{X}$ and $\mathbf{x}$ will correspond to the material and spatial coordinates of the coarse-scale domain. In the same way that for the coarse-scale, Θ_Y will correspond to the unit cell, or fine-scale, domain with boundary $\partial\Theta_Y$, where subscripts Y and y will refer to the reference and current configuration of the domain. Vectors $\mathbf{Y}$ and $\mathbf{y}$ will correspond to the material and spatial coordinates of the fine-scale domains respectively. This unit cell will be considered as locally periodic, which means that the

solution is taken to be constant over the unit cell dimensions in the macroscopic problem. Then, the composite domain can be defined as $\Omega_X^\xi \equiv \Omega_X \times \Theta_Y$ for the undeformed configuration and as $\Omega_x^\xi \equiv \Omega_x \times \Theta_y$ for the deformed configuration. Furthermore, macroscopic and microscopic coordinate systems are related by $\mathbf{Y} = \frac{1}{\xi}(\mathbf{X} - \hat{\mathbf{X}})$ with $0 < \xi \ll 1$ and where $\hat{\mathbf{X}}$ are the coordinates of the unit cell centroid.

Now, the approach of considering tensor fields depending on a composite domain will be changed by the dependance of any tensor field $\mathbf{A}$ in two-scale coordinates as $\mathbf{A}^\xi(\mathbf{X}) = \mathbf{A}(\mathbf{X}, \mathbf{Y})$. Then, the displacements field on the composite domain $\mathbf{u}^\xi$ can be approximated by an asymptotic expansion over the domains Ω_X, Θ_Y as follows

$$\mathbf{u}^\xi(\mathbf{X}) = \mathbf{u}(\mathbf{X}, \mathbf{Y}) = \mathbf{u}^{(0)}(\mathbf{X}) + \xi \mathbf{u}^{(1)}(\mathbf{X}, \mathbf{Y}) + \xi^2 \mathbf{u}^{(2)}(\mathbf{X}, \mathbf{Y}) + \mathcal{O}(\xi^3) \quad (3.47)$$

where it has been assumed that the leading order term of asymptotic expansion does not depend on fine-scale coordinates, which is valid for linear elliptic problems but constitutes only an approximation for nonlinear problems (Fish, 2013). After some mathematical procedure, equation 3.47 is expressed in terms of the unit cell centroid as

$$\mathbf{u}^\xi(\mathbf{X}) = \mathbf{u}(\hat{\mathbf{X}}, \mathbf{Y}) = \hat{\mathbf{u}}^{(0)}(\hat{\mathbf{X}}) + \xi \hat{\mathbf{u}}^{(1)}(\hat{\mathbf{X}}, \mathbf{Y}) + \xi^2 \hat{\mathbf{u}}^{(2)}(\hat{\mathbf{X}}, \mathbf{Y}) + \mathcal{O}(\xi^3) \quad (3.48)$$

where $\hat{\mathbf{u}}^{(0)}(\hat{\mathbf{X}}) = \mathbf{u}^{(0)}(\hat{\mathbf{X}}) \equiv \mathbf{u}^c(\hat{\mathbf{X}})$, which is the coarse-scale displacement in point $\hat{\mathbf{X}}$, also understood as a rigid body translation on the unit cell. Differentiating $\mathbf{u}^\xi$ with respect to $\mathbf{X}$ and suitably grouping terms $\hat{\mathbf{u}}^{(0)}, \hat{\mathbf{u}}^{(1)}, \hat{\mathbf{u}}^{(2)}$, the deformation gradient tensor for the composite material is obtained. Later, through asymptotic expansion it is expressed as

$$\mathbf{F}^\xi(\mathbf{X}) = \mathbf{I} + \frac{\partial \mathbf{u}^\xi}{\partial \mathbf{X}} = \mathbf{F}^{(0)}(\hat{\mathbf{X}}, \mathbf{Y}) + \xi \mathbf{F}^{(1)}(\hat{\mathbf{X}}, \mathbf{Y}) + \mathcal{O}(\xi^2) \quad (3.49)$$

where, matching asymptotic terms, expressions for the coarse-scale and fine-scale deformation gradients $\mathbf{F}^c, \mathbf{F}^f$ are obtained as

$$\mathbf{F}^{(0)}(\hat{\mathbf{X}}, \mathbf{Y}) = \mathbf{F}^c(\hat{\mathbf{X}}) + \frac{\partial \mathbf{u}^{(1)}}{\partial \mathbf{Y}}(\hat{\mathbf{X}}, \mathbf{Y}) \equiv \mathbf{F}^f(\hat{\mathbf{X}}, \mathbf{Y}) \quad (3.50)$$

$$\mathbf{F}^c(\hat{\mathbf{X}}) = \mathbf{I} + \frac{\partial \mathbf{u}^c}{\partial \mathbf{X}}(\hat{\mathbf{X}}) \quad (3.51)$$

The reason why $\mathbf{F}^{(0)} \equiv \mathbf{F}^f$ could be better understood when the equilibrium equations are formulated. Assuming Y-periodicity on $\mathbf{u}^{(1)}(\hat{\mathbf{X}}, \mathbf{Y})$, it is naturally obtained that

$$\mathbf{F}^c(\hat{\mathbf{X}}) = \frac{1}{|\Theta_Y|} \int_{\Theta_Y} \mathbf{F}^f(\hat{\mathbf{X}}, \mathbf{Y}) d\Theta_Y \quad (3.52)$$

Now, the stress tensor $\mathbf{P}(\mathbf{F}^\xi)$ can be also obtained and asymptotically expanded around the fine-scale deformation gradient $\mathbf{F}^f$, leading to:

$$\mathbf{P}(\mathbf{F}^\xi) = \mathbf{P}^{(0)}(\mathbf{X}, \mathbf{Y}) + \xi \mathbf{P}^{(1)}(\mathbf{X}, \mathbf{Y}) + \mathcal{O}(\xi^2) \quad (3.53)$$

Last expression is also expanded in a Taylor series around the unit cell centroid $\hat{\mathbf{X}}$ and then it is inserted into equation (3.42). Matching terms of (3.42) according to the power of ξ and equating to 0, two-scale equilibrium equations are obtained

$$\frac{\partial \mathbf{P}^f(\hat{\mathbf{X}}, \mathbf{Y})}{\partial \mathbf{Y}} = \mathbf{0} \quad (3.54)$$

$$\frac{\partial \mathbf{P}^f}{\partial \mathbf{X}}(\hat{\mathbf{X}}, \mathbf{Y}) + \frac{\partial \mathbf{P}^{(1)}(\hat{\mathbf{X}}, \mathbf{Y})}{\partial \mathbf{Y}} + \mathbf{B}^f(\hat{\mathbf{X}}, \mathbf{Y}) = \mathbf{0} \quad (3.55)$$

where it has been used that $\mathbf{P}^{(0)} \equiv \mathbf{P}^f$, corresponding to the fine-scale first Piola-Kirchhoff stress tensor, since equation (3.54) can be understood as the equilibrium at the fine-scale domain, when assuming that body forces at the microscale are too small. Furthermore, equation (3.55) can be integrated over the unit cell, considering fine-scale periodicity, to obtain the equilibrium equation in the coarse-scale domain. Thus, integration yields

$$\frac{\partial \mathbf{P}^c}{\partial \mathbf{X}} + \mathbf{B}^c = \mathbf{0} \quad (3.56)$$

where $\mathbf{P}^c$ and $\mathbf{B}^c$ are respectively the macroscopic first Piola-Kirchhoff stress tensor and body force vector, which are computed according to

$$\mathbf{P}^c(\hat{\mathbf{X}}) \equiv \frac{1}{|\Theta_Y|} \int_{\Theta_Y} \mathbf{P}^f(\hat{\mathbf{X}}, \mathbf{Y}) d\Theta_Y \quad (3.57)$$

$$\mathbf{B}^c \equiv \frac{1}{|\Theta_Y|} \int_{\Theta_Y} \mathbf{B}^f(\hat{\mathbf{X}}, \mathbf{Y}) d\Theta_Y \quad (3.58)$$

Moreover, since $\mathbf{P}^{(0)} \equiv \mathbf{P}^f$, it is natural to define $\mathbf{F}^{(0)} \equiv \mathbf{F}^f$ as defined in equation (3.50). If tensor $\boldsymbol{\sigma}^f$ is used as the case of simulations done in this work in the finite element software ABAQUS, $\mathbf{P}^c$ and $\boldsymbol{\sigma}^c$ are computed as

$$\mathbf{P}^c = \frac{1}{|\Theta_Y|} \int_{\Theta_Y} \boldsymbol{\sigma}^f \mathbf{F}^{-Tf} J^f d\Theta_Y = \frac{1}{|\Theta_Y|} \int_{\Theta_y} \boldsymbol{\sigma}^f \mathbf{F}^{-Tf} d\Theta_y \quad (3.59)$$

$$\boldsymbol{\sigma}^c = \frac{1}{|\Theta_y|} \int_{\Theta_y} \boldsymbol{\sigma}^f d\Theta_y \quad (3.60)$$

being $\boldsymbol{\sigma}^f$ and $\boldsymbol{\sigma}^c$ the fine-scale and coarse-scale Cauchy stress tensors respectively. It has also been used for the deformed unit cell domain Θ_y that $d\Theta_y = J^f d\Theta_Y$.

Having presented the main aspects about nonlinear elasticity homogenization have been presented, it is necessary to formulate the fine-scale equilibrium problem. Although periodicity on the fine-scale has been used to obtain equation (3.56), it has been demonstrated (Fish, 2013) that periodic or essential boundary conditions can be employed satisfying the same equilibrium requirements. Thus, in this work, essential boundary conditions were then imposed by means of

$$\mathbf{u}^f = (\mathbf{F}^c - \mathbf{I})\mathbf{Y} \quad \text{on } \partial\Theta_Y \quad (3.61)$$

where $\mathbf{u}^f$ will correspond to the fine-scale displacements until order one ($\mathcal{O}(1)$). Thus,

$$\mathbf{u}^f = \hat{\mathbf{u}}^{(1)} = (\mathbf{F}^c - \mathbf{I})\mathbf{Y} + \mathbf{u}^{(1)} \quad (3.62)$$

Hence, the strong formulation for the fine-scale equilibrium problem is as follows: given $\mathbf{F}^c$ on $\partial\Theta_Y$, find $\mathbf{u}^f$ on Θ_Y such that:

$$\frac{\partial \mathbf{P}^f(\hat{\mathbf{X}}, \mathbf{Y})}{\partial \mathbf{Y}} = \mathbf{0} \quad \text{in } \Theta_Y \quad (3.63)$$

$$\mathbf{P}^f = \frac{\partial W^f(\mathbf{F}^f)}{\partial \mathbf{F}^f} \quad \text{in } \Theta_Y \quad (3.64)$$

$$\mathbf{F}^f = \mathbf{I} + \frac{\partial \mathbf{u}^f}{\partial \mathbf{Y}} \quad \text{in } \Theta_Y \quad (3.65)$$

$$\mathbf{u}^f = (\mathbf{F}^c - \mathbf{I})\mathbf{Y} \quad \text{on } \partial\Theta_Y \quad (3.66)$$

where $W^f(\mathbf{F}^f)$ is the energy density function of the solid material from which the composite material is made.

Concerned by the multi-scale simulations of the lung, it is of interest to formulate the unit cell equilibrium problem including incompressibility. To this end, the incompressibility formulation introduced in equations (3.31) to (3.37) is employed. Hence, the strong formulation for the fine-scale equilibrium problem is as follows: given $\mathbf{F}^c$ on $\partial\Theta_Y$, find $\mathbf{u}^f$ on Θ_Y and p^f on Θ_Y such that:

$$\frac{\partial \mathbf{P}^f(\hat{\mathbf{X}}, \mathbf{Y})}{\partial \mathbf{Y}} = \mathbf{0} \quad \text{in } \Theta_Y \quad (3.67)$$

$$\mathbf{P}^f = \frac{\partial W^f(\mathbf{F}^f)}{\partial \mathbf{F}^f} - p^f J^f \mathbf{F}^{-T^f} \quad \text{in } \Theta_Y \quad (3.68)$$

$$\mathbf{F}^f = \mathbf{I} + \frac{\partial \mathbf{u}^f}{\partial \mathbf{Y}} \quad \text{in } \Theta_Y \quad (3.69)$$

$$\det(\mathbf{F}^f) - 1 = 0 \quad \text{in } \Theta_Y \quad (3.70)$$

$$\mathbf{u}^f = (\mathbf{F}^c - \mathbf{I})\mathbf{Y} \quad \text{on } \partial\Theta_Y \quad (3.71)$$

where $J^f = \det \mathbf{F}^f$ and, as mentioned in the previous section, the use of $(\hat{\cdot})$ has been omitted for simplicity, since in this work fine-scale features will be always including incompressibility.

Thus, a general flowchart for multi-scale simulations can be understood as: from the macroscopic problem a coarse-scale deformation gradient tensor $\mathbf{F}^c$ is known for a certain point $\mathbf{x}$. Then, $\mathbf{F}^c$ is used as the boundary condition for a fine-scale problem where

fine-scale displacements have to be found solving equations (3.67) to (3.71). Once it is achieved, fine-scale deformation gradients $\mathbf{F}^f$ and stresses $\boldsymbol{\sigma}^f$ are computed by means of equations (3.64) and (3.65) respectively. Finally, a coarse-scale stress tensor $\boldsymbol{\sigma}^c$ is found by averaging the fine-scale ones through equation (3.57) and they are returned to the coarse-scale problem. The equilibrium into the coarse-scale domain is checked using the deformation gradient previously given to the fine-scale and the received stresses and an iteration process is performed repeating all the steps mentioned until convergence is achieved between coarse-scale stresses and coarse-scale deformations.

4. THE HYPERELASTIC TETRAKAIDECAHEDRON MODEL

With the continuum mechanics and non-linear homogenization frameworks shown in the previous section, an incompressible hyperelastic foam material model will be proposed to compute in a straightforward and accurate way the coarse-scale or homogenized constitutive relation of the lung parenchyma, in order to be able of including the microstructure when modeling the whole organ. This model will try to resemble the real microstructure of the lung, given by the alveolar walls (Y. Fung, 1988) and to reproduce the same micromechanical behavior without solving a nonlinear finite element problem for each fine-scale representative volume element, saving a high computational cost. In general terms, in this section notation will follow that used in section 3.2.

Motivated by the lung microstructure shown in Figure 4.1 (Solomonov et al., 2014) the kind of foam structure used in this work corresponds to the Kelvin’s tetrakaidecahedron (Thomson, 1887) that can be seen in Figure 4.2. Moreover, based on the mentioned microstructure, the TKD has been assumed as constituted by struts rather than plates, following an open cell approach. In particular, motivated by the symmetry of both the geometry as the imposed deformation, a representative region of the TKD, named TKDr, will be used in this work, following the approach of (Warren & Kraynik, 1997). Nevertheless, despite of the use of the TKDr rather than the TKD as such, for simplicity and for being both referred to the same geometry, this thesis will talk about the “TKD model” to denote the developed model. This region is also shown in Figure 4.2, as well as the unit cell assigned (Warren & Kraynik, 1997) that can be found in Figure 4.3. For the reader better understanding of its geometry, nodal coordinates can be found in Appendix A.

Since the TKDr represents a periodic arrangement, lattice vectors will be used to connect equivalent nodes, see Appendix B. Following the approach given by (Warren & Kraynik, 1997), lattice vectors $\mathbf{b}_\alpha$, $\alpha = \{x, y, z\}$ at the reference configuration are given by:

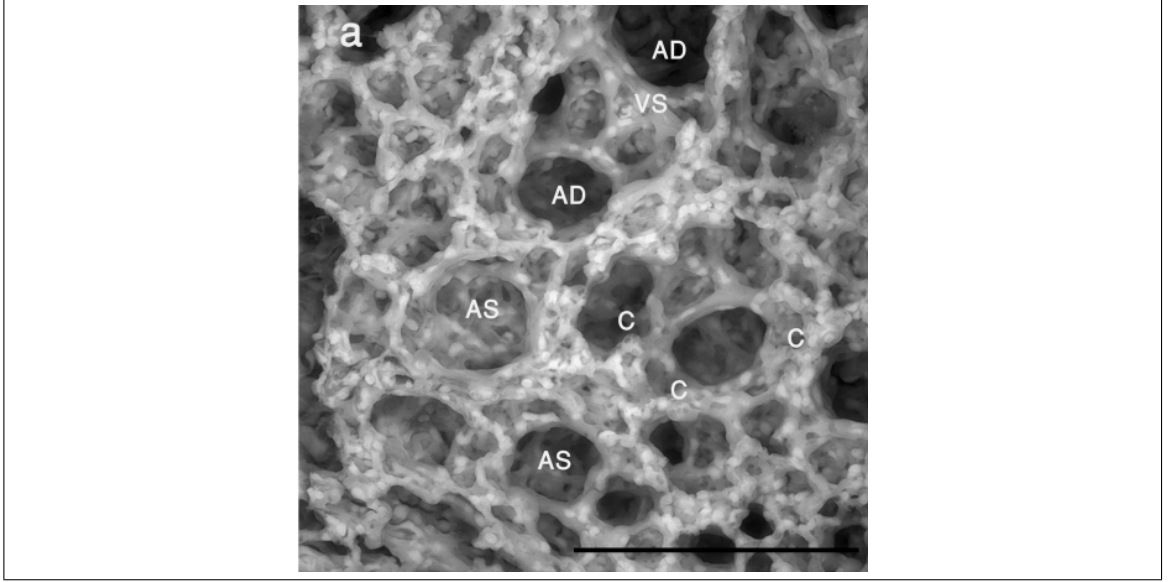


Figure 4.1. Microstructure of the lung tissue. Alveolar sacs (AS), alveolar ducts (AD), blood vessels (VS) and capillaries (C) are shown. Scale bar corresponds to $100\mu\text{m}$. Figure taken from (Solomonov et al., 2014).

$$\mathbf{b}_x = 2\sqrt{2}\delta \begin{bmatrix} -1 \\ 1 \\ 1 \end{bmatrix} \quad \mathbf{b}_y = 2\sqrt{2}\delta \begin{bmatrix} 1 \\ -1 \\ 1 \end{bmatrix} \quad \mathbf{b}_z = 2\sqrt{2}\delta \begin{bmatrix} 1 \\ 1 \\ -1 \end{bmatrix} \quad (4.1)$$

where δ is the initial strut half-length corresponding to $\frac{\sqrt{2}}{6}$ according to nodal coordinates of Appendix A. Thus, any variable ρ in a certain position $\mathbf{Y}$ can be found into the periodic array by means of

$$\rho(\mathbf{Y}) = \rho(\mathbf{Y} + n_1\mathbf{b}_x + n_2\mathbf{b}_y + n_3\mathbf{b}_z) \quad (4.2)$$

where $n_1, n_2, n_3 \in \mathbb{Z}$.

Since it is a widely used material model in literature when modeling the lung parenchyma, to simulate the TKDr material response, an incompressible Neo-Hookean density energy function will be used as follows

$$W^f = \frac{\mu}{2}(\text{tr}(\mathbf{F}^f \mathbf{F}^{fT}) - 3) - p^f(\det \mathbf{F}^f - 1) \quad (4.3)$$

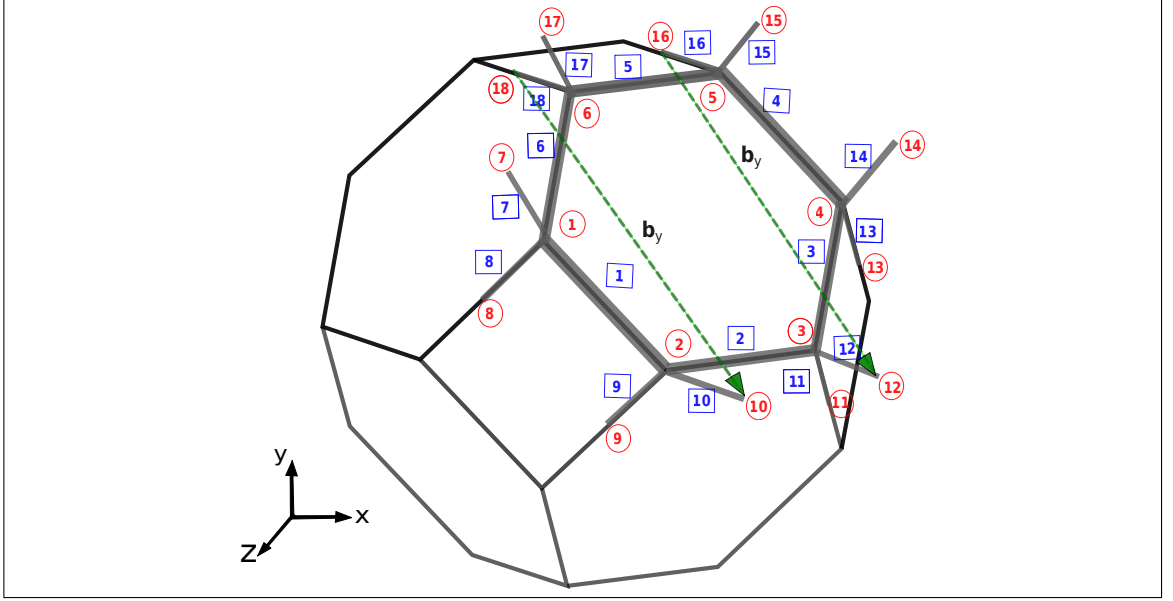


Figure 4.2. In black, Kelvin's tetrakaidecahedron (TKD). In dark grey, representative region used (TKDr). Numeration corresponds to the TKDr. Nodal numbers are into red circles as well as element numbers are into blue rectangles. Lattice vector $\mathbf{b}_y$ is shown in a green dotted line.

The incompressible fine-scale problem defined by (3.67) to (3.71) with constitutive law (4.3) is reformulated as the saddle-point mixed variational principle

$$\min_{\mathbf{F}^f \in \mathbf{F}_{adm}^f} \max_{\mathbf{p}^f \in L^2(\Theta_Y)} \int_{\Theta_Y} \left\{ \frac{\mu}{2} (\text{tr}(\mathbf{F}^{fT} \mathbf{F}^f - 3) - p^f (\det \mathbf{F}^f - 1)) \right\} d\Theta_Y \quad (4.4)$$

where, to remind, Θ_Y is the fine-scale domain which in this case corresponds to the TKDr unit cell domain and where

$$\mathbf{F}_{adm}^f \equiv \{ \mathbf{F}^f : \Theta_Y \rightarrow \mathbb{R}^{n \times n} : \det \mathbf{F}^f > 0 \text{ in } \Theta_Y \text{ and } \mathbf{F}^f = \mathbf{F}^c \text{ on } \partial\Theta_Y \} \quad (4.5)$$

Now, motivated by the resolution of the minimization problem, the continuum approach is changed by a discretized one. For this purpose, the TKDr is considered as composed by one-dimensional structural elements which are interconnected at nodes. This simplification results in a 3D truss structure with elements, see Figure 4.2. Displacement vectors at the nodes will serve as degrees of freedom (DOFs) for the structure, where the nodal displacement vector for the i -th node is denoted by $\mathbf{u}_i$. It is further assumed axial

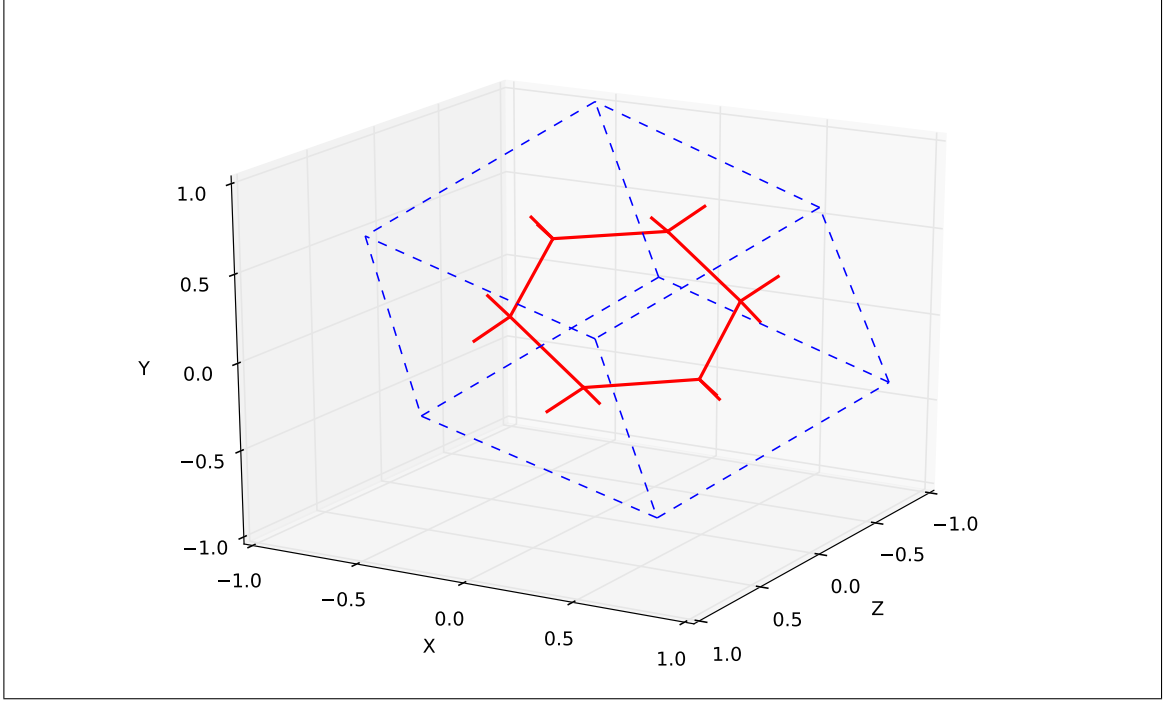


Figure 4.3. TKDr (red continuous line) and its unit cell (blue dotted line) (Warren & Kraynik, 1997).

symmetry for the struts, as well as a constant pressure throughout each element, and axial deformation defined by the difference of displacement of the boundary nodes. These assumptions are justified by the slender and predominantly axial geometry of the TKDr struts, and by the fact that deformation energy due to axial deformation will dominate over bending energy (Warren & Kraynik, 1991), (Wang & Cuitiño, 2000). Under these assumptions, one shows that the deformation gradient of the e -th element takes the form

$$\mathbf{F}^f = \begin{bmatrix} \lambda_e & 0 & 0 \\ 0 & \lambda_e^T & 0 \\ 0 & 0 & \lambda_e^T \end{bmatrix} \quad (4.6)$$

where λ_e, λ_e^T are the axial and transverse stretch ratios, respectively. In particular, the axial stretch ratio is defined as

$$\lambda_e \equiv \frac{\|\mathbf{q}_e\|}{L_{e_o}} \quad (4.7)$$

where $\mathbf{q}_e$ is the difference between end-node coordinates in the current configuration for the e -th element, see Appendix C. Similarly, $\mathbf{Q}_e$ is defined as the difference between end-node coordinates in the reference configuration, and it is noted that the initial element length $L_{e_o} = \|\mathbf{Q}_e\|$. Then, the element deformation energy takes the form

$$\Pi_e^{axial}(\mathbf{q}_e, \lambda_e^T, p_e) = \int_{L_{e_o}} \int_{A_o} \left\{ \frac{\mu}{2} (\lambda_e^2 + 2\lambda_e^{T^2} - 3) - p_e (\lambda_e \lambda_e^{T^2} - 1) \right\} dA_o dL_{e_o} \quad (4.8)$$

$$= A_o L_{e_o} \left\{ \frac{\mu}{2} (\lambda_e^2 + 2\lambda_e^{T^2} - 3) - p_e (\lambda_e \lambda_e^{T^2} - 1) \right\} \quad (4.9)$$

where p_e is the element pressure and A_o is the reference cross-sectional area assumed to be the same for all elements. Note that, even when all element features are referred to the TKDr and then to the fine-scale, superscript f has been omitted for the sake of clarity. In general terms, it will be considered that all quantities depending on the strut e or the node i will have a subscript e or i respectively but will have the superscript f neglected.

Since the pin-jointed TKDr structure represents a mechanism, i.e., it allows for non-zero displacements at no energy cost, it is considered the addition of rotational energy terms to equation (4.8) to stabilize the system. To this end, it is used the rotation as the difference between the initial and final cosine of the angle subtended between two elements connected to the same joint, identified by a pair $j = (j_1; j_2)$ from the pair set $\mathcal{J}$ listed in Appendix D. It can be noted that each vertex of the central hexagon of the TKDr has six rotational springs linking its four connected elements, then thirty six rotational springs should be considered for the TKDr. Thus, the energy contribution associated is assumed to take the form

$$\Pi_j^{rotational}(\mathbf{q}_{j_1}, \mathbf{q}_{j_2}) = \frac{1}{2} k_\theta \left\{ \frac{\mathbf{q}_{j_1} \cdot \mathbf{q}_{j_2}}{\|\mathbf{q}_{j_1}\| \|\mathbf{q}_{j_2}\|} - \frac{\mathbf{Q}_{j_1} \cdot \mathbf{Q}_{j_2}}{\|\mathbf{Q}_{j_1}\| \|\mathbf{Q}_{j_2}\|} \right\}^2 \quad (4.10)$$

where k_θ corresponds to the rotational stiffness assumed to take the same value for all possible rotations in the TKDr. Adding all energy contributions, the extended potential energy for the TKDr reads

$$\Pi = \sum_{e=1}^{18} \Pi_e^{axial} + \sum_{j \in \mathcal{J}} \Pi_j^{rotational} \quad (4.11)$$

With the purpose of reducing the number of independent DOFs of the TKDr and then, the number of computations to solve the TKDr, a number of relations between nodal displacements can be employed which will arise from kinematic and symmetry considerations for the TKD. In particular, periodicity and axial symmetry with respect to the plane given by $X = 0$ leads to the following assumptions about nodal displacements

$$u_{1x} = u_{6x} = 0 \quad (4.12)$$

$$u_{8x} = \frac{-u_{2x}}{2} \quad (4.13)$$

$$u_{9x} = \frac{u_{2x}}{2} \quad (4.14)$$

$$u_{10x} = \frac{u_{2x} + u_{3x}}{2} \quad (4.15)$$

$$u_{12x} = u_{3x} + \frac{u_{3x} - u_{2x}}{2} \quad (4.16)$$

Periodicity and axial symmetry with respect to the plane defined by $Y = 0$ leads to

$$u_{2y} = u_{3y} = 0 \quad (4.17)$$

$$u_{8y} = \frac{u_{1y}}{2} \quad (4.18)$$

$$u_{9y} = \frac{-u_{1y}}{2} \quad (4.19)$$

$$u_{11y} = \frac{-u_{4y}}{2} \quad (4.20)$$

$$u_{13y} = \frac{u_{4y}}{2} \quad (4.21)$$

Furthermore, periodicity and axial symmetry with respect to $Z = 0$ implies that

$$u_{4z} = u_{5z} = 0 \quad (4.22)$$

$$u_{10z} = u_{2z} + \frac{u_{2z} - u_{3z}}{2} \quad (4.23)$$

$$u_{11z} = \frac{u_{3z}}{2} \quad (4.24)$$

$$u_{12z} = \frac{u_{3z} + u_{2z}}{2} \quad (4.25)$$

$$u_{13z} = \frac{-u_{3z}}{2} \quad (4.26)$$

Beside of symmetry, another kind of kinematic constraint was imposed which consist on that nodes in rhomboid faces lie in a common plane, which for face with normal axis X implies that,

$$u_{3x} = u_{4x} = u_{11x} = u_{13x} \quad (4.27)$$

For face with normal axis Y

$$u_{5y} = u_{6y} = u_{16y} = u_{18y} \quad (4.28)$$

And for face with normal axis Z ,

$$u_{1z} = u_{2z} = u_{8z} = u_{9z} \quad (4.29)$$

It is further considered that $\mathbf{F}^c$ represents a principal deformation state, and therefore it takes the diagonal form.

$$\mathbf{F}^c = \begin{bmatrix} \lambda_1^c & 0 & 0 \\ 0 & \lambda_2^c & 0 \\ 0 & 0 & \lambda_3^c \end{bmatrix} \quad (4.30)$$

where $\lambda_1^c, \lambda_2^c, \lambda_3^c$ are the coarse-scale principal stretches. Moreover, lattice vectors defined in (4.1) and boundary conditions (3.71) deliver additional relations between nodal displacements that can be understood as constraints between certain degrees of freedom according to the following relations

$$\mathbf{u}_7 = \mathbf{u}_{11} + (\mathbf{F}^c - \mathbf{I})\mathbf{b}_x \quad (4.31)$$

$$\mathbf{u}_{10} = \mathbf{u}_{18} + (\mathbf{F}^c - \mathbf{I})\mathbf{b}_y \quad (4.32)$$

$$\mathbf{u}_{12} = \mathbf{u}_{16} + (\mathbf{F}^c - \mathbf{I})\mathbf{b}_y \quad (4.33)$$

$$\mathbf{u}_{14} = \mathbf{u}_9 + (\mathbf{F}^c - \mathbf{I})\mathbf{b}_z \quad (4.34)$$

$$\mathbf{u}_{15} = \mathbf{u}_8 + (\mathbf{F}^c - \mathbf{I})\mathbf{b}_z \quad (4.35)$$

$$\mathbf{u}_{17} = \mathbf{u}_{13} + (\mathbf{F}^c - \mathbf{I})\mathbf{b}_x \quad (4.36)$$

With the purpose of clarifying the origin of previous expressions (4.31) to (4.36), an example was included in Appendix E. Altogether, these assumptions allow to express nodal displacements in the TKDr in terms of a reduced set of DOFs, $\mathbf{r}$, and $\mathbf{F}^c$, which are written as $\mathbf{u}_i = \mathbf{u}_i(\mathbf{r}; \mathbf{F}^c)$, $i = [1...18]$, where

$$\mathbf{r} = \begin{bmatrix} u_{1y} \\ u_{2y} \\ u_{3z} \end{bmatrix} \quad (4.37)$$

is a vector with unknown DOFs, whose entries coincide with displacements of a reduced set of selected nodes. Thus, nodal displacements can be almost completely defined as can be seen in Appendix F. Let be $\mathbf{p} = [p_1, \dots, p_{18}]^T$, $\mathbf{l} = [\lambda_1^T, \dots, \lambda_{18}^T]^T$, using simplifications above, the variational principle (4.4) can be rewritten as the optimization problem

$$\min_{\mathbf{r} \in \mathbb{R}^3, \mathbf{l} \in \mathbb{R}^{18}} \max_{\mathbf{p} \in \mathbb{R}^{18}} \Pi(\mathbf{r}, \mathbf{l}, \mathbf{p}; \mathbf{F}^c) \quad (4.38)$$

where the extended Lagrangian Π takes the form

$$\begin{aligned} \Pi(\mathbf{r}, \mathbf{l}, \mathbf{p}; \mathbf{F}^c) \equiv & \sum_{e=1}^{18} A_o L_{eo} \left\{ \frac{\mu}{2} (\lambda_e^2 + 2\lambda_e^{T^2} - 3) - p_e (\lambda_e \lambda_e^{T^2} - 1) \right\} + \\ & \sum_{j \in \mathcal{J}} \frac{1}{2} k_\theta \left\{ \frac{\mathbf{q}_{j1} \cdot \mathbf{q}_{j2}}{\|\mathbf{q}_{j1}\| \|\mathbf{q}_{j2}\|} - \frac{\mathbf{Q}_{j1} \cdot \mathbf{Q}_{j2}}{\|\mathbf{Q}_{j1}\| \|\mathbf{Q}_{j2}\|} \right\}^2 \end{aligned} \quad (4.39)$$

As in any minimization or maximization approach, stationary points are searched. For the case of stationary points of pressure field p_e ,

$$\frac{\partial \Pi}{\partial p_e} = 0 \quad (4.40)$$

$$\lambda_e(\mathbf{r}; \mathbf{F}^c) (\lambda_e^T)^2 - 1 = 0 \quad (4.41)$$

$$\lambda_e^T = \lambda_e^{\frac{-1}{2}}(\mathbf{r}; \mathbf{F}^c) \quad (4.42)$$

And for the case of stationary points of the cross-sectional stretch λ_e^T ,

$$\frac{\partial \Pi}{\partial \lambda_e^T} = 0 \quad (4.43)$$

$$\mu \lambda_e^T - p_e \lambda_e(\mathbf{r}; \mathbf{F}^c) \lambda_e^T = 0 \quad (4.44)$$

$$p_e = \frac{\mu}{\lambda_e(\mathbf{r}; \mathbf{F}^c)} \quad (4.45)$$

which implies that transverse stretch and pressure can be solved at the element level in terms of displacements $\mathbf{r}$, a dependance that is expressed as $\mathbf{l} = \mathbf{l}(\mathbf{r}; \mathbf{F}^c)$ and $\mathbf{p} = \mathbf{p}(\mathbf{r}; \mathbf{F}^c)$. Thus, inserting equations (4.42) and (4.45) into equation (4.46), leads to the effective minimization problem

$$\min_{\mathbf{r} \in \mathbb{R}^3} \Pi^{eff}(\mathbf{r}, \mathbf{F}^c) \quad (4.46)$$

where

$$\Pi^{eff}(\mathbf{r}; \mathbf{F}^c) = \sum_{e=1}^{18} \frac{\mu}{2} A_o L_{e_o} \left(\lambda_e^2 + \frac{2}{\lambda_e} - 3 \right) + \sum_{j \in \mathcal{J}} \frac{1}{2} k_\theta \left\{ \frac{\mathbf{q}_{j_1} \cdot \mathbf{q}_{j_2}}{\|\mathbf{q}_{j_1}\| \|\mathbf{q}_{j_2}\|} - \frac{\mathbf{Q}_{j_1} \cdot \mathbf{Q}_{j_2}}{\|\mathbf{Q}_{j_1}\| \|\mathbf{Q}_{j_2}\|} \right\}^2 \quad (4.47)$$

Now, it is of interest relating A_o with physical parameters of lung parenchyma. Let $\|\Theta_Y\|$ be the total volume of the unit cell in the reference configuration, and $\|\Theta_{Y_s}\|$ be the solid phase volume, such that the TKD volume fraction f_o is defined by

$$f_o \equiv 1 - \frac{\|\Theta_{Y_s}\|}{\|\Theta_Y\|} \quad (4.48)$$

Following (Warren & Kraynik, 1997), in the sequel it will be considered that $\|\Theta_Y\| = 64\sqrt{2}\delta^3$, which is based on the fact that the present micromechanical model is scale-invariant. Assuming that all elements have the same the initial cross section A_o , it is written

$$|\Theta_{Y_s}| = (1 - f_o)|\Theta_Y| = A_o L_T \quad (4.49)$$

where L_T is the total effective length of the TKDr in the reference configuration. Noting that the TKDr has six elements with $L_{e_o} = 2\delta$ (elements 1 to 6) and twelve elements with

$L_{e_o} = \delta$ (elements 7 to 18), it follows that

$$L_T = 24\delta - L_{OL} \quad (4.50)$$

where L_{OL} is the total element overlap length from the element connections, which is subtracted to avoid volume duplication (Wang & Cuitiño, 2000). To estimate L_{OL} , the lung parenchyma microstructure is analyzed. As shown in Figure 4.4, elastin and collagen fibers are disposed in a network such that alveolar walls are assumed to have a rod-like shape in the central region and a tapered portion towards the junction with other walls, condition that is accentuated whether the lung is inflated or not (Figure 4.4). It will be assumed that regions with the tapered shape are the ones that overlap when connected, leaving the central zones as the purely connective tissue. Noting that there are six element joints for the TKDr (nodes 1 to 6), and that at each joint there are four connecting element, it is used that

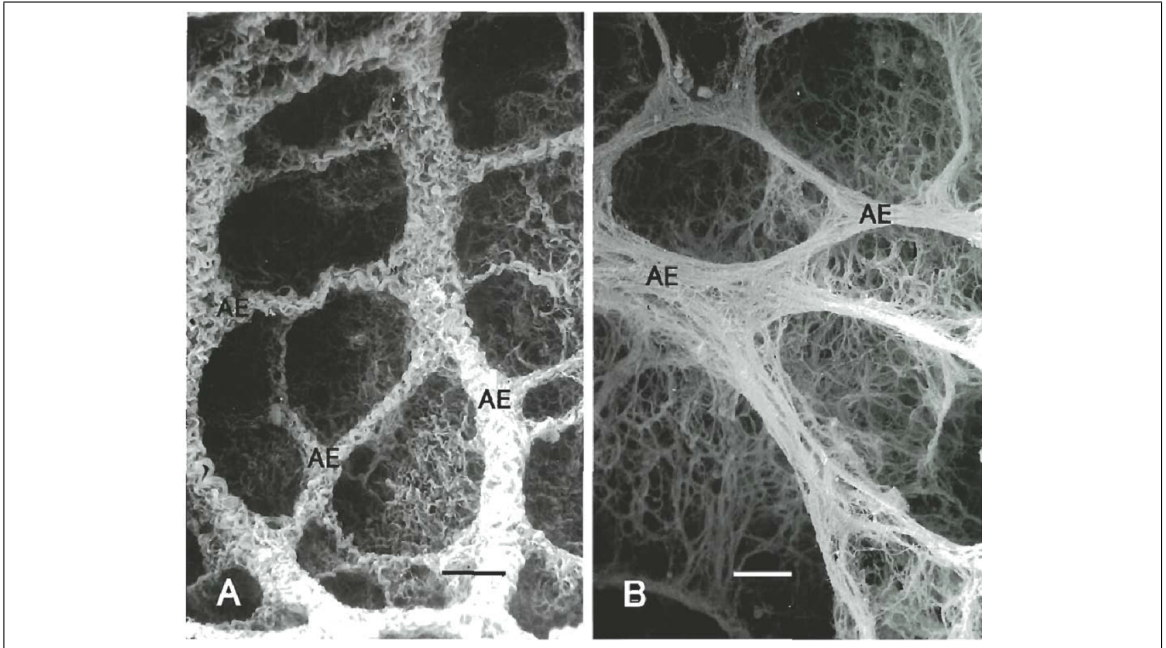


Figure 4.4. Collagen fibers in the lung microstructure. (AE): collagen fibers at the alveolar entrances for a collapsed lung (image A) and for an inflated lung (image B). Figure taken from (Toshima et al., 2004).

$$L_{OL} = 6 \times 3\delta \times d \quad (4.51)$$

$$= 18\delta d \quad (4.52)$$

where the ratio d corresponds to the first model parameter and represents the fraction of the strut duplicated by overlapping. Combining (4.49), (4.50) and (4.52), the cross-sectional area takes the form

$$A_o = \frac{32\sqrt{2}(1 - f_o)\delta^2}{12 - 9d} \quad (4.53)$$

Parameter d can be understood as the inclusion of the specific geometry data related to fiber network and therefore the inflation state in which the lung is. The more inflated the lung, the more the fibers are stretched, the shorter is the tapered region and the smaller are the proportional overlapping length and parameter d . So, in this line, the TKD model incorporates not only the shape, but also the initial microstructural connectivity, which improves the accuracy of its mechanical response prediction.

For the case of bending energy, it is assumed that $k_\theta = \alpha \frac{EI}{2\delta}$ where I is the inertia of a solid circular section with area A_o , which is computed as $I = \frac{A_o^2}{4\pi}$, and α is a second model parameter to be fixed. Thus, the following expression can be obtained which demonstrates the contribution of each model material and model parameter

$$k_\theta = \alpha \frac{EI}{2\delta} = \frac{768\delta^3}{\pi} \frac{\alpha\mu(1 - f_o)^2}{(12 - 9d)^2} \quad (4.54)$$

Once the TKDr model is solved, it will concern the stress averaging in the unit cell to determine the macroscopic stress tensor σ^c as defined by equation (3.60)

$$\sigma^c = \frac{1}{|\Theta_y|} \int_{\Theta_y} \sigma^f d\Theta_y = \frac{1}{|\Theta_y|} \int_{\Theta_{ys}} \sigma^f d\Theta_{ys} = \frac{1}{|\Theta_y|} \int_{\partial\Theta_y} \mathbf{t}^f \otimes \mathbf{y} d\partial\Theta_y \quad (4.55)$$

where $\mathbf{t}^f$ is the fine-scale traction vector on the solid surface and $\mathbf{y}$ is the current position of $\mathbf{t}^f$. Using that the TKDr unit cell surface matches the strut midpoints (Warren & Kraynik,

1997), equation (4.55) can be replaced by a discrete form as

$$\boldsymbol{\sigma}^c = \frac{1}{|\Theta_y|} \sum_{e=7}^{18} \mathbf{f}_e \otimes \mathbf{y}_e = \frac{1}{J^c |\Theta_Y|} \sum_{e=7}^{18} \mathbf{f}_e \otimes \mathbf{y}_e = \frac{1-f_o}{J^c |\Theta_{Y_s}|} \sum_{e=7}^{18} \mathbf{f}_e \otimes \mathbf{y}_e \quad (4.56)$$

where the current volume of the TKDr unit cell is computed as $|\Theta_y| = J^c |\Theta_Y|$ and where J^c is the determinant of $\mathbf{F}^c$. It is important to notice that term $\frac{1-f_o}{J^c |\Theta_{Y_s}|}$ incorporates to the TKD model the microstructure evolution, which has been found to be relevant for the accuracy of multi-scale models (Lopez-Pamies & Castañeda, 2007). Furthermore, equation (4.56) can be reduced by means of periodicity, using that struts lying in equivalent faces have same force magnitudes but opposed directions, besides of the fact that distance between equivalent nodes in opposed faces corresponds to a lattice vector. Then, the final equation for the coarse-scale stress tensor is

$$\boldsymbol{\sigma}^c = \frac{2}{|\Theta_y|} (\mathbf{f}_7 \otimes \mathbf{F}^c \mathbf{b}_x + \mathbf{f}_{10} \otimes \mathbf{F}^c \mathbf{b}_y + \mathbf{f}_{15} \otimes \mathbf{F}^c \mathbf{b}_z) \quad (4.57)$$

Finally, to compute the axial forces $\mathbf{f}_e$ on the elements $e = \{1...18\}$ belonging to the TKDr, it is used that

$$\|\mathbf{f}_e\| = \mu A_e (\lambda_e^2 - \lambda_e^{-1}) \quad (4.58)$$

$$A_e = \frac{A_o}{\lambda_e} \quad (4.59)$$

where A_e is the current strut cross-section area obtained by means of the Nanon's formula.

5. REPRESENTATIVE VOLUME ELEMENT COMPUTATIONAL MODELS

5.1. Lung microstructure acquisition

Micro-CT images were experimentally acquired using adults male Sprague-Dawley rats in healthy condition under a conventional diet, with a mass of approximately 300 grams each one. The specimens were first anaesthetized following international guidelines given by American Veterinary Medical Association (AVMA) and then killed via exsanguination through an incision in the vena cava. Furthermore, the drained blood and several other organs were used for other experiments. Then, the lungs were carefully extracted from the thorax in order to preserve them. The organs were fixed using a formalin buffered saline solution at 10 (p_A) and 20 (p_B) centimeters of H_2O of pressure and were kept into the fixation solution for at least 7 days (Parameswaran et al., 2009). In order to dry the organs and maintain their morphology for posterior measures, a desiccating process was performed based in graduating ethanol baths. First, the lung was inserted into a 50% ethanol and 50% PBS solution and maintained for 1 hour. Later the ethanol was gradually increased (60%, 70%, 80% and 90%), using the same procedure as before, until reaching 100% ethanol bath, then this last solution was maintained overnight (Dudak et al., 2016)(Scotton et al., 2013). Finally, before micro-CT imaging, the lung was drying at atmospheric conditions for 1 day in order to evaporate all the remnant ethanol.

Once the lungs were fixed, it was possible to perform micro-CT imaging process. The lungs were placed in a specialized sample holder into the commercial micro-CT model SkyScan 1272 from Bruker. The equipment possesses an X-ray source that operates at 10 kV and 250 μA , then the tomography cuts were acquired with resolutions of 2.72 μm , taking about four hours. Using the software NRecon, from Bruker, it was possible to reconstruct the 3D geometries of selected cuboid regions in the lung parenchyma, with an edge size of 0.5 mm. The reconstruction was performed taking in consideration the hardening and ring effects. With the software CTan, from Bruker also, the images were pre-treated using median and unsharp filters in order to reduce noise and enhance the

contrast, respectively. A three-dimensional view of the image reconstruction can be seen in Figure 5.1.

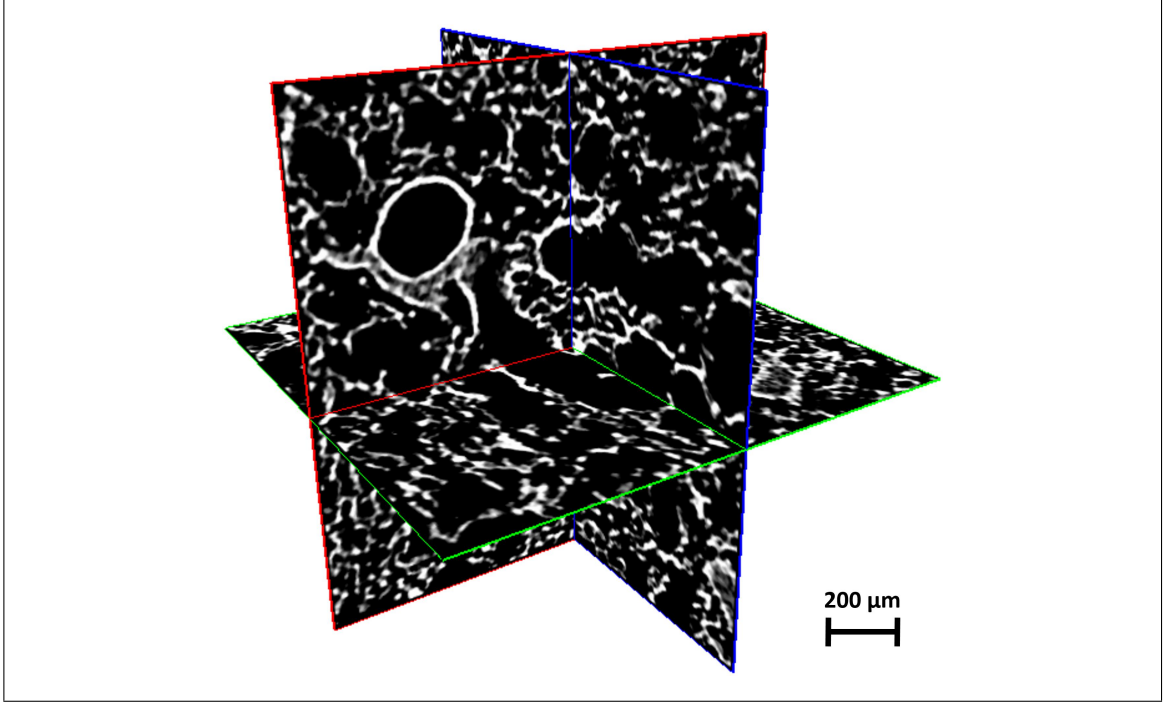


Figure 5.1. Three dimensional reconstruction of alveolar walls from micro-CT.

5.2. Representative volume element modeling

Two lung microstructures, at inflation pressures p_A and p_B were reconstructed and analyzed to study and compare its mechanical behavior with the proposed TKD model in order to assess its accuracy. For this purpose, micro-CT images obtained from the procedure detailed above were stacked in order to build 3D binary images. Since the computational cost of modeling the complete lung microstructure is huge, only certain regions of the reconstructed three-dimensional lungs were chosen to be modeled, ensuring a heterogeneous selection beside of a reasonable size choice such that it was as small as possible to reduce computational cost but as large as possible to accomplish convergence of coarse-scale properties. Regions were meshed with 10 nodes quadratic tetrahedron using the software ABAQUS version 6.14, creating finite element meshes as the one observed

at Figure 5.2. Since their purpose was to be representative of the mechanical behavior of the lung microstructure, hereinafter they will be called as representative volume elements (RVEs). For clarity, RVE is the complete “cubic” structure formed by the tissue and voids that surrounds the irregular green mesh being lung tissue. Using fine-scale notations, RVE domain is given by Θ_Y and lung tissue domain corresponds to Θ_{Y_s} as can be seen in Figure 5.3.

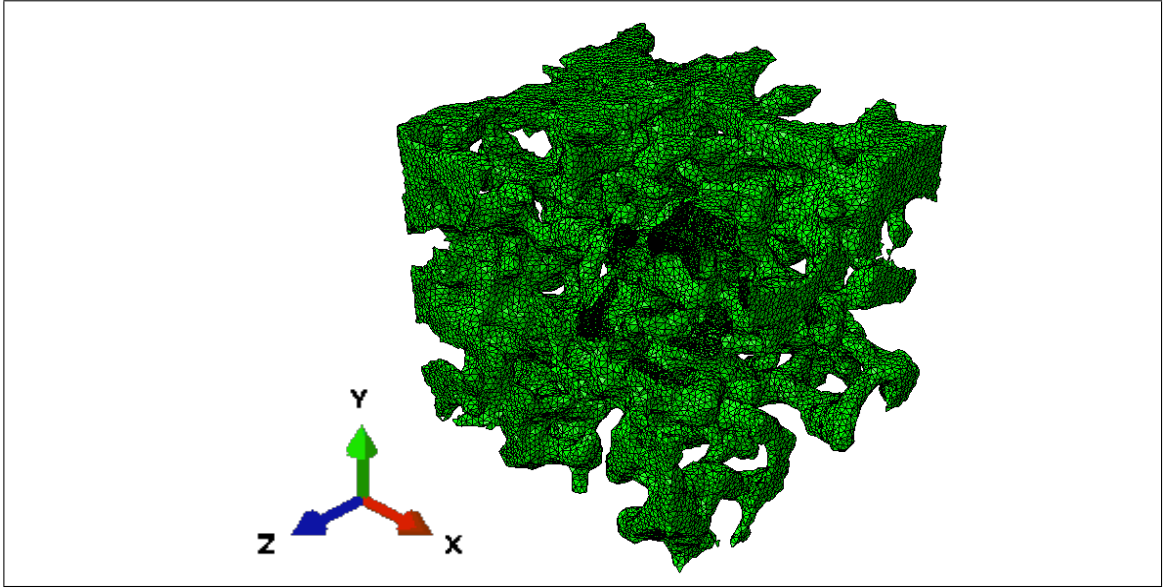


Figure 5.2. RVE corresponding to test 2 for pressure p_B in the reference configuration.

Several RVEs were created and numerically tested. Since they were obtained from different locations of two inflated lungs, they have different volume fractions and they were also meshed with different number of elements. Table 5.1, Table 5.2 and Table 5.3 summary those informations for each RVE for both lungs. It is important to consider that data correspondending to Table 5.3 has been used only for results presented in Figure 6.17 referent to analysis of mesh size, since the number of elements used there was significantly different.

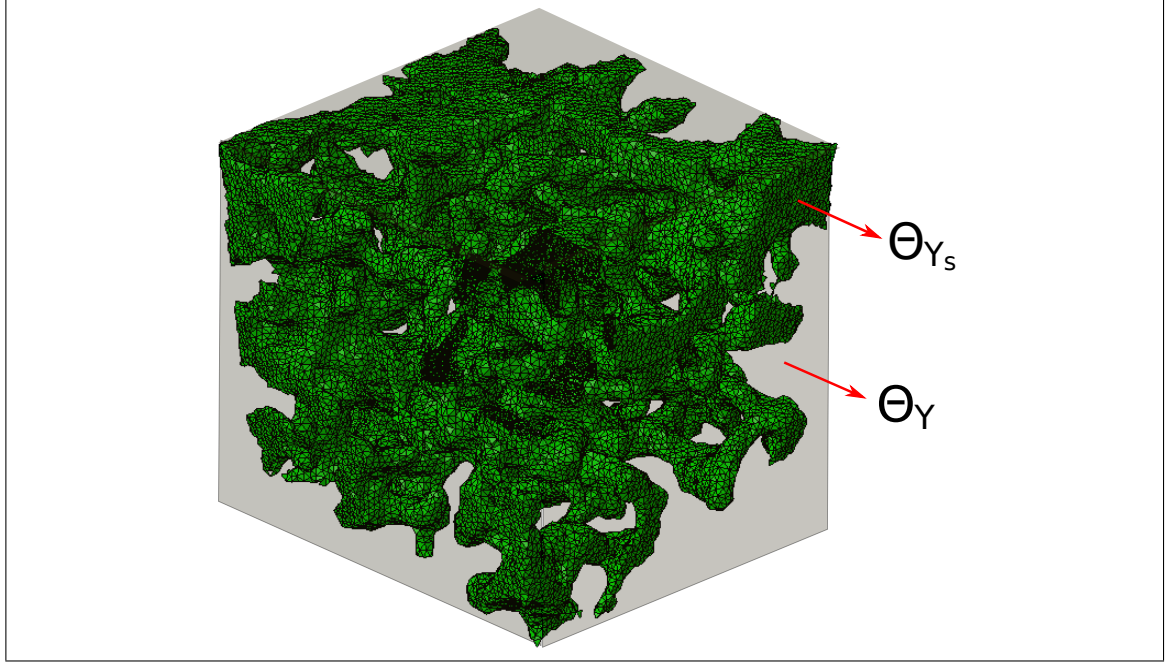


Figure 5.3. Fine-scale domains. In grey, “cubic” shape of RVE domain Θ_Y at the reference configuration. In green, lung tissue domain Θ_{Y_s} at the reference configuration.

Table 5.1. Geometric information for RVEs obtained from lung subjected to pressure p_A .

Data	Test 1	Test 2	Test 3	Test 4	Test5	Test 6
Volume fraction $\frac{V_v}{V_t}$	0.64	0.65	0.65	0.64	0.65	0.65
Side length [μm]	198.56	198.56	198.56	198.56	198.56	198.56
Number of elements	411,943	402,321	401,283	404,339	399,307	396,643

Table 5.2. Geometric information for RVEs obtained from lung subjected to pressure p_B .

Data	Test 2	Test 3	Test 4	Test5	Test 6	Test 7
Volume fraction $\frac{V_v}{V_t}$	0.72	0.72	0.71	0.73	0.71	0.72
Side length [μm]	149.6	149.6	198.56	198.56	198.56	198.56
Number of elements	379,919	378,181	456,927	449,088	483,943	466,671

Table 5.3. Geometric information for RVE obtained from lung subjected to pressure p_B . Data for large RVE mesh.

Data	Test 6b
Volume fraction $\frac{V_v}{V_t}$	0.71
Side length [μm]	198.56
Number of elements	2,250,192

An incompressible NeoHookean material model was assumed for all RVE models, with a Lamé constant set equal to $\mu \approx 1.66$ KPa according to the experimental values reported for the Young modulus in (Cavalcante et al., 2005), the incompressibility condition yielding $\nu = 0.495$ and the relation $\mu = \frac{E}{2(1+\nu)}$. A mixed displacement-pressure ($u - p$) formulation was considered for all simulations using P2-P0 tetrahedral elements, to avoid volumetric locking. Displacement boundary conditions were prescribed at the boundary of RVEs, with displacement values determined from the imposed coarse-scale deformation-gradient tensor as dictated by (3.71). The coarse-scale deformation gradient F^c was assumed to take the principal stretch form of (4.6). Four different loading conditions were analyzed: isotropic expansion, anisotropic expansion, equibiaxial stretching, and uniaxial stretching. In all cases, simulations using a monotonically increasing loading pattern were performed with up to forty steps. Table 5.4 reports the values for the maximum principal stretch values reached by each simulation. The isotropic expansion case corresponds to a volumetric dilation of 250%, which can be observed in normal human lungs under forced inspiration (Hurtado et al., 2017). The anisotropic volumetric expansion case was selected for being a real lung deformation state according to the work of Amelon et al. (Amelon et al., 2011), who found distribution maps of lung deformation indices. In their work, using approximate mean quantities, values of jacobian, ADI and SRI were selected to be 1.7, 0.4 and 0.5 respectively, which corresponds to principal stretches equals to 1.53, 1.19 and 0.93. Since in this work only stretches larger than 1.0 have been used, an anisotropic deformation state was considered maintaining the relation of approximately 1.3 between $\lambda_1^c - \lambda_2^c$ and $\lambda_2^c - \lambda_3^c$ but using $\lambda_3^c = 1.0$ instead of 0.93. Then, $\lambda_1^c = 1.7$ and $\lambda_2^c = 1.3$ were also used. To divide this deformation state into several steps

and roughly maintain an anisotropic relation between struts, λ_3^c was kept equal to 1 and λ_1^c and λ_2^c evolved according to $\lambda_1^c = \lambda_2^{c^2}$.

Table 5.4. Target principal stretches for each displacement pattern.

Loading case	λ_1^c	λ_2^c	λ_3^c
Isotropic volumetric	1.357	1.357	1.357
Anisotropic volumetric	1.700	1.300	1.000
Equibiaxial stretching	1.500	1.500	1.000
Uniaxial stretching	1.800	1.000	1.000

Non-linear finite element analyses were performed for all combinations of RVEs and loading cases driven by $\mathbf{F}^c$, computing for each simulation step $\boldsymbol{\sigma}^f$ and $\mathbf{F}^f$ fields. Hence, coarse-scale stresses $\boldsymbol{\sigma}^c$ were obtained by applying equation (3.60) on the whole domain of the RVE, which in terms of a finite element approach is given by

$$|\Theta_{Y_s}| = \sum_{e=1}^{N_e} \sum_{q=1}^{N_q} J_{e_q}^f(\mathbf{y}) w_q \quad (5.1)$$

$$|\Theta_y| = J^c |\Theta_Y| = \frac{J^c |\Theta_{Y_s}|}{1 - f_o} \quad (5.2)$$

$$\boldsymbol{\sigma}^c = \frac{1}{|\Theta_y|} \sum_{e=1}^{N_e} \sum_{q=1}^{N_q} \boldsymbol{\sigma}_{e_q}^f(\mathbf{y}) J_{e_q}^f(\mathbf{y}) w_l \quad (5.3)$$

where it has been used that N_e is the number of elements of the mesh as long as N_q is the number of quadrature points used for each element. Moreover, $J_{e_q}^f$ and $\boldsymbol{\sigma}_{e_q}^f$ are the discrete values of jacobian and Cauchy stress tensor at the fine-scale computed for the quadrature point q of the element e .

6. MODEL VALIDATION

From the RVE models under the deformation patterns exposed in Table 5.4, heterogeneous stress fields were obtained. To have an idea about how do they look like, the hydrostatic pressure distribution of an RVE sample can be seen in Figure 6.1 where stresses are shown in the current configuration under isotropic expansion. For clarity, fine-scale hydrostatic pressure is defined as

$$p_{hydro}^f = -\frac{1}{3}\text{tr } \sigma^f \quad (6.1)$$

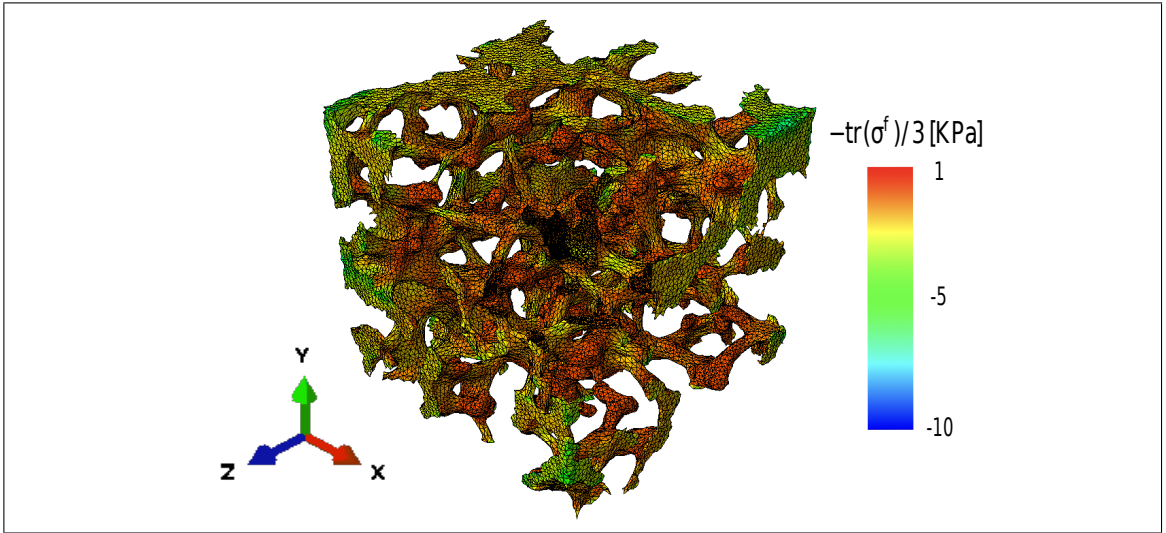


Figure 6.1. RVE corresponding to test 2 for pressure p_B in the current configuration. Color map shown corresponds to the hydrostatic pressure field computed as p_{hydro}^f . Statistically insignificant data has been omitted for the sake of clarity.

For the same sample, Von Misses stress field is shown in Figure 6.2. Also, as an example of the deformed RVE under the anisotropic deformation state, Figure 6.3 shows the Von Misses stress field in the current configuration of sample for test 4 in the lung at pressure p_A under anisotropic volumetric expansion

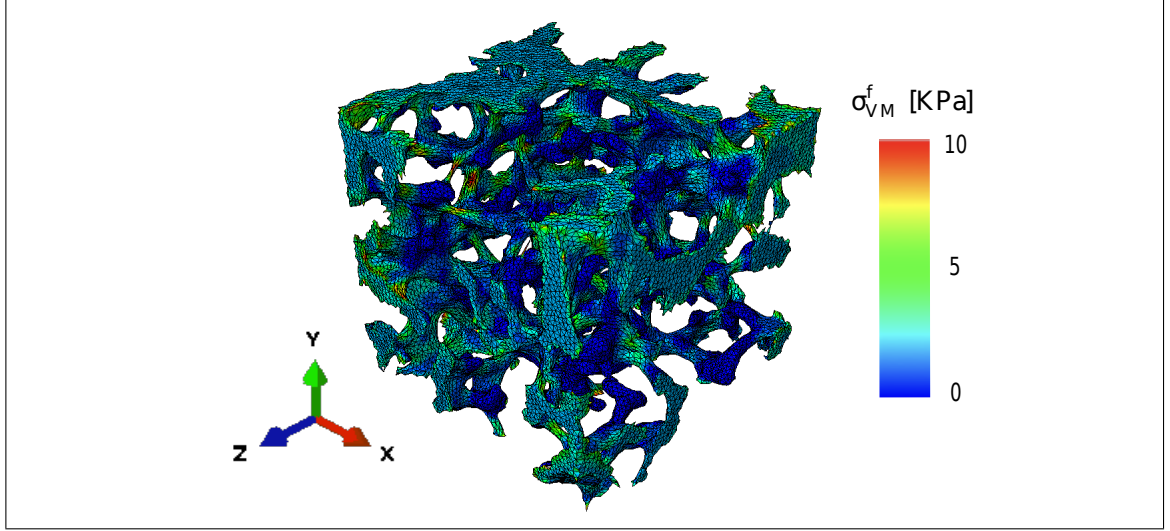


Figure 6.2. RVE corresponding to test 2 for pressure p_B in the current configuration under an isotropic deformation pattern. Color map shown corresponds to the Von Mises stress field. Statistically insignificant data has been omitted for the sake of clarity.

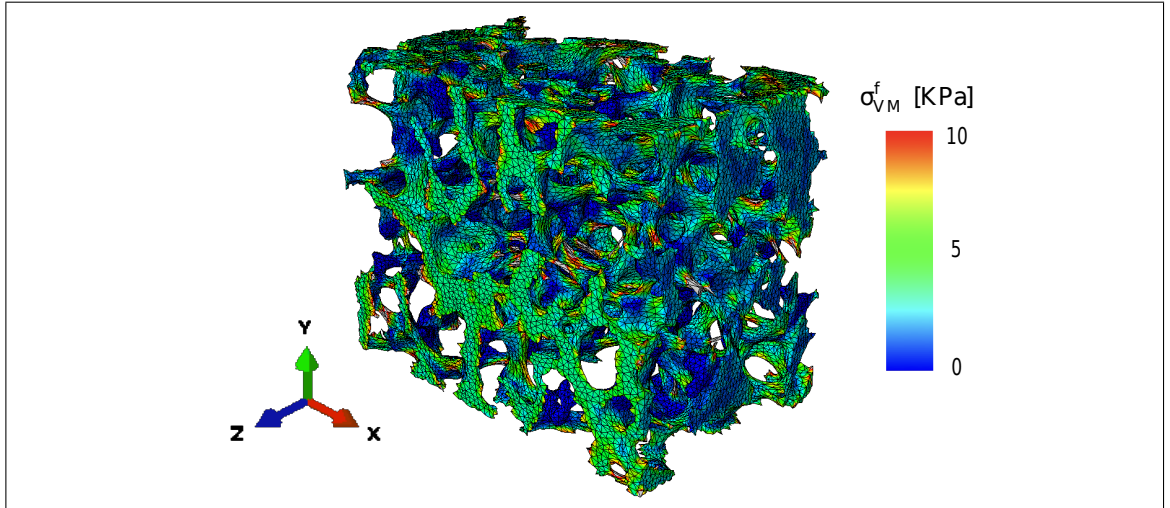


Figure 6.3. RVE corresponding to test 4 for pressure p_A in the current configuration under the anisotropic deformation pattern. Color map shown corresponds to the Von Mises stress field. Statistically insignificant data has been omitted for the sake of clarity.

It can be seen that heterogeneous responses are obtained, which extends to all fields of interest, denoting the importance about the use of averaged fields for the sake of multi-scale simulations. In this line, the developed TKD model has the main purpose of returning

the same averaged response under the deformation patterns applied. To assess its performance, coarse-scale σ^c - F^c relation for the TKD model has to be compared against direct numerical simulations performed on RVEs. To this end, first step consist on finding the optimal values for the TKD model parameters d, α , procedure that has been carried out by means of a sensitivity analysis. In this line, two sensitivity analysis were conducted depending on the case of inflation pressure used, p_A or p_B . Then, each analysis consist on obtaining $\sigma^c - F^c$ curves for several values of d and k_θ under the four displacement patterns test in this work. k_θ was used instead of α due to it enables to include the whole effect of rotation, which is not achieved only by α due to k_θ is function of both d and α . Tested parameters for each inflation case are summarized in Table 6.1 and Table 6.2

Table 6.1. Tested parameters for sensitivity analysis for inflation pressure p_A

Model parameter	tested value 1	tested value 2	tested value 3
d	0.6	0.65	0.7
k_θ	0.0	0.1	0.15

Table 6.2. Tested parameters for sensitivity analysis for inflation pressure p_B

Model parameter	tested value 1	tested value 2	tested value 3
d	0.0	0.2	0.45
k_θ	0.0	0.025	0.05

Note that each sensitivity analysis included has used different values for d and k_θ due to the mechanical behavior of microstructures obtained for inflation cases p_A, p_B were different. For clarity, results for both sensitivity analysis under each displacement pattern can be found in Appendix G. Furthermore, optimal values were found for d, k_θ and then for d, α , which are presented in Table 6.3.

Note that α has been considered as constant but d varies according to the volume fraction, since it arises from a physiological condition of fiber extension which depends on the inflation level of the lung microstructure. Using the optimal TKD model parameters,

Table 6.3. Optimal TKD model parameters

f_o	d	α
<0.7	0.7	6
≥ 0.7	0.42	6

results for the TKD model - RVEs comparison were obtained and can be seen in Figures 6.4 - 6.11. For all cases, results are shown for different levels of λ_1^c , since it was the only coarse-scale stretch different to 1 for all tests. Furthermore, stress values were normalized by μ with the purpose of obtaining dimensionless results useful for comparison with several kind of foam structures. As a visual demonstration of the TKD model, deformed configurations for the case p_B under each deformation pattern are shown in Figure 6.12.

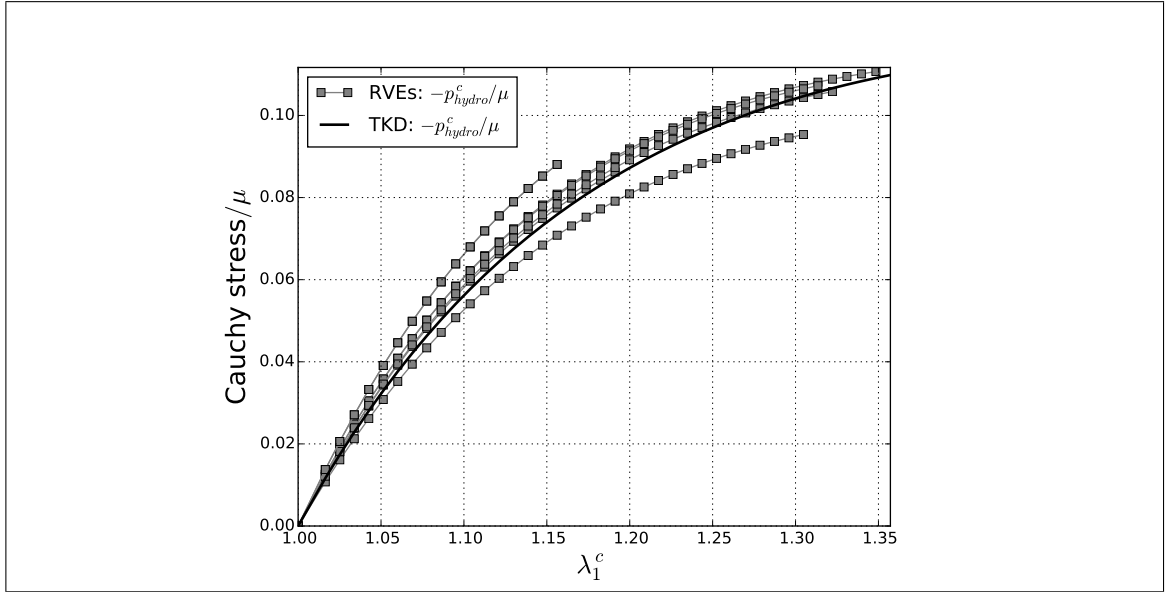


Figure 6.4. $\text{tr } \boldsymbol{\sigma}^c / 3\mu - \lambda_1^c$ relation for isotropic volumetric expansion on RVEs models (gray square markers) and TKD model (black continuous lines). Results shown for lung inflated at pressure p_A

As an extra validation of the TKD model performance, the stress-free uniaxial elongation behavior was studied and compared against results obtained by Cavalcante et al. (Cavalcante et al., 2005). Despite of the volume fraction used by Cavalcante is uncertain, comparison was performed with respect to three different volume fractions given by

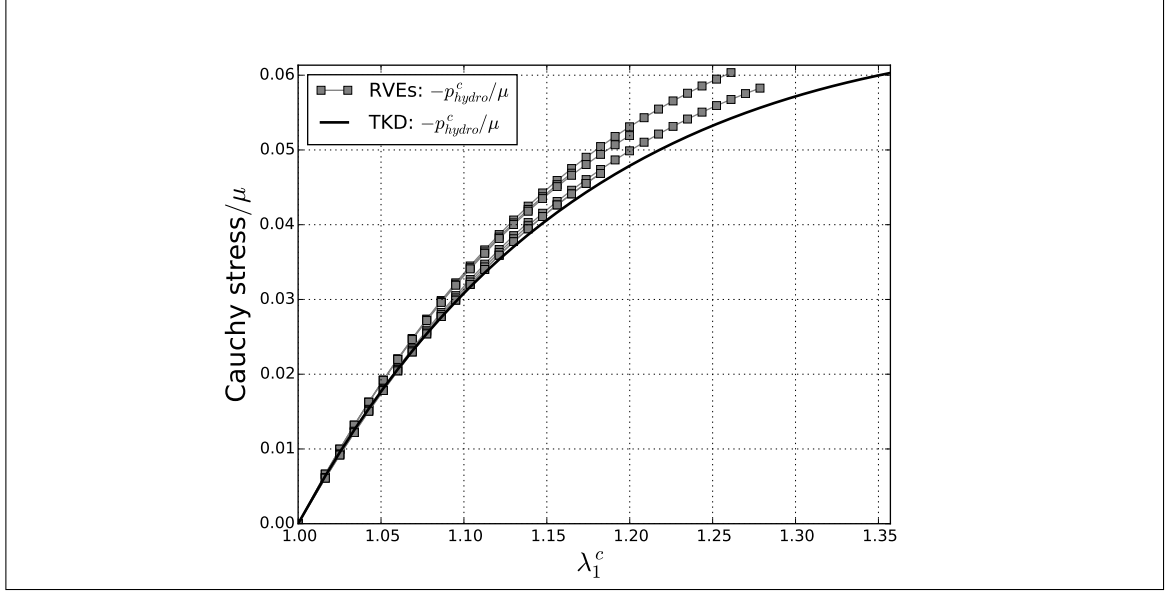


Figure 6.5. $\text{tr } \sigma^c / 3\mu - \lambda_1^c$ relation for isotropic volumetric expansion on RVEs models (gray square markers) and TKD model (black continuous lines). Results shown for lung inflated at pressure p_B .

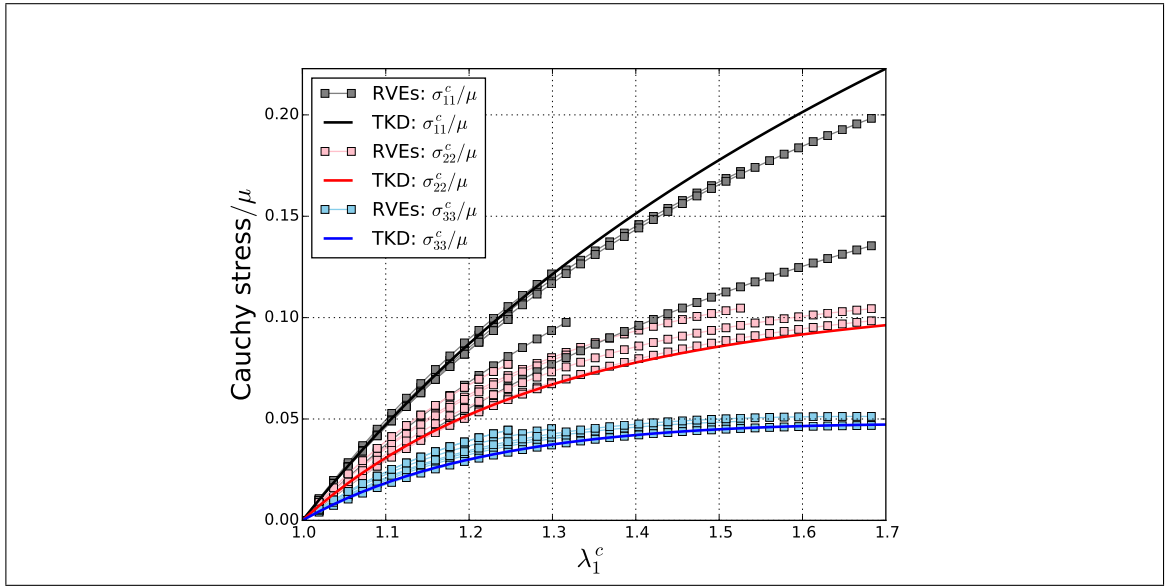


Figure 6.6. $\sigma_{11}^c / \mu - \lambda_1^c$, $\sigma_{22}^c / \mu - \lambda_1^c$ and $\sigma_{33}^c / \mu - \lambda_1^c$ relations for anisotropic volumetric expansion on RVEs models (gray, pink and skyblue square markers respectively) and TKD model (black, red and blue continuous lines respectively). Results shown for lung inflated at pressure p_A .

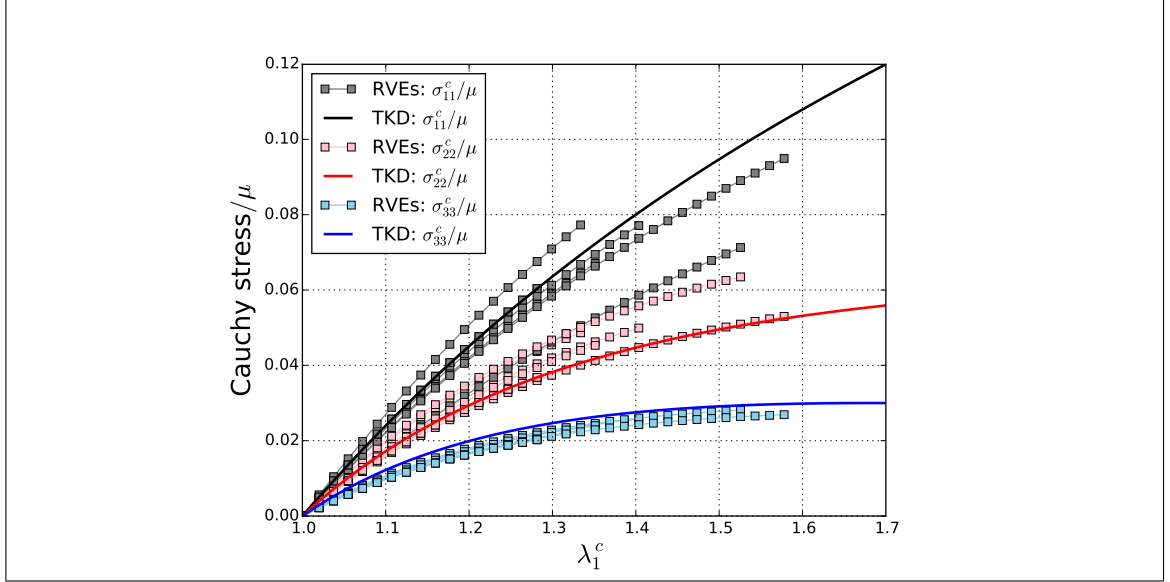


Figure 6.7. $\sigma_{11}^c/\mu-\lambda_1^c$, $\sigma_{22}^c/\mu-\lambda_1^c$ and $\sigma_{33}^c/\mu-\lambda_1^c$ relations for anisotropic volumetric expansion on RVEs models (gray, pink and skyblue square markers respectively) and TKD model (black, red and blue continuous lines respectively). Results shown for lung inflated at pressure p_B .

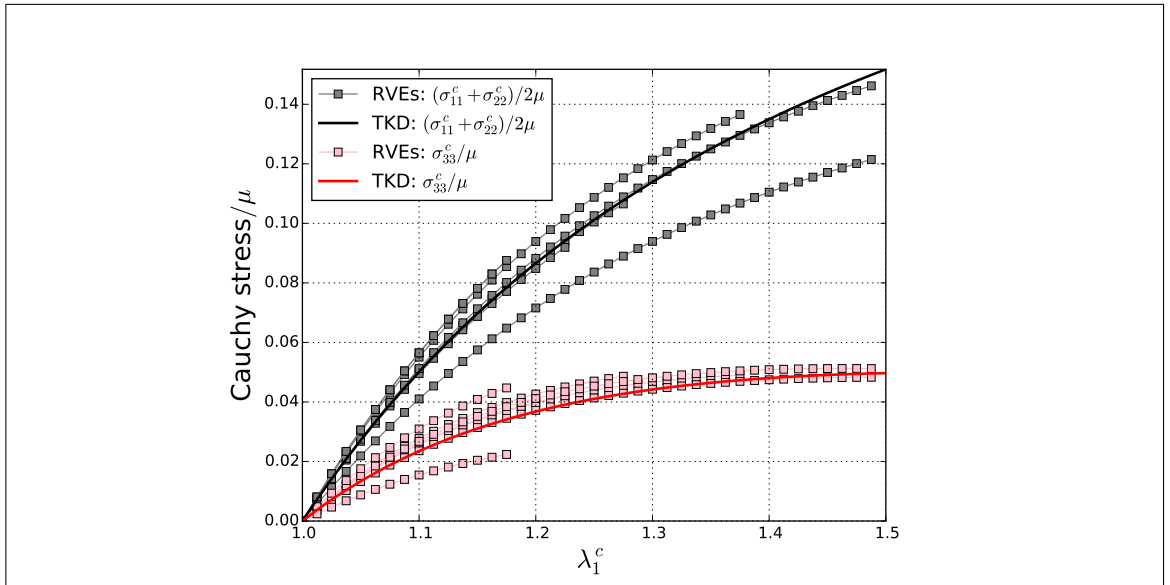


Figure 6.8. $(\sigma_{11}^c + \sigma_{22}^c)/2\mu-\lambda_1^c$ and $\sigma_{33}^c/\mu-\lambda_1^c$ relations for biaxial elongation on RVEs models (gray and pink square markers respectively) and TKD models (black and red continuous lines respectively). Results shown for lung inflated at pressure p_A .

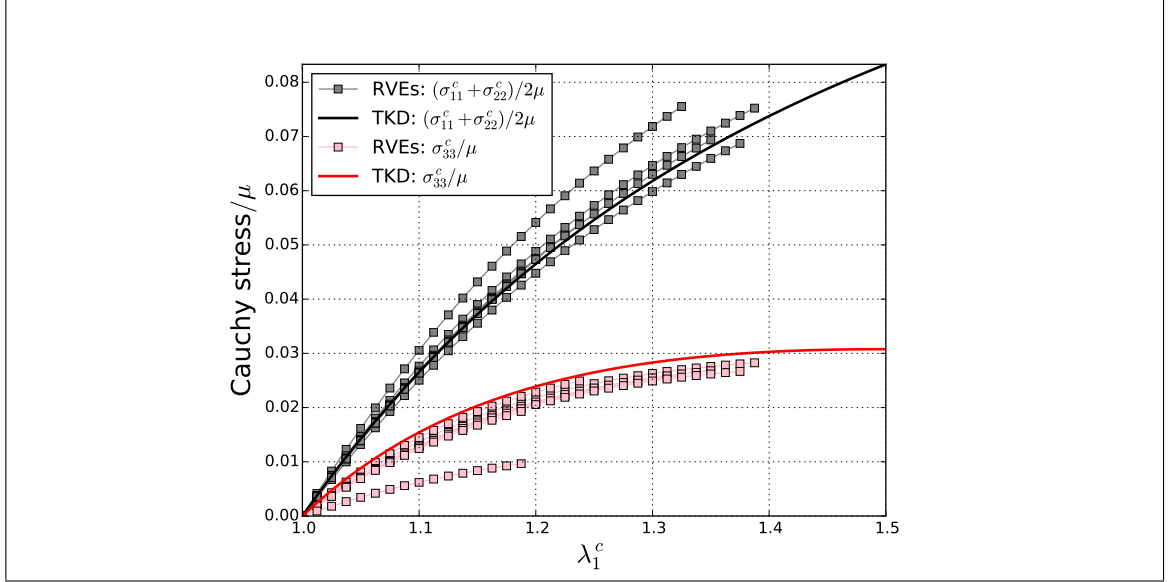


Figure 6.9. $(\sigma_{11}^c + \sigma_{22}^c)/2\mu - \lambda_1^c$ and $\sigma_{33}^c/\mu - \lambda_1^c$ relations for biaxial deformation on RVEs models (gray and pink square markers respectively) and TKD models (black and red continuous lines respectively). Results shown for lung inflated at pressure p_B .

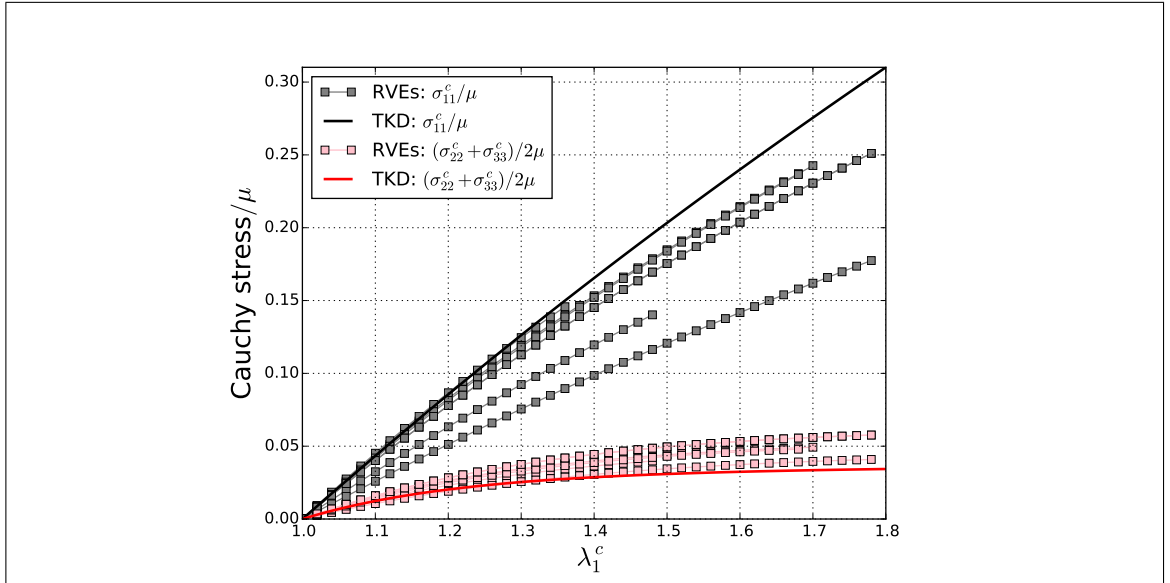


Figure 6.10. $\sigma_{11}^c/\mu - \lambda_1^c$ and $(\sigma_{22}^c + \sigma_{33}^c)/2\mu - \lambda_1^c$ relations for uniaxial deformation on RVEs models (gray and pink square markers respectively) and TKD models (black and red continuous lines respectively). Results shown for lung inflated at pressure p_A .

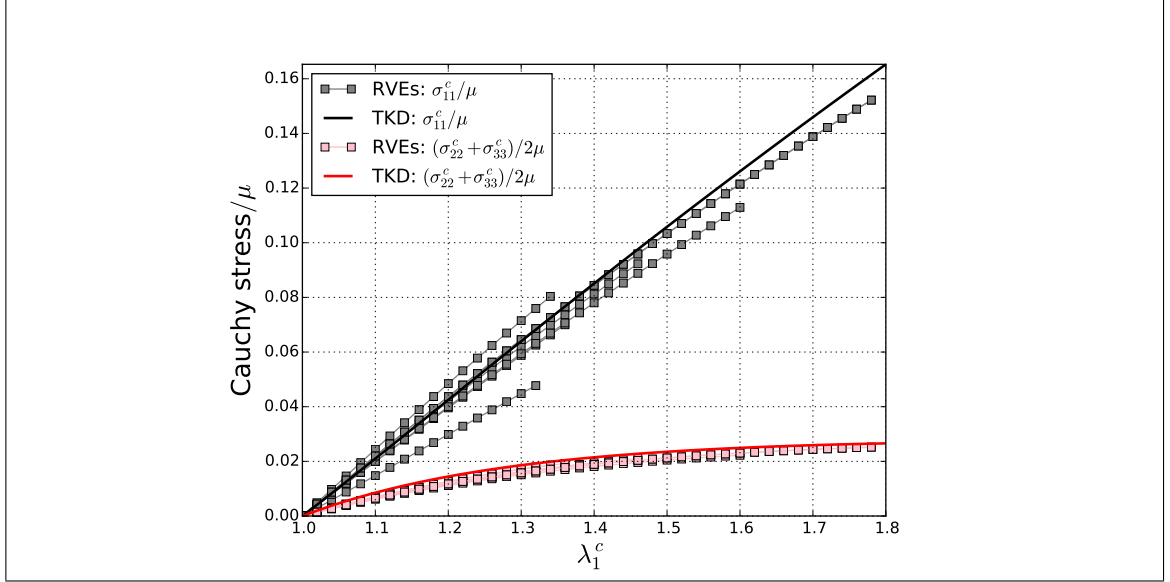


Figure 6.11. σ_{11}^c/μ - λ_1^c and $(\sigma_{22}^c + \sigma_{33}^c)/2\mu$ - λ_1^c relations for uniaxial deformation on RVEs models (gray and pink square markers respectively) and TKD models (black and red continuous lines respectively). Results shown for lung inflated at pressure p_B .

$f_o = 0.64$, $f_o = 0.68$ and $f_o = 0.72$, that are reasonable values for the lung parenchyma. Stress comparison between uniaxial behaviors can be seen in Figure 6.13, as long as, the coarse-scale Poisson effect obtained by the TKD model can be found in Figure 6.14. Results have used values of d, α defined in Table 6.3 according to the used volume fraction.

Leaving behind the mechanical response of the TKD model, an specific analysis was carried out for the RVEs under isotropic volumetric expansion, with the purpose of evaluating the isotropy of the lung microstructure. In this deformation pattern, same coarse-scale stretches $\lambda_1^c, \lambda_2^c, \lambda_3^c$ were applied for all directions and then, coarse-scale stresses $\sigma_{11}^c, \sigma_{22}^c, \sigma_{33}^c$ were independently studied. Results are shown in Figures 6.15 and 6.16 for normalized values of stresses and several values of $\lambda_1^c = \lambda_2^c = \lambda_3^c$. Not negligible differences were found for normalized coarse-scale stresses denoting an anisotropic behavior of the lung parenchyma.

Finally, It was also interesting to study the convergence of the obtained results for finer meshes. Although convergence test should be performed for each RVE sample under

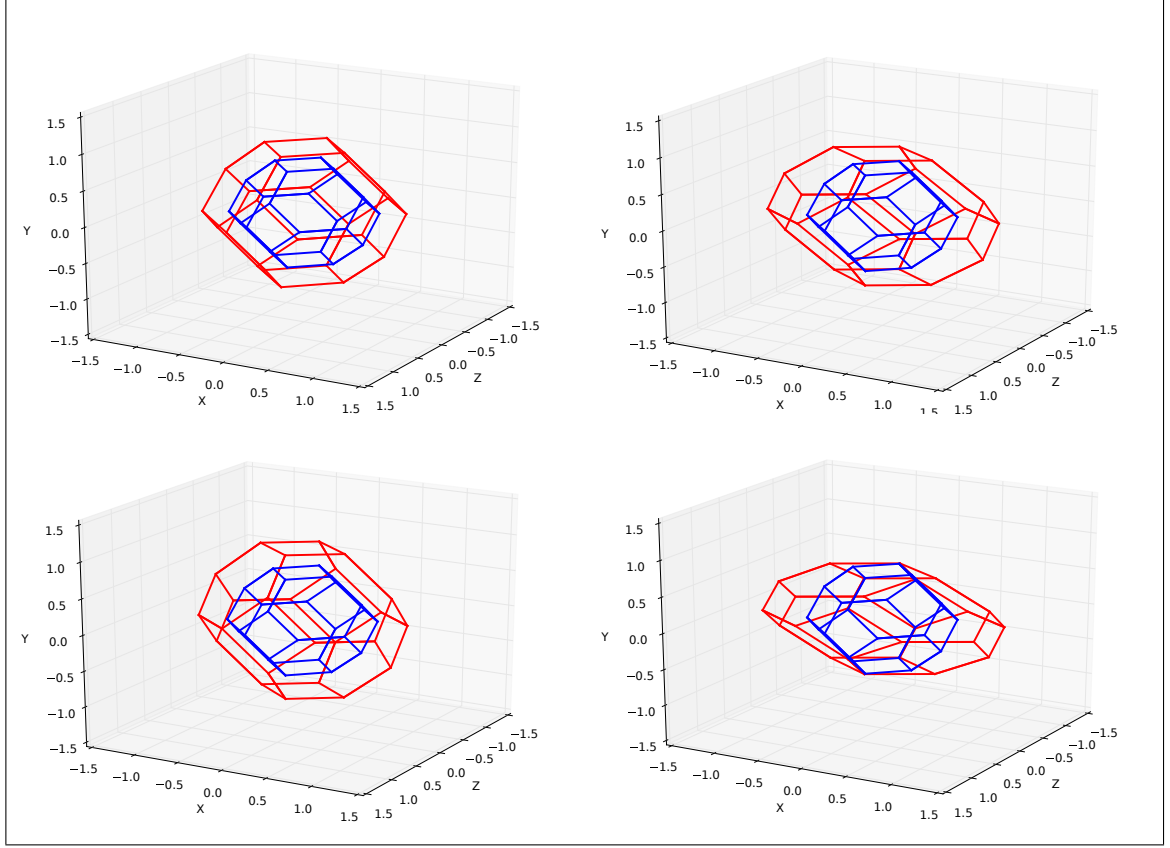


Figure 6.12. Current configurations of TKD model under final steps of isotropic volumetric expansion (upper left), anisotropic volumetric expansion (upper right), biaxial elongation (lower left) and uniaxial elongation (lower right). In blue, the reference configurations; in red, the current configurations. Results shown for lung inflated at pressure p_B .

every load patterns, in this work only test 6 for pressure p_B under anisotropic volumetric expansion was studied due to computational limitations. It was compared against test 8 for pressure p_B which has exactly the same geometry with the same volume fraction beside of having a refined mesh that includes more than two million of finite elements. Thus, $\sigma^c - F^c$ curves were compared, obtaining the following results shown in Figure 6.17.

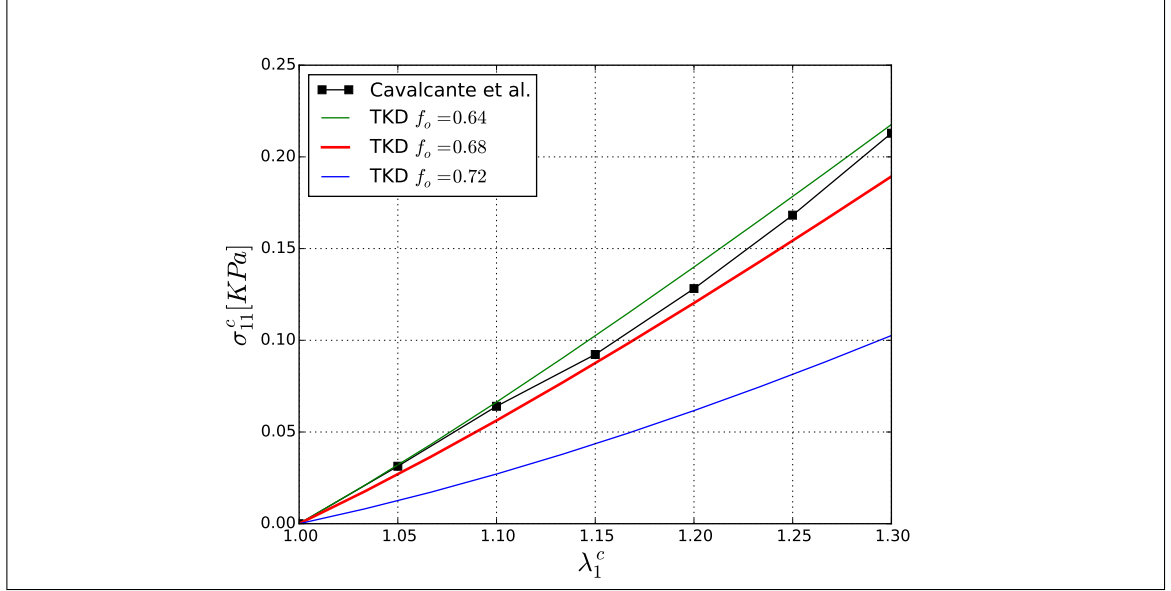


Figure 6.13. σ_{11}^c - λ_1^c comparison for the stress-free uniaxial elongation response among the TKD model with the experimental result obtained by (Cavalcante et al., 2005) using different values of volume fraction.

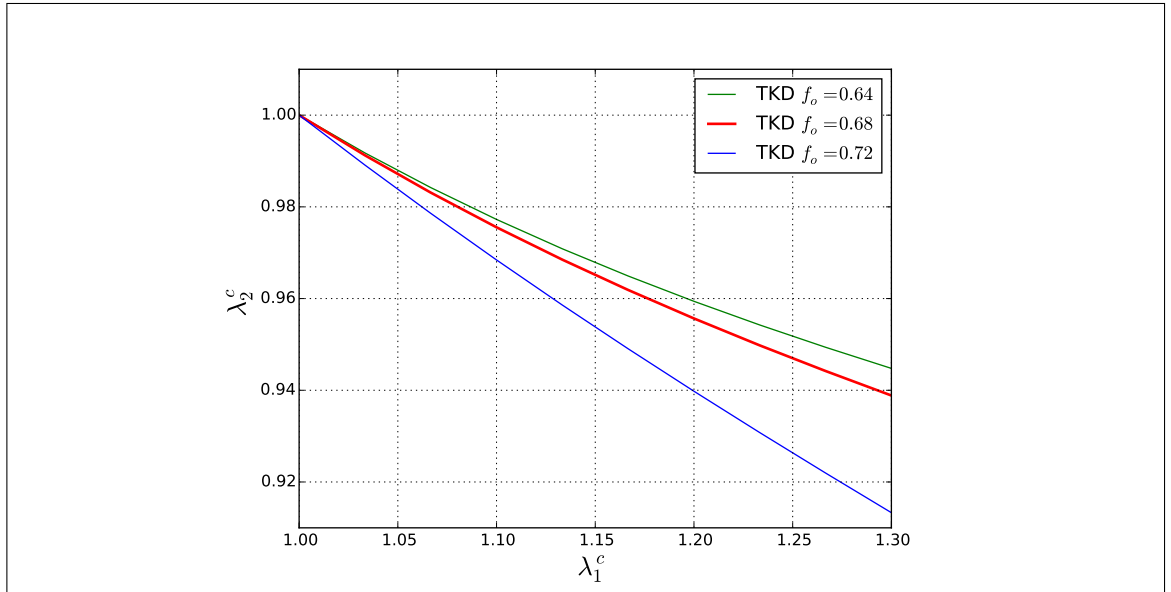


Figure 6.14. Coarse-scale Poisson effect obtained for the TKD model at stress-free uniaxial elongation for different values of volume fraction.

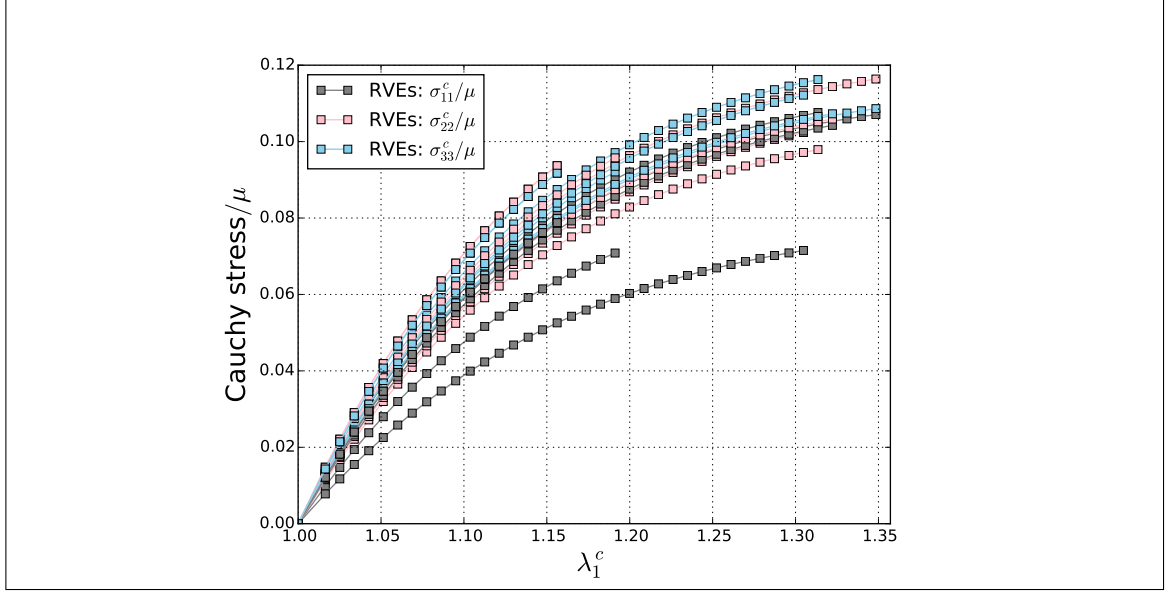


Figure 6.15. $\sigma_{11}^c/\mu-\lambda_1^c$, $\sigma_{22}^c/\mu-\lambda_1^c$ and $\sigma_{33}^c/\mu-\lambda_1^c$ relations for isotropic volumetric expansion on RVE models obtained at pressure p_A .

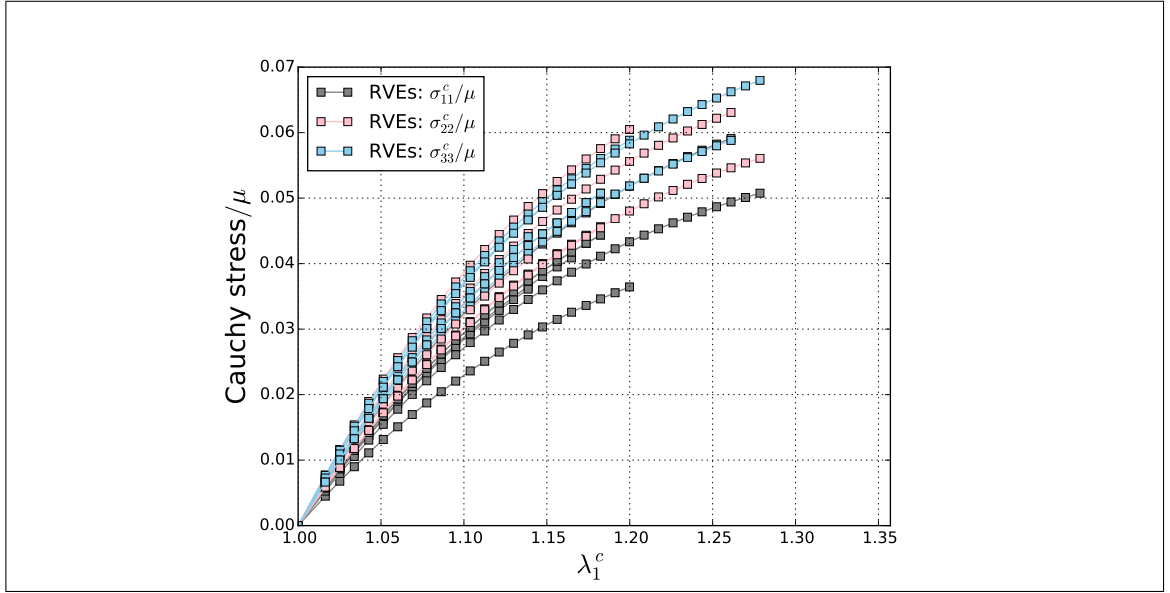


Figure 6.16. $\sigma_{11}^c/\mu-\lambda_1^c$, $\sigma_{22}^c/\mu-\lambda_1^c$ and $\sigma_{33}^c/\mu-\lambda_1^c$ relations for isotropic volumetric expansion on RVE models obtained at pressure p_B .

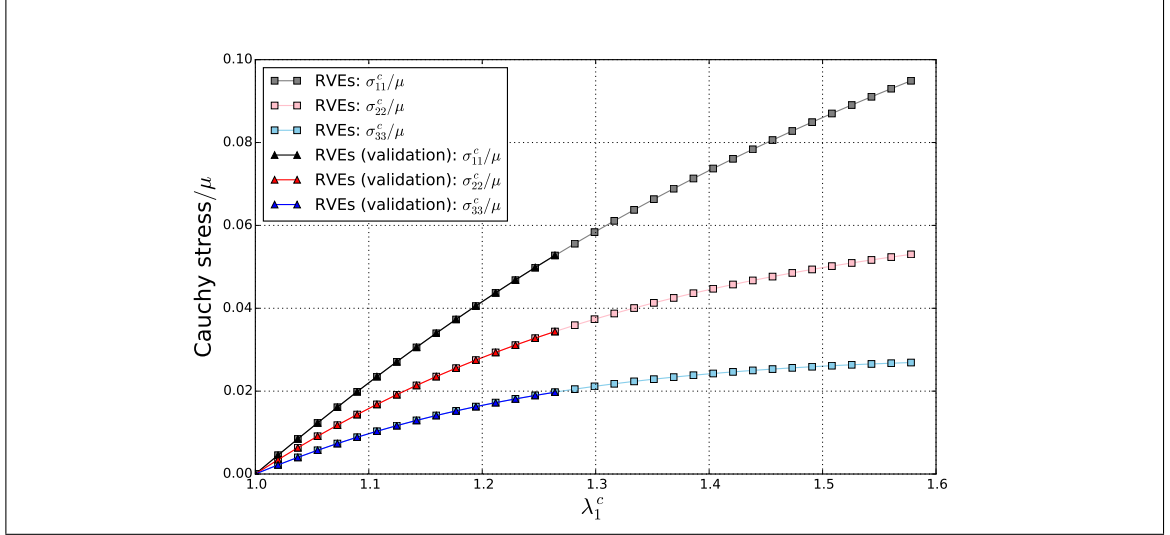


Figure 6.17. $\sigma_{11}^c/\mu-\lambda_1^c$, $\sigma_{22}^c/\mu-\lambda_1^c$ and $\sigma_{33}^c/\mu-\lambda_1^c$ comparison for RVEs under anisotropic volumetric expansion and inflation pressure p_B meshed with different numbers of elements. Light colors (gray, pink and skyblue) show results for test 6 of RVEs set under p_B (483,943 elements). Dark colors (black, red and blue) show results for test 8 of RVEs set under p_B (2,250,192 elements).

7. DISCUSSION AND FUTURE WORKS

7.1. Model parameters: physiological and physical basis

To get the obtained results, parameters d, α have been used and manually adjusted until reaching the best fitting possible following a sensitivity analysis approach. Nevertheless they are not only mathematical artifacts due to both of them have a physiological and physical basis. In this line, it is important to split the contribution of each parameter. By one hand, d arises from the need of including the real volume of solid tissue, discounting overlapping among struts of the TKD model. Looking at the physiological conditions shown in Figure 4.4, it is easy to notice that collagen fibers have a rod-like shape in their central regions that branches and open when they are close to the connection region with another collagen fibers. Such tapered region overlaps with tapered regions of other collagen fibers, decreasing the amount of truly elongated fibers. Hence, parameter d attempts to include this phenomena through incorporating a certain percentage of the struts length to nodal regions, with the purpose of being assumed as part of connections to be later discounted from the effective amount of TKDr material. In terms of modeling, dependence of the TKD model on d can be seen in Figures G.1 - G.4 for the case of lung microstructures inflated under pressure p_A and in Figures G.5 - G.8 for the case of lung microstructures inflated under pressure p_B , both in Appendix G. Note that different values for d are useful depending on p_A or p_B , however for both cases the qualitative behavior is the same. As shown, d has the only purpose of raising the coarse-scale stress-stretch curve generated by the TKD model for stresses $\sigma_{11}^c, \sigma_{22}^c, \sigma_{33}^c$. It makes a perfect sense due to stresses will be greater if stress average is performed in smaller solid volumes, which is obtained by discounting redundant volumes by using d . As expected, this behavior of arising the curve according to parameter d was carried out until reaching the coarse-scale stress-stretch curves generated by direct numerical simulation on RVEs.

By the other hand, rotational stiffness k_θ has been studied. This approach of including rotational energy has been previously used by a number of authors (Wang & Cuitiño,

2000), (Cavalcante et al., 2005) and constitutes almost a necessary condition when modeling idealized unit cells since pin-jointed structures are not physiologically reasonable. In terms of modeling, its effect is appreciated in Figures G.1 - G.4 and G.5 - G.8. As shown, coarse-scale stress-stretch curves move both up and down according to k_θ , increasing the magnitude of curve displacements when k_θ also increase. In general terms, $\sigma_{11}^c - \lambda_1^c$ relation tends to rise, as well as $\sigma_{33}^c - \lambda_1^c$ relation tends to go down. To understand this behavior, Figure 7.1 is analyzed. In this figure, deformed configuration of a whole TKD geometry subject to the uniaxial deformation pattern is shown. It was obtained by means of several TKDr disposed as an arrangement. Two cases of study were considered: one using $k_\theta = 0$ (blue) and another for $k_\theta = 0.04$ (red). This analysis was conducted for a volume fraction $f_o = 0.7$. In the upper right, frontal view is shown, it means, the TKD seen from the axis in which it was elongated. On the bottom, lateral view of the TKD is shown, it means, it shows the elongation of the TKD. For both cases, gray circle shows the region of interest to be analyzed. When including rotational stiffness, struts elongation of the TKD model should be higher in the TKDr deformation direction than when it is not included, since in this case, rotations involve a spent of energy. In front view, it can be seen that blue struts are larger than the red ones, which means that higher stresses are obtained for the directions corresponding to Y and Z: $\sigma_{22}^c, \sigma_{33}^c$. Furthermore, as shown by the lateral view, red struts are larger than the blue ones contributing to a major deformation in the direction of elongation, which means that higher stresses are obtained for direction X, i.e., σ_{11}^c . This behavior is consistent with the obtained in coarse-scale stress-stretch curves and explain the individual behavior of curves when varying parameter k_θ .

Then, the inclusion of rotational stiffness has two main advantages. First of all, it enables to obtain more accurate coarse-scale results when comparing with DNS of RVEs. Without the rotational energy involved, results shown in Figures 6.6 - 6.11 would not have a good agreement for all coarse-scale stresses simultaneously, getting results for σ_{11}^c or σ_{33}^c depending only on the value used for d . Thus, k_θ makes possible a simultaneous good fitting for $\sigma_{11}^c, \sigma_{22}^c, \sigma_{33}^c$ demonstrating that the inclusion of rotational energy has well conducted the distribution of deformation energy to be more realistic, limiting rotations and

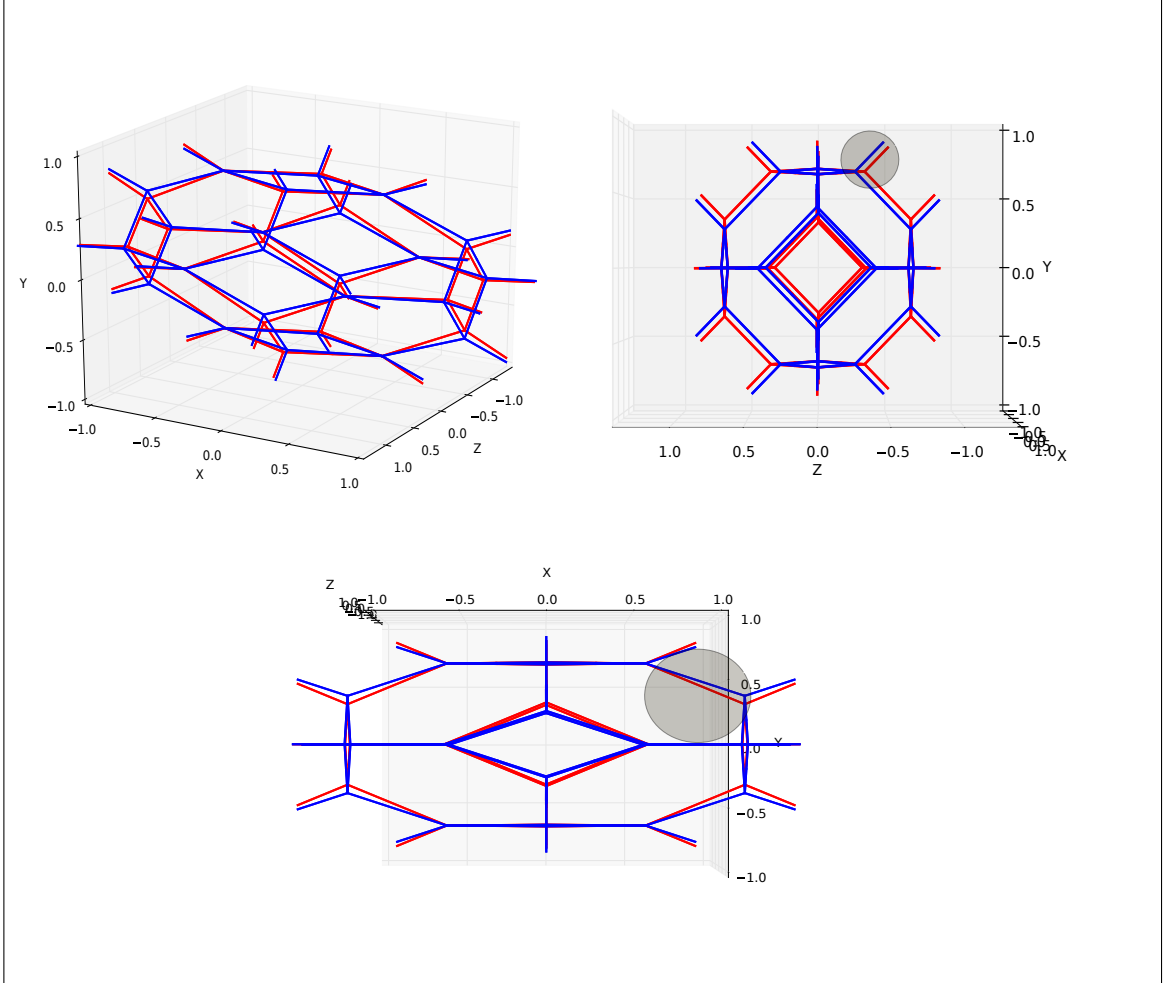


Figure 7.1. Deformed configuration of a whole TKD simulated by means of an array of TKD models under uniaxial elongation assuming $f_o = 0.7$, $\mu = \frac{5}{3}$ and two different values for k_θ . In blue, deformed configuration using $d = 0.42$, $k_\theta = 0.0$. In red, deformed configuration using $d = 0.42$, $k_\theta = 0.04$. Upper left: three-dimensional view. Upper right: frontal view (axis x). Down: lateral view (axis z). Gray circle indicates region of interest to be analyzed.

increasing axial elongations. The other main advantage contributed by rotational stiffness corresponds to avoid the appearance of rigid body motions in the TKDr structure, which can arise from struts that, seen sideways, moves down and forward. This issue has not been discussed elsewhere in this work but it is quite significant when developing multi-scale simulations, since coarse-scale models require a tangent matrix for successive

iterations of Newton-Raphson convergence procedures, which can not be correctly performed if tangent matrix is singular, corresponding to the case of a model with rigid body motions.

Finally, as shown in Table 6.3, optimal TKD model parameters have been classified according to the volume fraction. Even when the value for α can be considered as constant, k_θ will be modified for different levels of inflation since it depends on d and α and d does change for different volume fractions. Such establish a desirable condition because it enables to suitable modify k_θ for different f_o , improving the performance of the TKD model without changing model parameter α . Thus, it is like “change two model parameters” by means of only one. Furthermore, d should be classified for several values of f_o to improve accuracy, and mainly to have a continuous behavior, due to values chosen for this work produce discontinuity in the TKD model behavior for $f_o = 0.7$. Nevertheless, for the scope of this work, this issue has been considered as negligible.

7.2. Accuracy of the TKD model

In this work, the TKD model has been proposed and explained in detail. Its accuracy has been judged through comparison of averaged stress states with respect to direct numerical simulations on real lung microstructures. To this end, four displacement patterns have been used to validate the mechanical behavior at distinct situations. Even when patterns were selected to be quite different, the anisotropic deformation state was chosen, in particular, because it can be representative, in average, of the lung deformation field, whose modeling is the final purpose of this work. From Figures 6.4 - 6.11, it can be seen that the proposed TKD model is a predictive model that represents with a very good agreement results obtained from DNS on RVEs for several deformation patterns and inflation pressures. In this line, normalized stress-stretch constitutive relations predicted by the TKD model lie inside of the area formed by the corresponding numerical simulations of RVEs for each deformation state. Furthermore, for all kind of deformation patterns, the TKD model is capable of reproducing the same kind of curvature for constitutive relations

than in RVEs, which constitutes a minimum requirement to assess the good accuracy of a homogenization model since hardening or softening are basics concepts to qualitatively describe the mechanical behavior of a material.

Although the most important comparisons between the TKD model and RVEs were carried out for the displacement patterns shown in Figures 6.4 - 6.11, where the unit cell boundary is assumed as fully constrained by $\mathbf{F}^c$, which is the approach that has been taken for multi-scale simulations, another very interesting validation can be performed by testing the stress-free uniaxial behavior of the TKD model. To this end, experimental results obtained by Cavalcante et al. (Cavalcante et al., 2005) seems to be the more appropriate for the sake of comparison since they do not experience important stiffening and they lead to the Young modulus used in this work through a material model similar to the used here. From Figure 6.13 it can be seen that the TKD model returns an accurate response, given by σ_{11}^c , when it is tested under stress-free uniaxial deformation with a reasonable volume fraction, matching good enough with results obtained by (Cavalcante et al., 2005). Moreover, coarse-scale Poisson effect can be shown in Figure 6.14. When calculating Poisson coefficient as $\nu = \frac{-(\lambda_2^c-1)}{\lambda_1^c-1}$, it is obtained that $\nu \approx 0.22$, which is an expected result for a foam material as the lung microstructure since larger values of ν should be expected for “less compressible” materials, that is not the case of a foam material as lung parenchyma. Since not enough information about the lung microstructure has been reported and because of the good agreement, obtained stress-free uniaxial behavior increase the reliability of the proposed model.

As it can be seen, the proposed TKD model can accurately predict the mechanical behavior of porous materials with a medium level of volume fraction, which at the author’s knowledge, is not accomplished with good performance by the other homogenized models that can be found in the literature as inclusion models of Lopez Pamies et al. (Lopez-Pamies & Castañeda, 2007), or foam models of Gibson et al. (Gibson & Ashby, 1982). Even though those models have parameters for any volume fraction, they are not designed or tested for medium porosity mediums. In this line, the TKD model has been validated

for porosities that goes from 65 to 75 % depending on only two parameters which makes the model not only accurate, but also easy to use. As can be seen in Figures 6.4 - 6.11 comparing the same deformation pattern for both inflation cases, it is important to note that the TKD model has a better performance with respect to RVEs simulations when the material volume fraction f_o increase, due to this structure has been proposed originally for foam materials (Warren & Kraynik, 1997), (Zhu et al., 1997).

7.3. Computing advantages

Nevertheless, coarse-scale stresses agreement is not the only fact to support the TKD model. Comparing the procedure about how coarse-scale stresses are obtained for the TKD model and for RVEs is quite important due to the computational limitations that could be associated. First of all, the TKD model has the advantage of having only three degrees of freedom and only two model parameters against the heavy finite element simulations on real lung microstructure, which have at least two millions of degrees of freedom. In this line, Figure 6.12 shows undeformed (blue) and deformed (red) configurations for the TKD model under each deformation pattern used, denoting its simplicity, specially considering that the really solved geometry is the named TKDr rather than the whole TKD. Thus, computing time has been shown to be less than 0.03 seconds for python simulations capable of computing, without major optimization, the equilibrium configuration in addition to the coarse-scale stress state. In the same way, Figures 6.1 - 6.3 show very complex deformed RVE geometries that were obtained after a lot of hours in a powerful finite element software as ABAQUS, even when multiprocessing has been used, demonstrating the suitability of the TKD model in terms of saving computing time. Beside of high computing time, numerical simulations on RVEs involve high complexity in the problem solving due to the several facts as the inclusion of material incompressibility, which forces the use of elements of high interpolation order to avoid volumetric locking, the generation of geometry, and numerical problems associated to extreme deformations in small regions that make necessary a lot of simulation steps for reaching the target deformation state. In

contrast to the above, constitutive response of homogenized models do not have this problem because stress-stretch relations can be straightforwardly obtained. These issues take relevancy when multi-scale simulations are carried out as the approach of FE² proposed in (Wiechert et al., 2011) where if one quadrature point fails, the whole model also does it, making homogenized models suitable approaches to be used in multi-scale simulations due to they minimize problems associated to numerical convergence in the fine-scale.

7.4. Uncertainty and disadvantages

It is also interesting to discuss about the isotropy assumption of the lung. In Figures 6.15 and 6.16, coarse-scale normalized stresses $\sigma_{11}^c, \sigma_{22}^c, \sigma_{33}^c$ were plotted against principal stretch λ_1^c imposed on an isotropic volumetric expansion state. As it can be seen, normalized stresses are different not only among RVEs at different volume fractions, but also among directions for the same volume fraction and inflation pressure. It means, that even when same stretches in different directions were imposed on RVEs, stresses were different, denoting an anisotropic behavior of the lung microstructure just by considering the effect of the geometry and therefore without dependance on the real material model of the lung parenchyma. This is quite interesting, because the lung parenchyma has been always considered as an isotropic tissue in literature (S. Rausch et al., 2012), (Mercer & Crapo, 1990), being this a wrong assumption according to these results. However, this anisotropic behavior is neither represented by the TKD model, which returns an isotropic response under isotropic deformations. Since considering the anisotropic behavior of the lung could be a really hard task and orders of magnitude are the same for all curves, it is reasonable modeling the lung as an isotropic solid in the coarse-scale, without forgetting that it constitutes just an approximation.

Furthermore, despite of in this work several RVEs with the same volume fractions and inflation pressures have been used, there are a not negligible deviation of averaged results. From the above, it concludes that the coarse-scale constitutive response not only

depends on the volume fraction, but also on its distribution (Brown Jr, 1955), beside of microstructural properties inherent to the lung tissue and its substructures as alveolar ducts, blood vessels, minor airways, etc. Note that this deviation could be as important as the anisotropic behavior (see Figures 6.15, 6.16), then the best way to overcome this problem is by means of average stresses taken both in a directional sense (averaging stresses related to directions where imposed deformation is symmetrical) as in a sample sense (averaging results from different RVEs with same f_o). That is why, in this work results have been presented through the trace of tensor σ^c (isotropic volumetric deformation state) and other averages of stresses according to directions under same stretches (equibiaxial and uniaxial deformation cases), beside of using only one curve to show results obtained from the TKD model for a certain level or porosity.

In this work, it has been chosen an incompressible Neo-Hookean material model to simulate the constitutive relation of the alveolar walls. It leads to a mechanical behavior at the coarse-scale that, for high levels of deformation, shows always a softening response. However, experimental evidence has shown that the lung parenchyma does have hardening (see the comparison made by (S. Rausch et al., 2011)), which is a characteristic not reflected by the model. This is evident not only for mechanical essays, but also for pressure volume curves found in literature (Ethier & Simmons, 2007). This represents a limitation of the proposed model due to the hyperelastic material chosen to simulate the alveolar walls, which is an assumption of this work because of, at the author's knowledge, there are not theoretical hyperelastic constitutive relations proposed for three dimensional alveolar walls. In this line, only the work of Cavalcante et al. (Cavalcante et al., 2005) can be found, being a simple two dimensional model that reports the Young modulus used in this work. Then, to reproduce coarse-scale constitutive relation with hardening, a more appropriated fine-scale constitutive relation should be used both for RVEs as for TKD model simulations, which is totally a future work necessary to extend the good performance of our model.

Leaving behind discussion about performance of the TKD model and its comparison with numerical results of RVEs, it is necessary to refer to the convergence and validity of results contributed by such DNS on the lung microstructure. Then, three approaches can be discussed: the capability to solve the equilibrium for RVEs subjected to several deformation states, the convergence of the finite element solution to the real solution and the convergence of results in terms of the averaged response of RVEs according to their sizes. First of all, it can be noticed that numerical results shown in Figures 6.4 - 6.11, 6.15 and 6.16 cover different ranges of λ_1^c . This condition is due to failures when running nonlinear finite element simulations constituting an important disadvantage when demonstrating the TKD performance, since less information is available. In general, convergence failures could arise mainly from mesh defects, as poor quality of elements and large deformations on them, and lung tissue buckling. First case is the most probable since the RVEs have really complex geometries including angled bounds and poor-quality elements, which turns worst when deformation is applied. Furthermore, as shown in Figure 6.17, an increase in the number of mesh elements, leads to a minor convergence, which could be due to the major chances of existing a mesh problem. To demonstrate the appearance of defective elements when deformation is applied, Figure 7.2 shows a study performed on test 6 under pressure p_B that compares the histograms of mesh quality before (blue) and after (red) deformation. As expected the poorest quality in the reference configuration is much greater than the poorest quality for the deformed case (four times). As reference, when finite element mesh were created, no mesh quality lower than 0.2 were accepted due to the probable occurrence of convergence issues, which makes evident the problem when RVE is deformed as shown. To overcome this problem, remeshing should be considered after a certain number of load steps.

Second case could occur due to lung tissue will evolve to long and narrow strips that can easily buckle under compression. However, it constitutes one of the uncertainties of this work, and more efforts should be put on the study of this convergence behavior. Although buckling is a physiologically correct condition, it constitutes an undesirable behavior because it makes all the simulation fail. To overcome this problem, a common

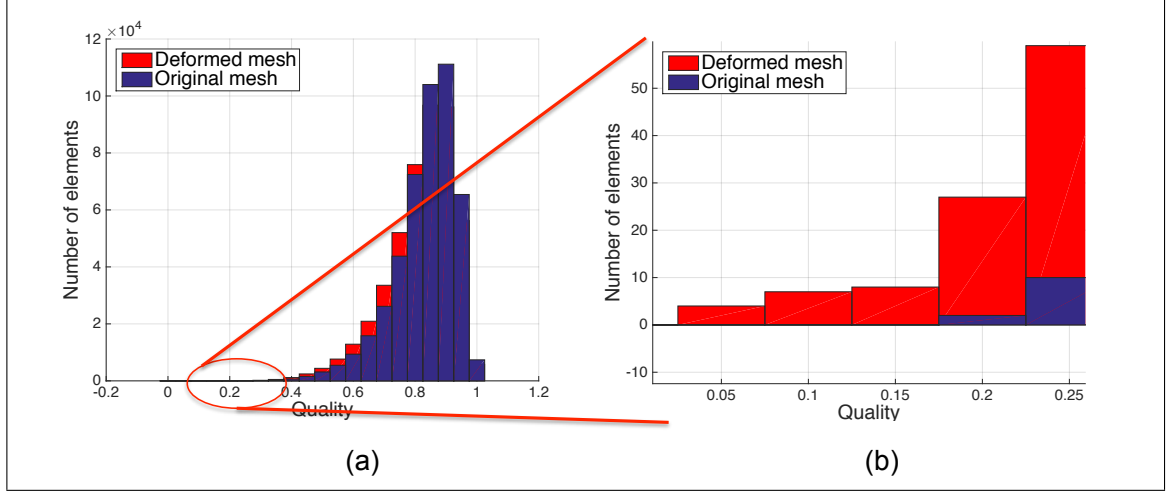


Figure 7.2. Comparison of mesh quality for test 6 of pressure case p_B under anisotropic volumetric expansion. In blue, mesh quality histogram for the undeformed RVE. In red, mesh quality histogram for the deformed RVE. At left, complete histogram comparison is shown. At right, zoom in the poorest quality zone.

approach consists on including viscosity, but this topic goes beyond the scope of this work. Nevertheless a suitable approach that is also physiologically correct is the inclusion of traction prestress when modeling the lung tissue because under compression, the microstructure will keep stressed. Although it also exceeds the scope of this work, it can be easily incorporated in the TKD model by including prestress at the struts level.

Mesh size also establish an important issue to asses the validity of obtained results due to in general, smaller the mesh size, closer is the numerical solution to the theoretical one. As a short attempt to study the convergence of the coarse-scale stresses obtained, one comparison was performed under anisotropic volumetric expansion for samples corresponding to test 6 and test 8 for pressure case p_B with properties according to Tables 5.2 and 5.3. For these simulations, results are shown in Figure 6.17. Averaged $\sigma^c - \mathbf{F}^c$ curves matches with an almost perfect agreement, being differences of around 0.5%. Although, the RVE used for validation have just around five times more elements than the base case, it could be considered as enough for the sake of numerical convergence to theoretical results since variation of results is negligible. Furthermore, although using validation RVEs

of tens of millions of elements and differences between averaged responses were obtained, the order of magnitude of such differences should be the same than the obtained between several samples of RVEs with similar volume fractions and number of elements, which means that for homogenized response, they would not imply problems for the validity of the proposed TKD model. Similar analysis could be done to assess the accurate size of RVEs. Specific analysis were not performed to study this issue, but as shown by Tables 5.1 and 5.2, two kinds of RVEs were employed, one having a side length equal to $149.6 \mu\text{m}$ and other with side length $198.56 \mu\text{m}$. As shown by Figures 6.4 - 6.11, coarse-scale stresses for different RVEs and side lengths have not negligible differences that, to the author's experience, should not be attributed to the RVEs size since differences also exist for RVEs with the same sizes.

7.5. Limitations and future works

Even when the TKD model has resulted to be a really predictive model with a very low computational cost, it has some limitations that can be separated in terms of their physiological and mathematical nature and that will be described below. First of all, future works should focus on the characterization of the mechanical behavior of the lung tissue, given by the alveolar walls, at least for elastic behavior. In this line, it is expected that an hyperelastic model be proposed to enable the obtention of realistic results and more accurate models. For this purpose, the study of the lung alveolar walls should be addressed through *in-vivo* or *in-vitro* experiences following the approach taken by (Luque et al., 2013), but including higher levels of details, or through *in-silico* experiences compared with real data as done by (Cavalcante et al., 2005). To this end, and taking advantage of the suitable mechanical behavior of the TKD model proposed, inverse finite element analysis could be conducted to obtain fine-scale energy density functions by means of reproducing coarse-scale stress-stretch curves and comparing them to experimental curves. A first attempt on this issue is the work of (Naini et al., 2011), but in this approach lung microstructure was neglected, motivating the need of the TKD model for the obtention of realistic results.

As known, the TKD model is a purely elastic model tested for quasi-static deformation states, thus lung tissue viscosity, in addition to viscosity contributed by the surfactant in the alveolar regions, were not considered in this work. Thus, future versions of the TKD model could incorporate degrees of freedom to account for velocities including the dynamics of breathing as part of the multi-scale simulation and maybe also incorporate dampers to simulate the hysteretical behavior arising from alveolar walls surface tension.

An important issue to be considered in future works is the study of compressive deformation states. Although highly predictive material models were developed, if they are not capable of accurately reproducing the mechanical response of the lung under compression, they will not be totally useful for real multi-scale simulations. Thus arises the need of performing unit cell modeling and comparison with direct numerical simulations on RVEs, following an analogous procedure that taken in this work, but focusing on compressive deformation patterns. Moreover, the study of compression has to incorporate the understanding of buckling and if possible its representation, since it is a physiological phenomena. Nevertheless, in lungs, buckling is avoided by means of the stability supported by surface tension and prestress, being both approaches that can be included into unit cell models as the TKD model. As mentioned before, prestress could be considered at the strut level representing a slight modification on the TKD model formulation. In particular, prestress should be added to vector $\mathbf{f}_e$ into equation (4.56), assuming that prestress constitutes an axial prestress for strut elements, being consistent with all the theoretical framework developed.

Anisotropy also constitutes a research resource for future works. From Figures 6.15 and 6.16, the anisotropic behavior of the lung, given by only geometrical reasons, has become evident. To date, anisotropy of the lung has not been widely studied due to the general assumption consist on that elastin and collagen fibers shown an anisotropic behavior but that condition becomes neglected when fibers at random directions were considered as the case of the lung. Future works should assess the real importance of anisotropy and if necessary, unit cell models capable of including this condition should be developed. The

TKD model has not been designed to reproduce this behavior since it has been assumed isotropic from its geometrical and material response point of view. Furthermore, it seems to be complicated to include incompressibility in this kind of models because anisotropic directions should have to be known for each coarse-scale point of the lung, significantly increasing the modeling difficulties in terms of having detailed information of the whole lung microstructure, that could lead to the need of additional model parameters.

Now, in terms of modeling, there are some issues that should be subjected to further investigation, such that previously discussed better convergence of DNS on RVEs and parametric studies about the RVE sizes. For the first case, high quality finite element meshes are fundamental for the good performance of simulations in addition to the physiologically reliable inclusion of prestress, enabling the obtention of stress fields for the complete range of deformations imposed. Although it has not overshadowed the obtained results, since a clear trend can be observed for the coarse-scale stress-stretch curves, it should be suitable for more reliable comparisons or to well compare more complex responses. Furthermore, even when numerical convergence to theoretical results did not show to be a real problem in this work, finer meshes should be considered for the study of RVEs, specially if attention is payed on the RVE response fields involving gradients (Moraleda et al., 2007) and the existence of hotspots.

8. TKD MODEL IMPLEMENTATION ON A COARSE-SCALE MODEL

In this chapter, the implementation of the TKD model as part of the material model of a coarse-scale simulation is covered. First of all, it will be considered that TKD model parameters d, α in addition to lung tissue parameters f_o, μ are known and constants for a given iteration step of the simulation. Thus, receiving as input a non-principal coarse-scale deformation gradient $\check{\mathbf{F}}^c$, two main results have to be computed. By one hand, the non-principal coarse-scale Cauchy stress tensor $\check{\boldsymbol{\sigma}}^c$ has to be returned to the macroscopic model in order to eval the residual and make it tends to $\mathbf{0}$, and by the other hand the coarse-scale spatial elasticity tensor $\mathbb{C}_s^c$ that relates the increment of stresses with the increment of strains has to be computed to obtain the next increment to be generated inside of the iterative process of convergence to find equilibrium.

First of all, under a non-principal deformation state, the principal deformation state $\mathbf{F}^c$ has to be computed. For this purpose the next procedure is performed

$$\check{\mathbf{b}}^c = \check{\mathbf{F}} \check{\mathbf{F}}^c \quad (8.1)$$

$$\det(\check{\mathbf{b}}^c - \lambda_i^{c^2} \mathbf{I}) = 0 \quad \forall i \in \{1, 2, 3\} \quad (8.2)$$

$$\check{\mathbf{b}}^c \lambda_i^{c^2} = \lambda_i^{c^2} \check{\mathbf{n}}_i^c \quad \forall i \in \{1, 2, 3\} \quad (8.3)$$

$$\mathbf{F}^c = \begin{bmatrix} \lambda_1^c & 0 & 0 \\ 0 & \lambda_2^c & 0 \\ 0 & 0 & \lambda_3^c \end{bmatrix} \quad (8.4)$$

where $\check{\mathbf{b}}^c$ is the non-principal coarse-scale left Cauchy-Green strain tensor and $\lambda_i^{c^2}, \check{\mathbf{n}}_i^c$ for $i = \{1, 2, 3\}$ are the principal stretches and directions of tensor $\check{\mathbf{b}}^c$. Moreover $\lambda_1^c, \lambda_2^c, \lambda_3^c$ are the already known principal coarse-scale stretches. Now, focus will be in the computation of $\boldsymbol{\sigma}^c$.

To remind, computation of $\boldsymbol{\sigma}^c$ has been already detailed in Chapter 4 and it can be summarized as obtaining the equilibrium configuration of the TKDr by means of equations (4.46) and (4.47) to later calculating $\boldsymbol{\sigma}^c$ by using equation (4.57). Tensor $\boldsymbol{\sigma}^c$ is function of

$\mathbf{F}^c$, then it is a principal stress state, so the computation of the non-principal stress state $\tilde{\boldsymbol{\sigma}}^c$ can be performed as follows

$$\tilde{\boldsymbol{\sigma}}^c = \sum_{a=1}^3 \sigma_a^c \check{\mathbf{n}}_a^c \otimes \check{\mathbf{n}}_a^c \quad (8.5)$$

where, same than in Chapter 3, only one index has been used for referring to principal values.

Now, to compute the spatial elasticity tensor, procedure will be based on equation (3.21) since it requires only principal stretches and stresses, which are easy to compute by the approach of the TKD model. First of all, it is necessary to keep in mind that $\boldsymbol{\sigma}^c$ is not only a straightforward function of $\mathbf{F}^c$, but also it is function of the solved degrees of freedom $\mathbf{r}^*$ that were obtained by means of a minimization procedure of equations that are functions of $\mathbf{F}^c$. Thus, in the next, $\mathbf{r}^* = \mathbf{r}^*(\mathbf{F}^c)$. Then, the approach assumed for $\boldsymbol{\sigma}^c$ is changed according to

$$\boldsymbol{\sigma}^c(\mathbf{F}^c) \equiv \tilde{\boldsymbol{\sigma}}^c(\mathbf{r}^*(\mathbf{F}^c); \mathbf{F}^c) \quad (8.6)$$

Equation (4.57) has indicated that

$$\boldsymbol{\sigma}^c(\mathbf{F}^c) = \frac{2}{|\Theta_y|} (\mathbf{f}_7 \otimes \mathbf{F}^c \mathbf{b}_x + \mathbf{f}_{10} \otimes \mathbf{F}^c \mathbf{b}_y + \mathbf{f}_{15} \otimes \mathbf{F}^c \mathbf{b}_z) \quad (8.7)$$

Then,

$$\begin{aligned} \tilde{\boldsymbol{\sigma}}^c(\mathbf{r}^*; \mathbf{F}^c) = \frac{2}{|\Theta_y|} [\mathbf{f}_7(\mathbf{r}^*, \mathbf{F}^c) \otimes \mathbf{F}^c \mathbf{b}_x + \mathbf{f}_{10}(\mathbf{r}^*; \mathbf{F}^c) \otimes \mathbf{F}^c \mathbf{b}_y + \\ \mathbf{f}_{15}(\mathbf{r}^*; \mathbf{F}^c) \otimes \mathbf{F}^c \mathbf{b}_z] \end{aligned} \quad (8.8)$$

where it has been used that $\mathbf{f}_7, \mathbf{f}_{10}, \mathbf{f}_{15}$ are functions of strut elongations, which are then functions of nodal displacements and thus, functions of $\mathbf{r}^*$. For the sake of clarity, dependence of $\mathbf{r}^*$ on $\mathbf{F}^c$ has been omitted.

To compute the coarse-scale spatial elasticity tensor $\mathbb{C}_s^c$, the coarse-scale second Piola-Kirchhoff stress tensor $\mathbf{S}^c$ is also necessary. It can be computed as follows

$$\mathbf{S}^c = J^c \mathbf{F}^{c^{-1}} \boldsymbol{\sigma}^c \mathbf{F}^{c^{-T}} \quad (8.9)$$

$$S_{ij}^c = J^c F_{ik}^{c^{-1}} \sigma_{kl}^c F_{lj}^{c^{-T}} \quad i, j \in \{1, 2, 3\} \quad (8.10)$$

Replacing expression for $\boldsymbol{\sigma}^c$ from equation (4.57), it yields

$$S_{ij}^c = \frac{2J^c}{|\Theta_y|} \left[F_{ik}^{c^{-1}} f_{7k} F_{lp}^c b_{x_p} F_{lj}^{c^{-T}} + F_{ik}^{c^{-1}} f_{10k} F_{lp}^c b_{y_p} F_{lj}^{c^{-T}} + F_{ik}^{c^{-1}} f_{15k} F_{lp}^c b_{z_p} F_{lj}^{c^{-T}} \right] \quad (8.11)$$

which, rearranging terms

$$S_{ij}^c = \frac{2J^c}{|\Theta_y|} \left[F_{ik}^{c^{-1}} f_{7k} F_{jl}^{c^{-1}} F_{lp}^c b_{x_p} + F_{ik}^{c^{-1}} f_{10k} F_{jl}^{c^{-1}} F_{lp}^c b_{y_p} + F_{ik}^{c^{-1}} f_{15k} F_{jl}^{c^{-1}} F_{lp}^c b_{z_p} \right] \quad (8.12)$$

Simplifying

$$S_{ij}^c = \frac{2J^c}{|\Theta_y|} \left[F_{ik}^{c^{-1}} f_{7k} \delta_{jp} b_{x_p} + F_{ik}^{c^{-1}} f_{10k} \delta_{jp} b_{y_p} + F_{ik}^{c^{-1}} f_{15k} \delta_{jp} b_{z_p} \right] \quad (8.13)$$

$$S_{ij}^c = \frac{2J^c}{|\Theta_y|} \left[F_{ik}^{c^{-1}} f_{7k} b_{x_j} + F_{ik}^{c^{-1}} f_{10k} b_{y_j} + F_{ik}^{c^{-1}} f_{15k} b_{z_j} \right] \quad (8.14)$$

In tensorial notation last expression leads to

$$\mathbf{S}^c = \frac{2J^c}{|\Theta_y|} \mathbf{F}^{c^{-1}} [\mathbf{f}_7 \otimes \mathbf{b}_x + \mathbf{f}_{10} \otimes \mathbf{b}_y + \mathbf{f}_{15} \otimes \mathbf{b}_z] \quad (8.15)$$

Now, it will be computed $\mathbb{C}_s^c$ according to equation (3.21), but considering that all terms now refer to coarse-scale tensors and vectors. Thus, equation (3.21) now yields

$$\begin{aligned} \mathbb{C}_s^c = & \sum_{a,b=1}^3 J^{c^{-1}} \lambda_a^{c^2} \lambda_b^c \frac{\partial S_a^c}{\partial \lambda_b^c} \check{\mathbf{n}}_a^c \otimes \check{\mathbf{n}}_a^c \otimes \check{\mathbf{n}}_b^c \otimes \check{\mathbf{n}}_b^c + \\ & \sum_{a,b=1, a \neq b}^3 \frac{\sigma_b^c \lambda_a^{c^2} - \sigma_a^c \lambda_b^{c^2}}{\lambda_b^{c^2} - \lambda_a^{c^2}} (\check{\mathbf{n}}_a^c \otimes \check{\mathbf{n}}_b^c \otimes \check{\mathbf{n}}_a^c \otimes \check{\mathbf{n}}_b^c + \check{\mathbf{n}}_a^c \otimes \check{\mathbf{n}}_b^c \otimes \check{\mathbf{n}}_b^c \otimes \check{\mathbf{n}}_a^c) \end{aligned} \quad (8.16)$$

Next step is to calculate the term $\frac{\partial S_a^c}{\partial \lambda_a^c}$ for $a = \{1, 2, 3\}$ being S_a^c the principal stresses of $\mathbf{S}^c$ and λ_a^c the principal stretches. Analogous to $\boldsymbol{\sigma}^c$ and $\tilde{\boldsymbol{\sigma}}^c$, it is proposed that

$$\mathbf{S}^c(\mathbf{F}^c) \equiv \tilde{\mathbf{S}}^c(\mathbf{r}^*; \mathbf{F}^c) \quad (8.17)$$

where,

$$\begin{aligned} \tilde{\mathbf{S}}^c(\mathbf{r}^*; \mathbf{F}^c) = \frac{2J^c}{|\Theta_y|} \mathbf{F}^{c^{-1}} [f_7(\mathbf{r}^*; \mathbf{F}^c) \otimes \mathbf{b}_x + f_{10}(\mathbf{r}^*; \mathbf{F}^c) \otimes \mathbf{b}_y + \\ f_{15}(\mathbf{r}^*; \mathbf{F}^c) \otimes \mathbf{b}_z] \end{aligned} \quad (8.18)$$

In indicial notation

$$\tilde{S}_{ij}^c(\mathbf{r}^*; \mathbf{F}^c) = \frac{2J^c}{|\Theta_y|} F_{ik}^{c^{-1}} [f_{7k}(\mathbf{r}^*; \mathbf{F}^c) b_{xj} + f_{10k}(\mathbf{r}^*; \mathbf{F}^c) b_{yj} + f_{15k}(\mathbf{r}^*; \mathbf{F}^c) b_{zj}] \quad (8.19)$$

Then, if principal stress $\tilde{S}_a^c$ is obtained when $i = j = a$, then it is also obtained when $j = k$, since the index of a principal stress is related to the same index of principal stretch, then $a = i = j = k$. Hence,

$$\tilde{S}_a^c(\mathbf{r}^*; \mathbf{F}^c) = \frac{2J^c}{|\Theta_y|} \frac{1}{\lambda_a^c} [f_{7a}(\mathbf{r}^*; \mathbf{F}^c) b_{x_a} + f_{10a}(\mathbf{r}^*; \mathbf{F}^c) b_{y_a} + f_{15a}(\mathbf{r}^*; \mathbf{F}^c) b_{z_a}] \quad (8.20)$$

So, derivative $\frac{\partial S_a^c}{\partial \lambda_b^c}$ corresponds to

$$\frac{\partial S_a^c}{\partial \lambda_b^c} = \frac{\partial \tilde{S}_a^c}{\partial \lambda_b^c} + \frac{\partial \tilde{S}_a^c}{\partial \mathbf{r}^*} : \frac{\partial \mathbf{r}^*}{\partial \lambda_b^c} \quad (8.21)$$

where has been used that $\mathbf{r}^* = \mathbf{r}^*(\mathbf{F}^c)$. Terms of above can be computed according to

$$\begin{aligned} \frac{\partial \tilde{S}_a^c}{\partial \lambda_b^c} = \frac{2J^c}{|\Theta_y|} \frac{-1}{\lambda_a^{c^2}} \delta_{ab} (f_{7a} b_{x_a} + f_{10a} b_{y_a} + f_{15a} b_{z_a}) + \\ \frac{2J}{|\Theta_y|} \frac{1}{\lambda_a^c} \left(\frac{\partial f_{7a}}{\partial \lambda_b^c} b_{x_a} + \frac{\partial f_{10a}}{\partial \lambda_b^c} b_{y_a} + \frac{\partial f_{15a}}{\partial \lambda_b^c} b_{z_a} \right) \end{aligned} \quad (8.22)$$

And

$$\frac{\partial \tilde{S}_a^c}{\partial \mathbf{r}^*} = \frac{2J^c}{|\Theta_y|} \frac{1}{\lambda_a^c} \left(\frac{\partial f_{7a}}{\partial \mathbf{r}^*} b_{x_a} + \frac{\partial f_{10a}}{\partial \mathbf{r}^*} b_{y_a} + \frac{\partial f_{15a}}{\partial \mathbf{r}^*} b_{z_a} \right) \quad (8.23)$$

where $\frac{\partial f_{7a}}{\partial \mathbf{r}}$, $\frac{\partial f_{10a}}{\partial \mathbf{r}}$, $\frac{\partial f_{15a}}{\partial \mathbf{r}}$ have to be computed analytically from expressions for strut forces that are functions of strut stretches, and then, functions of nodal displacements.

It only remains to compute $\frac{\partial \mathbf{r}^*}{\partial \lambda_b^c}$. For that purpose, the effective Lagrangian $\Pi^{eff}(\mathbf{r}, \mathbf{F}^c)$ is used again. To solve the equilibrium configuration for the TKD model, the stationary points of Π^{eff} have been searched with respect to $\mathbf{r}$, yielding

$$\min_{\mathbf{r}} \Pi^{eff}(\mathbf{r}; \mathbf{F}^c) \iff \frac{\partial \Pi^{eff}}{\partial \mathbf{r}}(\mathbf{r}^*; \mathbf{F}^c) = \mathbf{0} \quad (8.24)$$

Now, deriving equation (8.24), right, with respect to $\mathbf{F}^c$, it is obtained that

$$\frac{\partial^2 \Pi^{eff}(\mathbf{r}; \mathbf{F}^c)}{\partial \mathbf{F}^c \partial \mathbf{r}} + \frac{\partial^2 \Pi^{eff}(\mathbf{r}; \mathbf{F}^c)}{\partial \mathbf{r} \partial \mathbf{r}} : \frac{\partial \mathbf{r}^*}{\partial \mathbf{F}^c} = \mathbf{0} \quad (8.25)$$

Using the approach of principal values, indicial notation is used and $\mathbf{F}^c$ changes to λ_b^c . Then,

$$\frac{\partial^2 \Pi^{eff}(\mathbf{r}; \mathbf{F}^c)}{\partial \lambda_b^c \partial \mathbf{r}} + \frac{\partial^2 \Pi^{eff}(\mathbf{r}; \lambda_b^c)}{\partial \mathbf{r} \partial \mathbf{r}} \frac{\partial \mathbf{r}^*}{\partial \lambda_b^c} = \mathbf{0} \quad (8.26)$$

Hence, solving for $\frac{\partial \mathbf{r}^*}{\partial \lambda_b^c}$,

$$\frac{\partial \mathbf{r}^*}{\partial \lambda_b^c} = - \left(\frac{\partial^2 \Pi^{eff}(\mathbf{r}; \lambda_b^c)}{\partial \mathbf{r} \partial \mathbf{r}} \right)^{-1} \frac{\partial^2 \Pi^{eff}(\mathbf{r}; \mathbf{F}^c)}{\partial \lambda_b^c \partial \mathbf{r}} \quad (8.27)$$

where derivatives of Π^{eff} have to be computed from analytical expressions obtained for the TKD model. Finally, equations (8.22), (8.23), (8.27) are inserted into equation (8.21) obtaining all terms necessities to compute equation (8.16). Furthermore, an analogous procedure can be performed to compute $\frac{\partial \sigma_a^c}{\partial \lambda_b^c}$, which can be needed when computing expression (8.16) for cases where $\lambda_a^c \neq \lambda_b^c$ by following procedure detailed by (Holzapfel, 2000).

To conclude, equation (8.16) represents the tangent matrix necessary to predict the direction and magnitude to evolve inside an iterative process for reaching convergence of a coarse-scale finite element simulation. If simulation are carried out in the finite element software ABAQUS, a slightly modification has to be included to compute the suitable

spatial elasticity tensor used by ABAQUS, $\mathbb{C}_s^{c^{abaqus}}$ according to

$$\mathbb{C}_s^{c^{abaqus}} = \mathbb{C}_s^c + \mathbb{C}_s^{c'} \quad (8.28)$$

where expression of $\mathbb{C}_s^{c'}$ and details about this modification can be found in (Costabal et al., 2017).

9. CONCLUDING REMARKS

In order to accurately modeling the mechanical behavior of the lung by including its microstructure and then, its porous geometry, in this work a homogenized model of the lung parenchyma microstructure has been developed: the TKD model. It is a micromechanical model suitable for multi-scale simulations that can stand for incompressibility, hyperelasticity, large deformations, medium-porosity domains in addition to incorporating the microstructure evolution, all of this with only a simple unit cell. This model is capable of receiving a coarse-scale deformation gradient in principal coordinates $\mathbf{F}^c$ and return the principal coarse-scale stresses $\boldsymbol{\sigma}^c$ working then as the “homogenized” constitutive relation of the lung tissue at the coarse-scale, understood as a continuum non porous geometry. To assess its accurate, the TKD model was compared against direct numerical simulations performed in representative volume elements (RVEs) of the lung microstructure under four displacement patterns: isotropic and anisotropic volumetric expansion, in addition to equibiaxial and uniaxial elongations. In all cases, essential boundary conditions were imposed on the whole boundary of RVEs, constituting a suitable approach for homogenization models. From the obtained results, an excellent agreement was found for the coarse-scale stress-stretch curves suggesting that the proposed TKD model is highly predictive in addition to require a very low computational cost, making it a completely suitable approach for multi-scale simulations.

Beside of the already mentioned advantages, there are some other quite convenient issues. The TKD model constitutes a simple unit cell geometry with also an understandable mathematical formulation that can be widely and simply extended to include several kind of additional effects, such as those arising from viscosity, prestress or different hyperelastic models for the fine-scale tissue, which means that, rather than being only a predictive model, it establish a starting point for the development and implementation of more sophisticated models including all kind of physical and physiological phenomena, contributing to the study and understanding about the mechanical behavior of not only the lung, but also a number of porous materials existent in nature.

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APPENDIX

A. NODAL COORDINATES

Nodal coordinates correspond to:

$$\begin{aligned}
\mathbf{Y}_1 &= \begin{bmatrix} 0 & \frac{1}{3} & \frac{2}{3} \end{bmatrix}^T & \mathbf{Y}_2 &= \begin{bmatrix} \frac{1}{3} & 0 & \frac{2}{3} \end{bmatrix}^T & \mathbf{Y}_3 &= \begin{bmatrix} \frac{2}{3} & 0 & \frac{1}{3} \end{bmatrix}^T \\
\mathbf{Y}_4 &= \begin{bmatrix} \frac{2}{3} & \frac{1}{3} & 0 \end{bmatrix}^T & \mathbf{Y}_5 &= \begin{bmatrix} \frac{1}{3} & \frac{2}{3} & 0 \end{bmatrix}^T & \mathbf{Y}_6 &= \begin{bmatrix} 0 & \frac{2}{3} & \frac{1}{3} \end{bmatrix}^T \\
\mathbf{Y}_7 &= \begin{bmatrix} 0 & \frac{1}{2} & \frac{5}{6} \end{bmatrix}^T & \mathbf{Y}_8 &= \begin{bmatrix} \frac{-1}{6} & \frac{1}{6} & \frac{2}{3} \end{bmatrix}^T & \mathbf{Y}_9 &= \begin{bmatrix} \frac{1}{6} & \frac{-1}{6} & \frac{2}{3} \end{bmatrix}^T \\
\mathbf{Y}_{10} &= \begin{bmatrix} \frac{1}{2} & 0 & \frac{5}{6} \end{bmatrix}^T & \mathbf{Y}_{11} &= \begin{bmatrix} \frac{2}{3} & \frac{-1}{6} & \frac{1}{6} \end{bmatrix}^T & \mathbf{Y}_{12} &= \begin{bmatrix} \frac{5}{6} & 0 & \frac{1}{2} \end{bmatrix}^T \\
\mathbf{Y}_{13} &= \begin{bmatrix} \frac{2}{3} & \frac{1}{6} & \frac{-1}{6} \end{bmatrix}^T & \mathbf{Y}_{14} &= \begin{bmatrix} \frac{5}{6} & \frac{1}{2} & 0 \end{bmatrix}^T & \mathbf{Y}_{15} &= \begin{bmatrix} \frac{1}{2} & \frac{5}{6} & 0 \end{bmatrix}^T \\
\mathbf{Y}_{16} &= \begin{bmatrix} \frac{1}{6} & \frac{2}{3} & \frac{-1}{6} \end{bmatrix}^T & \mathbf{Y}_{17} &= \begin{bmatrix} 0 & \frac{5}{6} & \frac{1}{2} \end{bmatrix}^T & \mathbf{Y}_{18} &= \begin{bmatrix} \frac{-1}{6} & \frac{2}{3} & \frac{1}{6} \end{bmatrix}^T
\end{aligned}$$

B. LATTICE VECTORS

Lattice vectors connect TKDr nodes according to

$$\mathbf{b}_x = \mathbf{Y}_{17} - \mathbf{Y}_{13} = \mathbf{Y}_7 - \mathbf{Y}_{11} \quad (\text{B.1})$$

$$\mathbf{b}_y = \mathbf{Y}_{12} - \mathbf{Y}_{16} = \mathbf{Y}_{10} - \mathbf{Y}_{18} \quad (\text{B.2})$$

$$\mathbf{b}_z = \mathbf{Y}_{15} - \mathbf{Y}_8 = \mathbf{Y}_{14} - \mathbf{Y}_9 \quad (\text{B.3})$$

C. ELEMENT VECTORS

With nodal coordinates defined, vectors used to represent the TKDr elements are listed below for the reference (left) and current (right) configuration

$$Q_1 = Y_2 - Y_1 \quad q_1 = (Y_2 + u_2) - (Y_1 + u_1) \quad (C.1)$$

$$Q_2 = Y_3 - Y_2 \quad q_2 = (Y_3 + u_3) - (Y_2 + u_2) \quad (C.2)$$

$$Q_3 = Y_4 - Y_3 \quad q_3 = (Y_4 + u_4) - (Y_3 + u_3) \quad (C.3)$$

$$Q_4 = Y_5 - Y_4 \quad q_4 = (Y_5 + u_5) - (Y_4 + u_4) \quad (C.4)$$

$$Q_5 = Y_6 - Y_5 \quad q_5 = (Y_6 + u_6) - (Y_5 + u_5) \quad (C.5)$$

$$Q_6 = Y_1 - Y_6 \quad q_6 = (Y_1 + u_1) - (Y_6 + u_6) \quad (C.6)$$

$$Q_7 = Y_7 - Y_1 \quad q_7 = (Y_7 + u_7) - (Y_1 + u_1) \quad (C.7)$$

$$Q_8 = Y_8 - Y_1 \quad q_8 = (Y_8 + u_8) - (Y_1 + u_1) \quad (C.8)$$

$$Q_9 = Y_9 - Y_2 \quad q_9 = (Y_9 + u_9) - (Y_2 + u_2) \quad (C.9)$$

$$Q_{10} = Y_{10} - Y_2 \quad q_{10} = (Y_{10} + u_{10}) - (Y_2 + u_2) \quad (C.10)$$

$$Q_{11} = Y_{11} - Y_3 \quad q_{11} = (Y_{11} + u_{11}) - (Y_3 + u_3) \quad (C.11)$$

$$Q_{12} = Y_{12} - Y_3 \quad q_{12} = (Y_{12} + u_{12}) - (Y_3 + u_3) \quad (C.12)$$

$$Q_{13} = Y_{13} - Y_4 \quad q_{13} = (Y_{13} + u_{13}) - (Y_4 + u_4) \quad (C.13)$$

$$Q_{14} = Y_{14} - Y_4 \quad q_{14} = (Y_{14} + u_{14}) - (Y_4 + u_4) \quad (C.14)$$

$$Q_{15} = Y_{15} - Y_5 \quad q_{15} = (Y_{15} + u_{15}) - (Y_5 + u_5) \quad (C.15)$$

$$Q_{16} = Y_{16} - Y_5 \quad q_{16} = (Y_{16} + u_{16}) - (Y_5 + u_5) \quad (C.16)$$

$$Q_{17} = Y_{17} - Y_6 \quad q_{17} = (Y_{17} + u_{17}) - (Y_6 + u_6) \quad (C.17)$$

$$Q_{18} = Y_{18} - Y_6 \quad q_{18} = (Y_{18} + u_{18}) - (Y_6 + u_6) \quad (C.18)$$

D. PAIRS FOR ROTATIONAL SPRINGS

When computing the rotational energy potential $\Pi^{rotational}$, thirty six rotational springs have to be included, which are given by certain pairs of struts. For this purpose, combinations are listed by means of the element numbers detailed in the set $\mathcal{J}$, as:

$$\begin{aligned}\mathcal{J} = \quad & \{ (1, 6); (1, 7); (1, 8); (7, 6); (7, 8); (8, 6); \dots \\ & (2, 1); (2, 9); (2, 10); (9, 1); (9, 10); (10, 1); \dots \\ & (3, 2); (3, 11); (3, 12); (11, 2); (11, 12); (12, 2); \dots \\ & (4, 3); (4, 13); (4, 14); (13, 3); (13, 14); (14, 3); \dots \\ & (5, 4); (5, 15); (5, 16); (15, 4); (15, 16); (16, 4); \dots \\ & (6, 5); (6, 17); (6, 18); (17, 5); (17, 18); (18, 5) \} \end{aligned}$$

E. EXAMPLE OF MACRO-MICRO CONDITION

The approach of considering $\mathbf{F}^c$ operating on the boundary of the TKDr can be slightly modified by $\mathbf{F}^c$ operating on the lattice vectors. To demonstrate it, the following procedure has been considered: let be $\mathbf{Y}_{12}, \mathbf{Y}_{16}$ the absolute positions of nodes 12 and 16 respectively at the reference configuration. Nodal numbering of the TKDr can be seen in Figure 4.2. Under a homogeneous macroscopic deformation state $\mathbf{F}^c$, they are respectively displaced to the new positions $\mathbf{y}_{12}$ and $\mathbf{y}_{16}$ in the current configuration, such that

$$\mathbf{y}_{12} = \mathbf{F}^c \mathbf{Y}_{12} \quad (\text{E.1})$$

$$\mathbf{y}_{16} = \mathbf{F}^c \mathbf{Y}_{16} \quad (\text{E.2})$$

but one can think in their relative distance

$$\mathbf{y}_{12} - \mathbf{y}_{16} = \mathbf{F}^c (\mathbf{Y}_{12} - \mathbf{Y}_{16}) \quad (\text{E.3})$$

and also, in their relative displacement

$$(\mathbf{u}_{12} + \mathbf{Y}_{12}) - (\mathbf{u}_{16} + \mathbf{Y}_{16}) = \mathbf{F}^c (\mathbf{Y}_{12} - \mathbf{Y}_{16}) \quad (\text{E.4})$$

$$\mathbf{u}_{12} - \mathbf{u}_{16} = (\mathbf{F}^c - \mathbf{I})(\mathbf{Y}_{12} - \mathbf{Y}_{16}) \quad (\text{E.5})$$

Moreover, it is known that

$$\mathbf{b}_y = \mathbf{Y}_{12} - \mathbf{Y}_{16} \quad (\text{E.6})$$

Then,

$$\mathbf{u}_{12} - \mathbf{u}_{16} = (\mathbf{F}^c - \mathbf{I})\mathbf{b}_y \quad (\text{E.7})$$

F. NODAL DISPLACEMENTS

Nodal displacements as function of $\lambda_1^c, \lambda_2^c, \lambda_3^c$ and u_{1y}, u_{2x}, u_{3z} are:

$$\mathbf{u}_1 = \begin{bmatrix} 0, & u_{1y}, & \frac{-2}{3}(1 - \lambda_3^c) \end{bmatrix}^T \quad (\text{F.1})$$

$$\mathbf{u}_2 = \begin{bmatrix} u_{2x}, & 0, & \frac{-2}{3}(1 - \lambda_3^c) \end{bmatrix}^T \quad (\text{F.2})$$

$$\mathbf{u}_3 = \begin{bmatrix} \frac{-2}{3}(1 - \lambda_1^c), & 0, & u_{3z} \end{bmatrix}^T \quad (\text{F.3})$$

$$\mathbf{u}_4 = \begin{bmatrix} \frac{-2}{3}(1 - \lambda_1^c), & -u_{1y} - \frac{2}{3}(1 - \lambda_2^c), & 0 \end{bmatrix}^T \quad (\text{F.4})$$

$$\mathbf{u}_5 = \begin{bmatrix} -u_{2x} - \frac{2}{3}(1 - \lambda_1^c), & -\frac{2}{3}(1 - \lambda_2^c), & 0 \end{bmatrix}^T \quad (\text{F.5})$$

$$\mathbf{u}_6 = \begin{bmatrix} 0, & -\frac{2}{3}(1 - \lambda_2^c), & -u_{3z} - \frac{2}{3}(1 - \lambda_3^c) \end{bmatrix}^T \quad (\text{F.6})$$

$$\mathbf{u}_7 = \begin{bmatrix} 0, & \frac{1}{2}u_{1y} - \frac{1}{3}(1 - \lambda_2^c), & \frac{1}{2}u_{3z} - \frac{2}{3}(1 - \lambda_3^c) \end{bmatrix}^T \quad (\text{F.7})$$

$$\mathbf{u}_8 = \begin{bmatrix} \frac{-1}{2}u_{2x}, & \frac{1}{2}u_{1y}, & \frac{-2}{3}(1 - \lambda_3^c) \end{bmatrix}^T \quad (\text{F.8})$$

$$\mathbf{u}_9 = \begin{bmatrix} \frac{1}{2}u_{2x}, & \frac{-1}{2}u_{1y}, & \frac{-2}{3}(1 - \lambda_3^c) \end{bmatrix}^T \quad (\text{F.9})$$

$$\mathbf{u}_{10} = \begin{bmatrix} \frac{1}{2}u_{2x} - \frac{1}{3}(1 - \lambda_1^c), & 0, & \frac{-1}{2}u_{3z} - (1 - \lambda_3^c) \end{bmatrix}^T \quad (\text{F.10})$$

$$\mathbf{u}_{11} = \begin{bmatrix} \frac{-2}{3}(1 - \lambda_1^c), & \frac{1}{2}u_{1y} + \frac{1}{3}(1 - \lambda_2^c), & \frac{1}{2}u_{3z} \end{bmatrix}^T \quad (\text{F.11})$$

$$\mathbf{u}_{12} = \begin{bmatrix} \frac{-1}{2}u_{2x} - (1 - \lambda_1^c), & 0, & \frac{1}{2}u_{3z} - \frac{1}{3}(1 - \lambda_3^c) \end{bmatrix}^T \quad (\text{F.12})$$

$$\mathbf{u}_{13} = \begin{bmatrix} \frac{-2}{3}(1 - \lambda_1^c), & \frac{-1}{2}u_{1y} - \frac{1}{3}(1 - \lambda_2^c), & \frac{-1}{2}u_{3z} \end{bmatrix}^T \quad (\text{F.13})$$

$$\mathbf{u}_{14} = \begin{bmatrix} \frac{1}{2}u_{2x} - \frac{2}{3}(1 - \lambda_1^c), & \frac{-1}{2}u_{1y} - \frac{2}{3}(1 - \lambda_2^c), & 0 \end{bmatrix}^T \quad (\text{F.14})$$

$$\mathbf{u}_{15} = \begin{bmatrix} \frac{-1}{2}u_{2x} - \frac{2}{3}(1 - \lambda_1^c), & \frac{1}{2}u_{1y} - \frac{2}{3}(1 - \lambda_2^c), & 0 \end{bmatrix}^T \quad (\text{F.15})$$

$$\mathbf{u}_{16} = \begin{bmatrix} \frac{-1}{2}u_{2x} - \frac{1}{3}(1 - \lambda_1^c), & \frac{-2}{3}(1 - \lambda_2^c), & \frac{1}{2}u_{3z} + \frac{1}{3}(1 - \lambda_3^c) \end{bmatrix}^T \quad (\text{F.16})$$

$$\mathbf{u}_{17} = \begin{bmatrix} 0, & \frac{-1}{2}u_{1y} - (1 - \lambda_2^c), & \frac{-1}{2}u_{3z} - \frac{2}{3}(1 - \lambda_3^c) \end{bmatrix}^T \quad (\text{F.17})$$

$$\mathbf{u}_{18} = \begin{bmatrix} \frac{1}{2}u_{2x} + \frac{1}{3}(1 - \lambda_1^c), & \frac{-2}{3}(1 - \lambda_2^c), & \frac{-1}{2}u_{3z} - \frac{1}{3}(1 - \lambda_3^c) \end{bmatrix}^T \quad (\text{F.18})$$

G. SENSITIVITY ANALYSIS

Sensitivity analysis for case of inflation pressure p_A : isotropic volumetric expansion

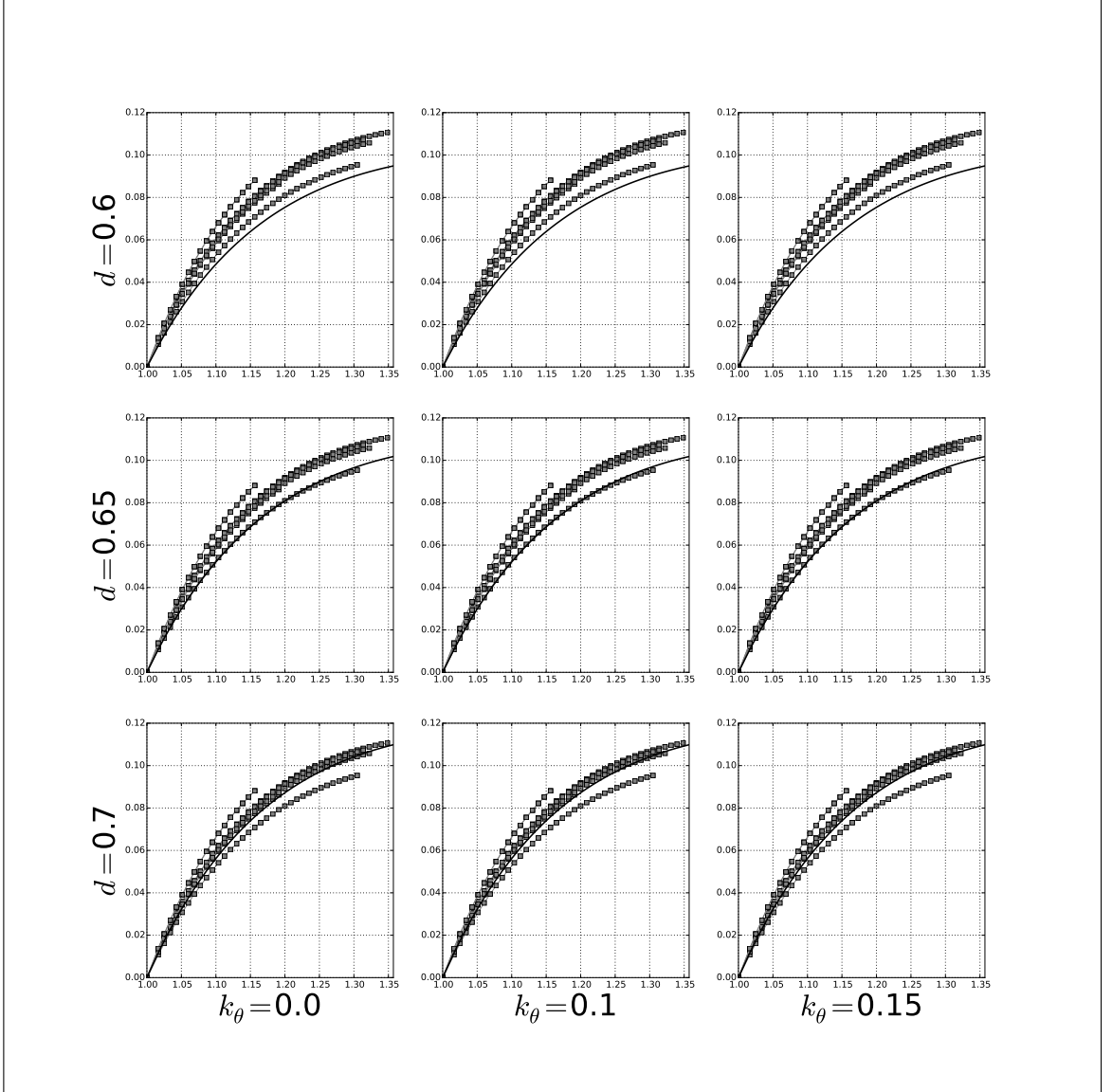


Figure G.1. Sensitivity analysis for $\frac{\text{tr} \boldsymbol{\sigma}^c}{3\mu} - \lambda_1^c$ relation for isotropic volumetric expansion on RVEs models (gray square markers) and TKD model (black continuous lines) under inflation pressure p_A . Rows have tested $d = 0.6, 0.65, 0.7$. Columns have tested $k_\theta = 0.0, 0.1, 0.15$

Sensitivity analysis for case of inflation pressure p_A : anisotropic volumetric expansion

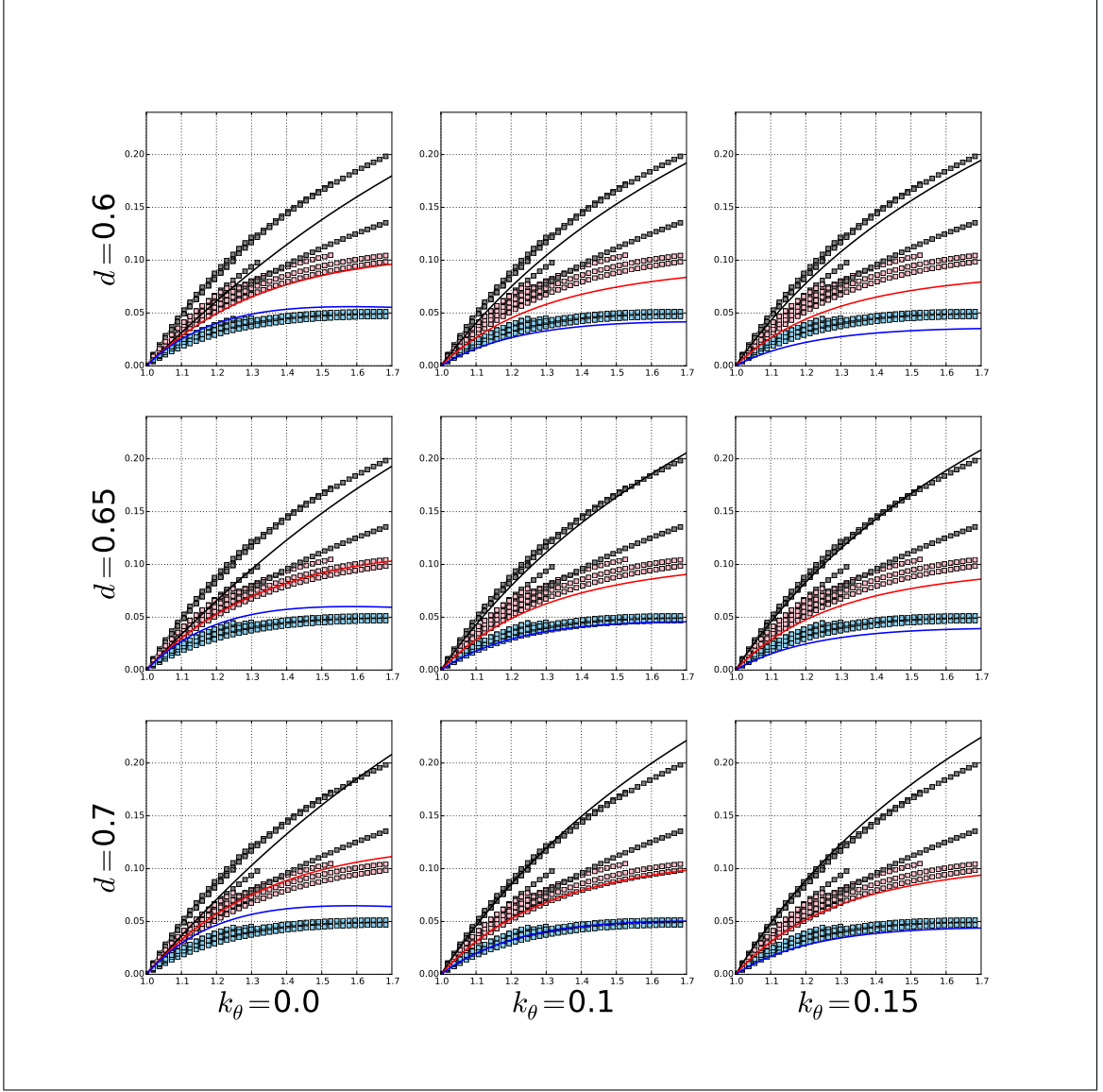


Figure G.2. Sensitivity analysis for $\frac{\sigma_{11}^c}{\mu} - \lambda_1^c$, $\frac{\sigma_{22}^c}{\mu} - \lambda_1^c$, $\frac{\sigma_{33}^c}{\mu} - \lambda_1^c$ relations for anisotropic volumetric expansion on RVEs models (gray, pink and sky-blue square markers respectively) and TKD model (black, red and blue continuous lines respectively) under inflation pressure p_A . Rows have tested $d = 0.6, 0.65, 0.7$. Columns have tested $k_\theta = 0.0, 0.1, 0.15$.

Sensitivity analysis for case of inflation pressure p_A : equibiaxial elongation

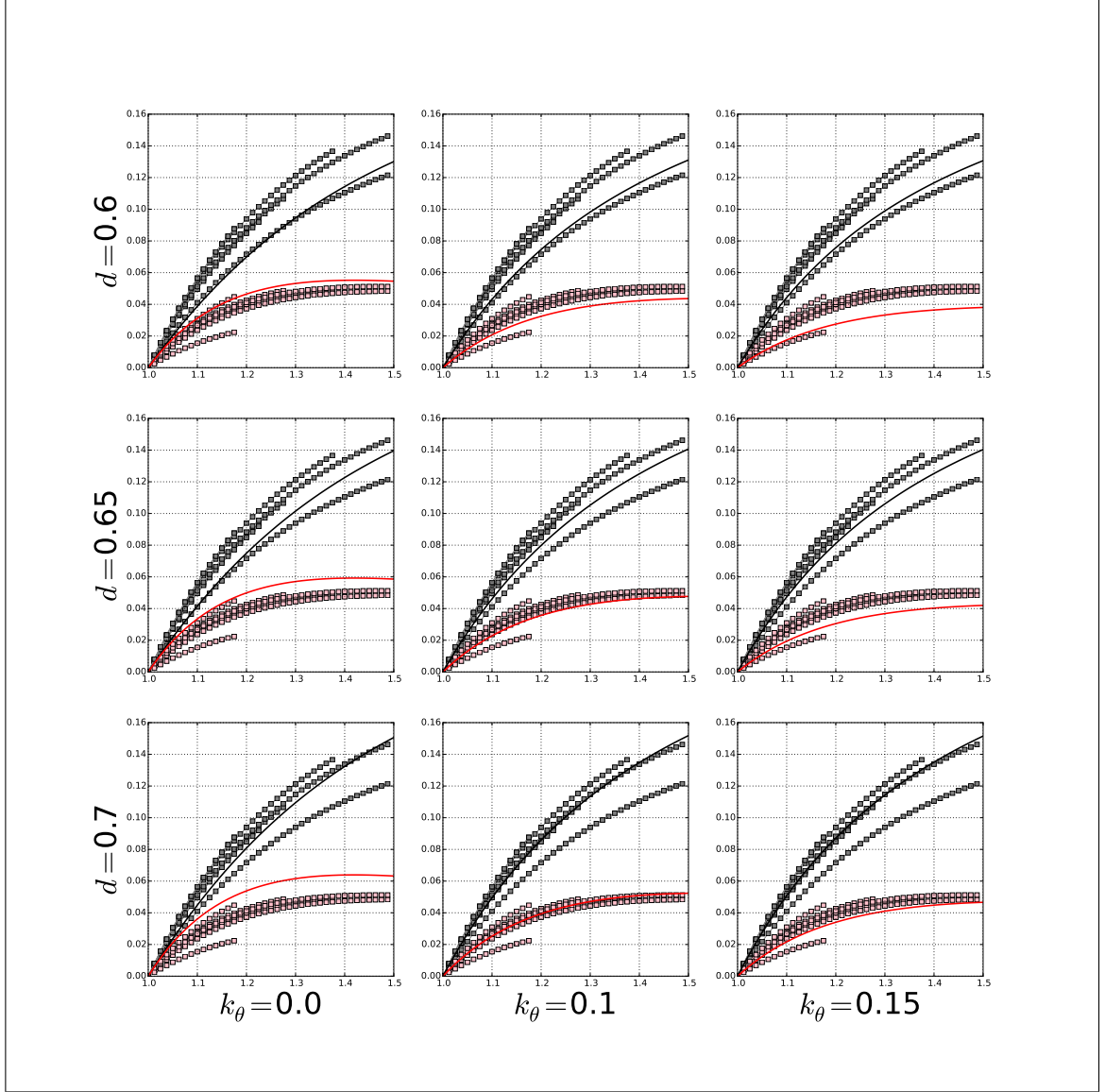


Figure G.3. Sensitivity analysis for $\frac{\sigma_{11}^c + \sigma_{22}^c}{2\mu} - \lambda_1^c$ and $\frac{\sigma_{33}^c}{\mu} - \lambda_1^c$ relations for equibiaxial elongation on RVEs models (gray and pink square markers respectively) and TKD models (black and red continuous lines respectively) under inflation pressure p_A . Rows have tested $d = 0.6, 0.65, 0.7$. Columns have tested $k_\theta = 0.0, 0.1, 0.15$.

Sensitivity analysis for case of inflation pressure p_A : uniaxial elongation

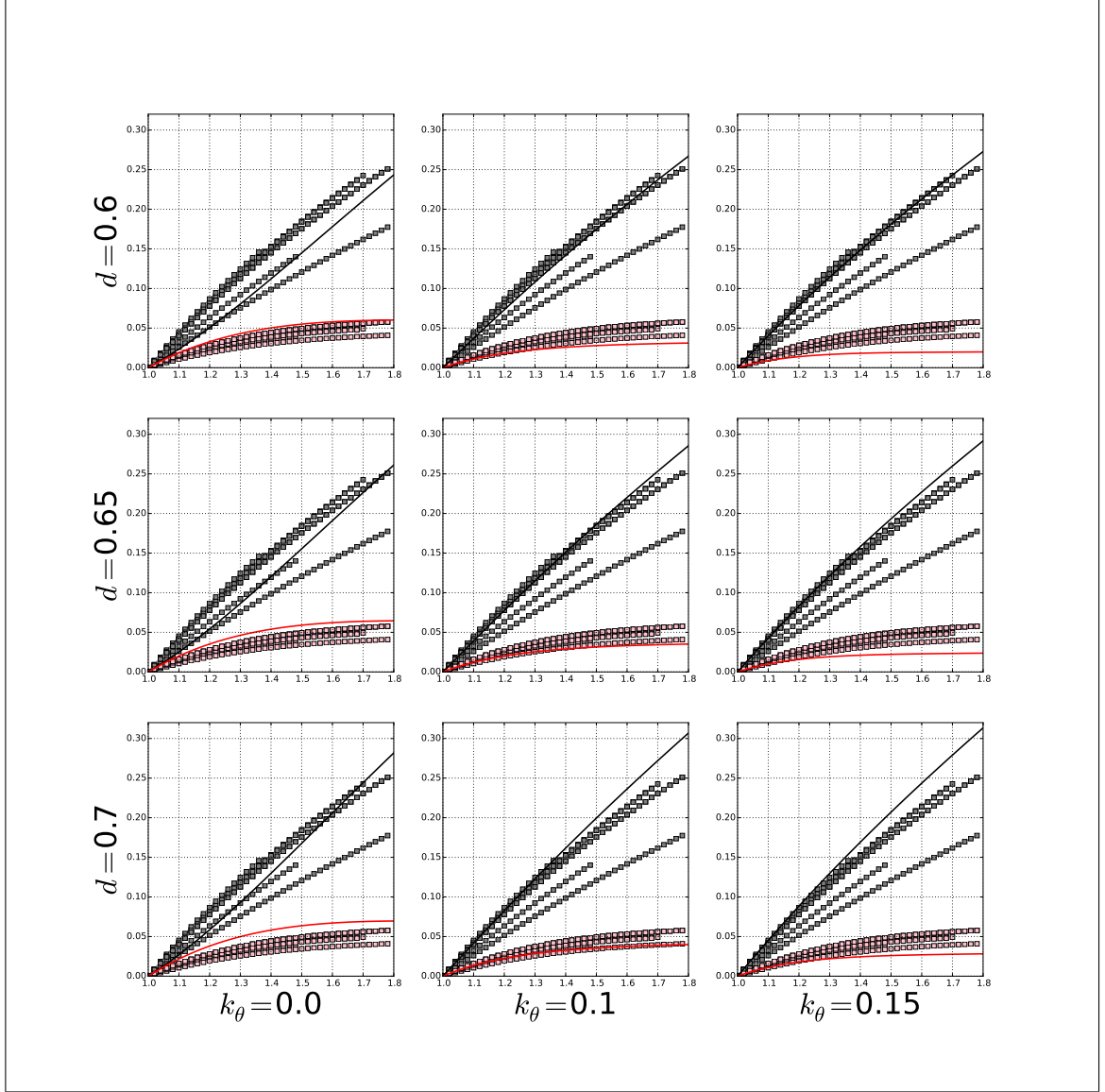


Figure G.4. Sensitivity analysis for $\frac{\sigma_{11}^c}{\mu} - \lambda_1^c$ and $\frac{\sigma_{22}^c + \sigma_{33}^c}{2\mu} - \lambda_1^c$ relations for uniaxial deformation on RVEs models (gray and pink square markers respectively) and TKD models (black and red continuous lines respectively) under inflation pressure p_A . Rows have tested $d = 0.6, 0.65, 0.7$. Columns have tested $k_\theta = 0.0, 0.1, 0.15$.

Sensitivity analysis for case of inflation pressure p_B : isotropic volumetric expansion

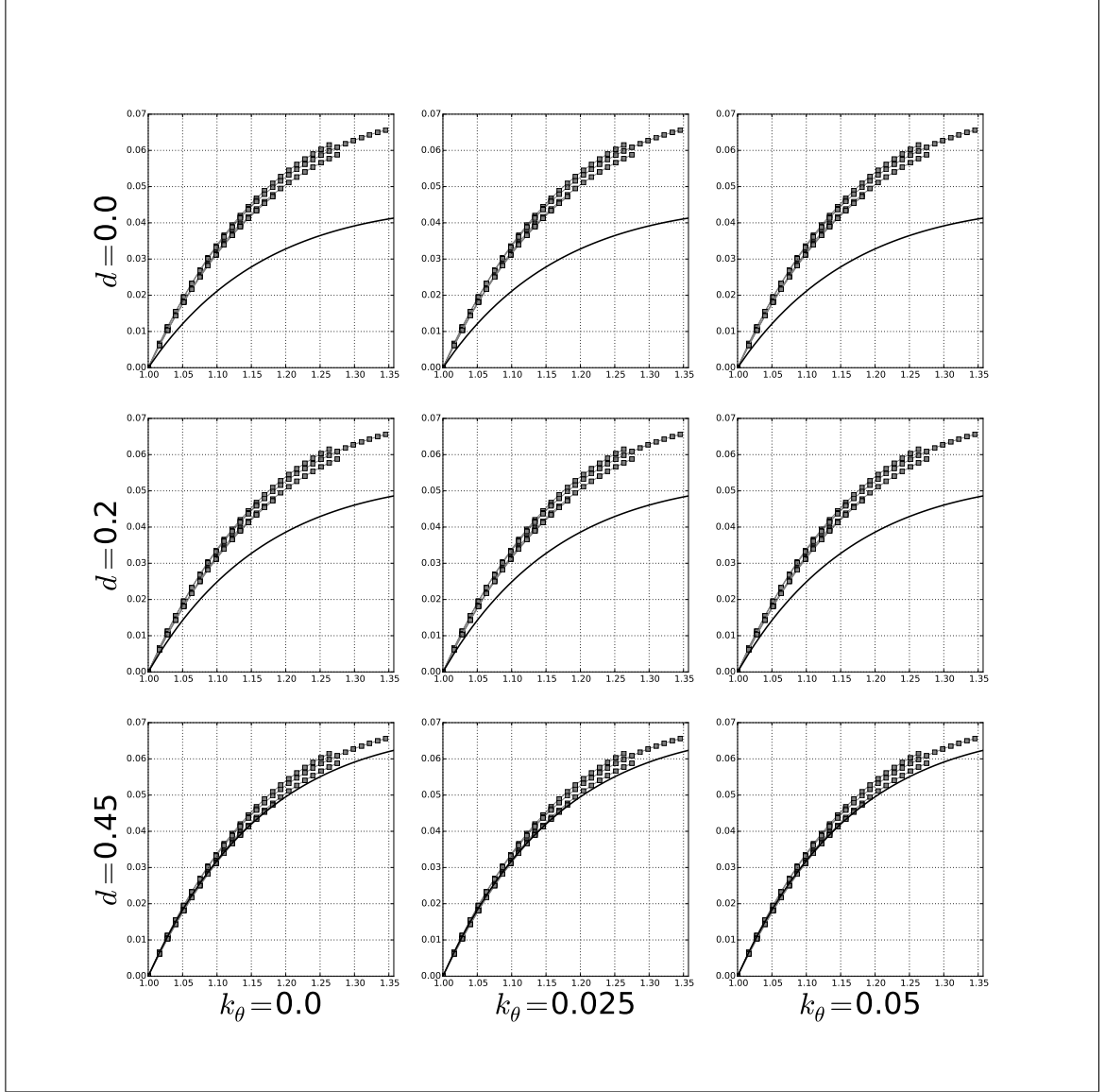


Figure G.5. Sensitivity analysis for $\frac{\text{tr} \sigma^c}{3\mu} - \lambda_1^c$ relation for isotropic volumetric expansion on RVEs models (gray square markers) and TKD model (black continuous lines) under inflation pressure p_B . Rows have tested $d = 0.0, 0.2, 0.45$. Columns have tested $k_\theta = 0.0, 0.025, 0.05$.

Sensitivity analysis for case of inflation pressure p_B : anisotropic volumetric expansion

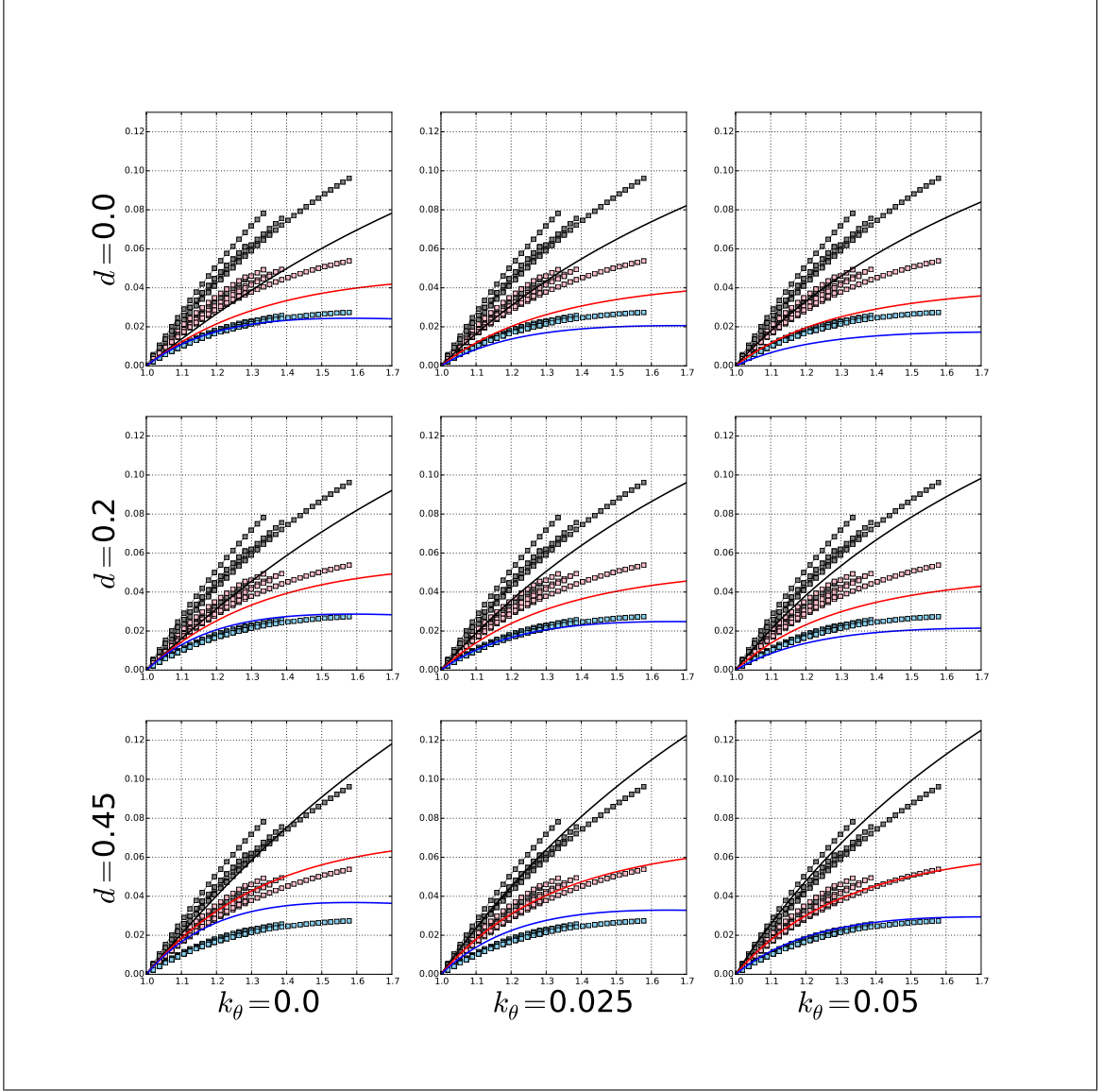


Figure G.6. Sensitivity analysis for $\frac{\sigma_{11}^c}{\mu} - \lambda_1^c$, $\frac{\sigma_{22}^c}{\mu} - \lambda_1^c$, $\frac{\sigma_{33}^c}{\mu} - \lambda_1^c$ relations for anisotropic volumetric expansion on RVEs models (gray, pink and sky-blue square markers respectively) and TKD model (black, red and blue continuous lines respectively) under inflation pressure p_B . Rows have tested $d = 0.0, 0.2, 0.45$. Columns have tested $k_\theta = 0.0, 0.025, 0.05$.

Sensitivity analysis for case of inflation pressure p_B : equibiaxial elongation

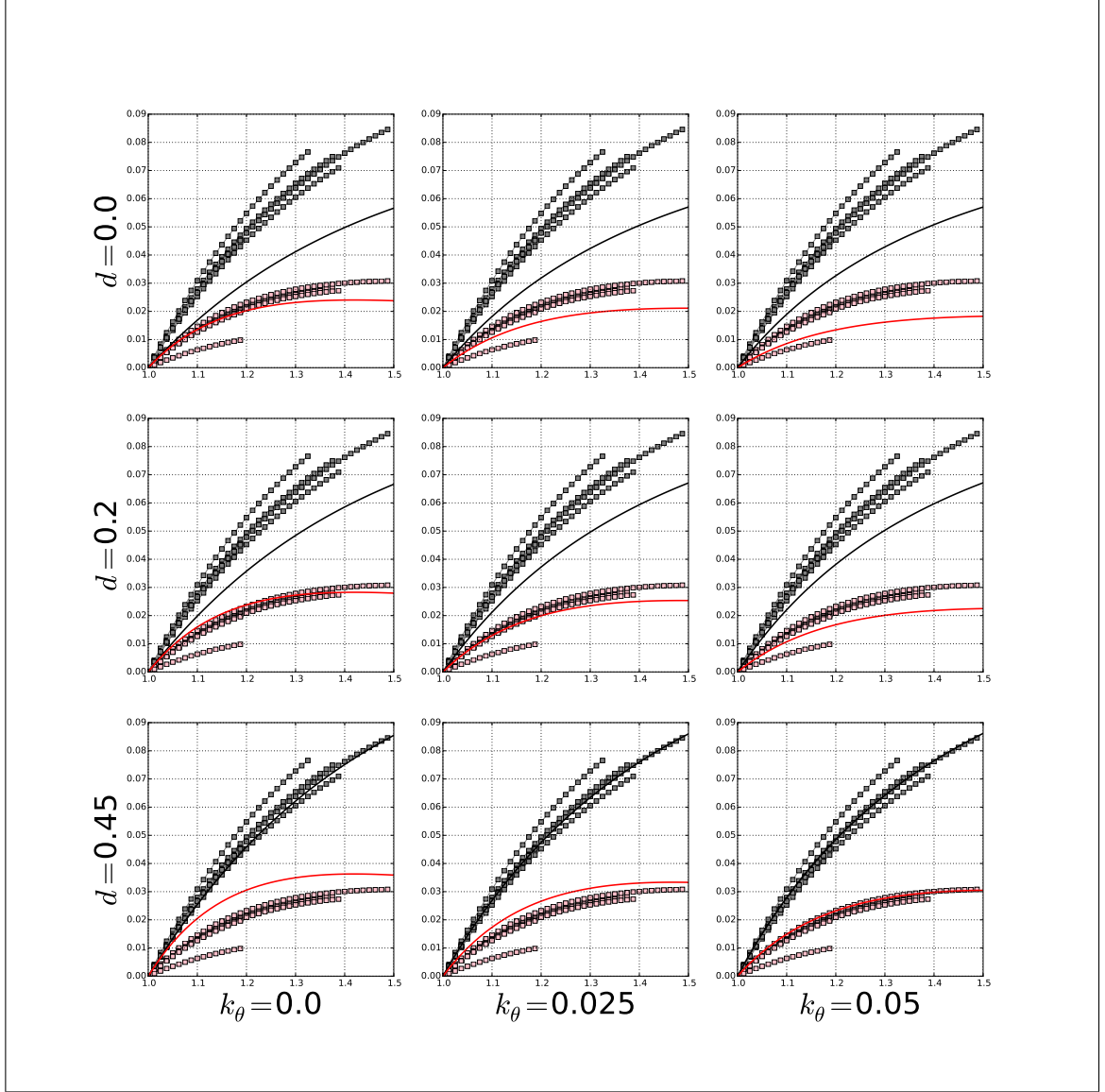


Figure G.7. Sensitivity analysis for $\frac{\sigma_{11}^c + \sigma_{22}^c}{2\mu} - \lambda_1^c$ and $\frac{\sigma_{33}^c}{\mu} - \lambda_1^c$ relations for equibiaxial elongation on RVEs models (gray and pink square markers respectively) and TKD models (black and red continuous lines respectively) under inflation pressure p_B . Rows have tested $d = 0.0, 0.2, 0.45$. Columns have tested $k_\theta = 0.0, 0.025, 0.05$.

Sensitivity analysis for case of inflation pressure p_B : uniaxial elongation

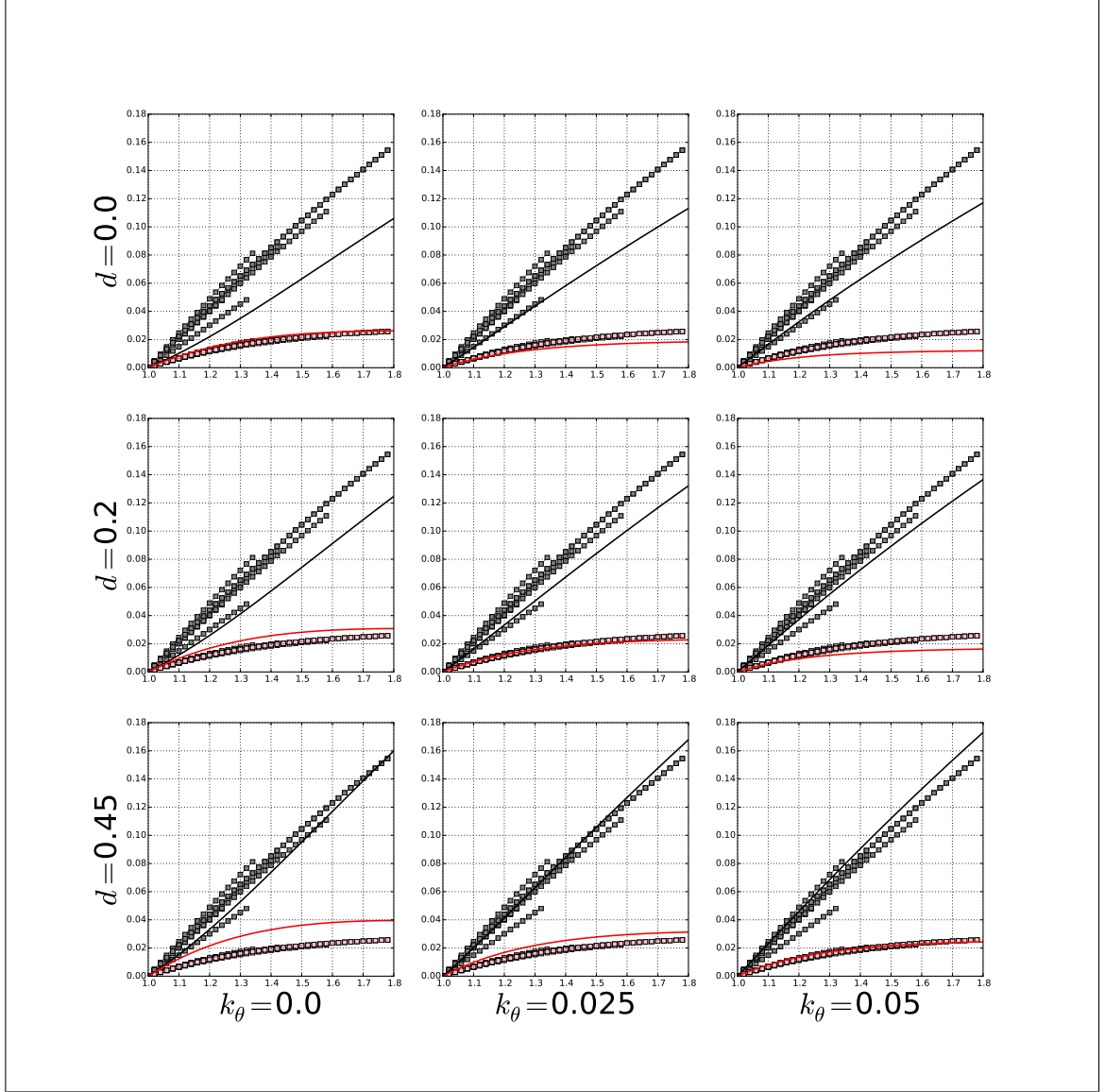


Figure G.8. Sensitivity analysis for $\frac{\sigma_{11}^c}{\mu} - \lambda_1^c$ and $\frac{\sigma_{22}^c + \sigma_{33}^c}{2\mu} - \lambda_1^c$ relations for uniaxial deformation on RVEs models (gray and pink square markers respectively) and TKD models (black and red continuous lines respectively) under inflation pressure p_B . Rows have tested $d = 0.0, 0.2, 0.45$. Columns have tested $k_\theta = 0.0, 0.025, 0.05$.