Analysis and Quantification of Chronic Obstructive Pulmonary Disease Based on HRCT Images

Pena, Isabel Pino

DOI (link to publication from Publisher):
10.5278/vbn.phd.med.00077

Publication date:
2016

Document Version
Publisher's PDF, also known as Version of record

ANALYSIS AND QUANTIFICATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE BASED ON HRCT IMAGES

BY
ISABEL PINO PEÑA

DISSERTATION SUBMITTED 2016

AALBORG UNIVERSITY
DENMARK

ANALYSIS AND QUANTIFICATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE BASED ON HRCT IMAGES

by

Isabel Pino Peña

AALBORG UNIVERSITY
DENMARK

Dissertation submitted

.

Dissertation submitted: October 4, 2016

PhD supervisor: Associate Prof. Lasse Riis Østergaard, Ph.D.
Aalborg University

Assistant PhD supervisor: Associate Prof. Jesper Carl, Ph.D.
Aalborg University

PhD committee: Associate Professor Ulrike Pielmeier (chairman)
Aalborg University

Professor, Head of Department Rasmus Larsen
Technical University of Denmark

Dr., Associate Professor Raul San Jose Estepar
Harvard Medical School

PhD Series: Faculty of Medicine, Aalborg University

ISSN (online): 2246-1302
ISBN (online): 978-87-7112-820-8

Published by:
Aalborg University Press
Skjernvej 4A, 2nd floor
DK – 9220 Aalborg Ø
Phone: +45 99407140
aauf@forlag.aau.dk
forlag.aau.dk

Printed in Denmark by Rosendahls, 2016

The thesis is based on the following three papers:

Paper A:

Isabel Pino Peña, Morten Vuust, Helene Møller Nielsen, Ulla Møller Weinreich, Jesper Carl, Lasse Riis Østergaard. Quantitative High-Resolution CT Analysis of Air Trapping and Airway Thickening in Patients with COPD. Jacobs Journal of Pulmonology, 1.2 (2015) pp. 1–7., 2015.

Paper B:

Isabel Pino Peña, Thomas Holm Sandberg, Morten Vuust, Ulla Møller Weinreich, Jesper Carl, Anne Sofie Korsager, Lasse Riis Østergaard. Automated lung segmentation with main airway extraction in patients with chronic obstructive pulmonary disease. Submitted to Journal of Medical Imaging.

Paper C:

Isabel Pino Peña, Veronika Cheplygina, Sofia Paschaloudi, Morten Vuust, Jesper Carl, Ulla Møller Weinreich, Lasse Riis Østergaard, Marleen de Bruijne. Automatic Emphysema Detection using Weakly Labeled HRCT Lung Images. Submitted to Medical Physics.

Additionally, the following work was conducted during the Ph.D.:

Veronika Cheplygina, Isabel Pino Peña, Jesper Holst Pedersen, Lauge Sørensen, Marleen de Bruijne. Transfer learning for multi-center classification of chronic obstructive pulmonary disease. In preparation to be submitted to IEEE Transactions on Medical Imaging.

ENGLISH SUMMARY

Chronic obstructive pulmonary disease (COPD) is a growing health problem worldwide, and in 2030, it is expected to be the third leading cause of mortality. Tobacco abuse is the main cause of COPD, but prolonged exposure to fumes and chemical dust has also been proved to cause COPD. COPD is a treatable but not curable disease that is characterized by airway obstruction and loss of lung tissue elasticity. The main manifestations of COPD are emphysema and chronic bronchitis.

The diagnosis and assessment of disease severity and progression rely on a pulmonary function test (PFT), clinical estimation and chest imaging. The most common PFT is spirometry, which has been used for many years as the sole test to diagnose and classify COPD. However, spirometry only provides information about obstruction in the lungs. In contrast, high-resolution computed tomography (HRCT) scans are a powerful tool to assess the global and local quantification of COPD. HRCT scans are used clinically to assess emphysema and the extension of it. This qualitative assessment is performed visually by radiologists. However, the qualitative interpretation is time-consuming and relies on the ability and experience of the radiologist, making it prone to errors and introducing intra- and inter-observer variability. Therefore, automated quantitative methods to characterize COPD are desired.

This thesis aims to provide automatic methods to quantify emphysema and chronic bronchitis using HRCT scans. Three studies were conducted as part of this Ph.D. thesis. The first study investigates the relationship between the airway wall thickness measured in inspiratory scans and the air trapping quantified in expiratory scans and how the measurements are related with spirometry. The second study presents an automatic method to segment lungs affected by COPD. Although lung segmentation is not required for clinicians to assess emphysema or chronic bronchitis, it is a major step for the automatic quantification of diseases in the lung parenchyma. The lung segmentation method introduced in the second study is used as the starting point of the third study. In the final study, the focus is to quantify emphysema lesions in the lung parenchyma. Traditional automatic emphysema quantification relies on manual annotations of emphysema areas. In the study presented in this thesis, the automatic quantification of emphysema uses HRCT scans that do not contain manual annotations.

In conclusion, this Ph.D. thesis presents automatic methods to bring objectivity in the assessment of COPD.

DANSK RESUME

Kronisk obstruktiv lungesygdom (KOL) er et voksende sundhedsproblem og forventes i 2030 at være den tredje hyppigste dødsårsagglobalt. Tobaksekspositionen er den hyppigste årsag til KOL, men også længerevarende eksponering med kemiske dampe eller støv er blevet påvist at kunne forårsage KOL. KOL kan behandles men ikke kureres og er karakteriseret ved luftvejsobstruktion og tab af elasticitet i lungevævet. KOL kendetegnes primært ved emfysem og kronisk obstruktiv bronkitis.

Diagnostik, bedømmelse af sværhedsgrad og sygdomsudviklingen afhænger af lungefunktionstest, klinisk vurdering og skanninger af brystkassen. . Den mest anvendte lungefunktionstest er spirometri, der har været anvendt i mange år som den eneste test til diagnostik og klassificering af KOL. Det er imidlertid blevet påvist, at spirometri kun kan beskrive lungernes obstruktivitet. I modsætning hertil giver høj opløsning computertomografi (HRCT) skanninger et stærkt værktøj til at kvantificere både globale og lokale forekomster af KOL. Normalt anvendes HRCT skanninger til at bedømme forekomsten og udbredelsen af emfysem. Denne kvalitative bedømmelse foretages visuelt af radiologer. En sådan kvalitativ bedømmelse er imidlertid tidskrævende og afhænger af radiologens erfaring og formåen, hvilket resulterer i en tilbøjelighed til fejl og indebærer inter- og intraobservatørvariationer. Det er derfor ønskværdigt at have en automatisk kvantitativ metode til at karakterisere KOL.

Denne afhandling har til formål, at udvikle automatiske metoder til at kvantificere emfysem og kronisk obstruktiv bronkitis ved at bruge HRCT skanninger. Tre studier er derfor blevet udført som en del af denne Ph.d. afhandling. Det første studie undersøger forholdet mellem luftvejsforsnævring målt under inspiratoriske skanninger og luftvejsobstruktion målt under ekspiratoriske skanninger, samt hvordan begge målinger relaterer til resultaterne fra spirometri. Andet studie er en automatisk metode til segmentering af lunger med KOL. Segmentering af lungerne er ikke en forudsætning for klinisk bedømmelse af emfysem og kronisk obstruktiv bronkitis, men er et stort skridt i retningen af automatisk kvantificering af sygdomme i lungeparenkymet. Lungesegmenteringen fra andet studie benyttes derfor som grundlag for tredje studie. I det tredje og sidste studie fokuseres der på, at kvantificere emfysem i lungeparenkymet. Traditionelt har automatisk emfysemkvantificering været afhængig af manuel annotation af det emfysem ramte område. I det tredje studie i denne afhandling benytter den automatiske kvantificering af emfysem HRCT skanninger uden manuel annotation.

Denne Ph.d. afhandling præsentere automatiske værktøjer, der forventes at kunne hjælpe i den kliniske bedømmelse af KOL på en objektiv måde.

PREFACE

This Ph.D. thesis has been submitted for assessment in partial fulfillment of the Ph.D. degree at the Department of Health Science and Technology, Aalborg University, Denmark. This thesis presents the work conducted during this Ph.D. study during the period of August 2013 to August 2016. This Ph.D. was supervised by Lasse Riis Østergaard, Jesper Carl and Ulla Møller Weinreich, Aalborg University.

The work was conducted in collaboration with the Pulmonary Department at Aalborg University Hospital and the Radiological Department at Vendsyssel Hospital in Frederikshavn. Both departments collaborated with the data used in all studies during this Ph.D. Part of this Ph.D. research was performed at the Biomedical Imaging Group Rotterdam, Erasmus MC, The Netherlands, under the supervision of Associate Professor, Ph.D., Marleen de Bruijne.

This thesis is based on three studies conducted during the Ph.D. research, which resulted in three articles. In addition to the articles, the thesis includes an introduction with an overview of the research field and a discussion of the presented work, as well as limitations, future perspectives, and conclusions.

ACKNOWLEDGEMENTS

First, I would like to thank my supervisor Lasse Riis Østergaard for his supervision throughout the course of my Ph.D. program. He gave me the opportunity to explore the research world, and he helped me to understand it, to not give up and to continue looking forward, even if that world did not look so bright at some moments. I would also like to thank him for his understanding at some difficult times. My gratitude is also extended to my co-supervisors Jesper Carl and Ulla Møller Weinreich, who have helped me to understand the clinical perspective of this research and have always been willing to answer my questions and give me feedback.

I am in debt to Morten Vuust because without his inestimable collaboration, this research would not have been possible. Thank you so much for being willing to help me from the very beginning and for teaching me what can be observed in an HRCT scan. I am also very glad to have worked with Sofia Paschaloudi. It has been a pleasure for me to have the opportunity to work with you. Both of you were always ready to help me and provided ideas for finding solutions when we faced problems. I want to thank both for spending many hours of your free time doing manual annotations, for trying to learn new software to perform the tasks that I asked of you, and for always having the time to meet with me and have a nice conversation together.

Last year, I was a visiting Ph.D. at the Model-based Medical Image Analysis Group at the Biomedical Imaging Group in Rotterdam. Thank you to Marleen de Bruijne for her supervision and for giving me the opportunity to be a part of such an inspiring place. I want to thank Veronika Cheplygina for assisting with the experiments of the third study. I have learned many new things related to machine learning by working with you. During my visit at the Biomedical Imaging Group, I met Yao Yao and Gadea Mata, who deserve a big thank you. Both of you made my stay in Rotterdam more enjoyable, and we know that we can count on each other at any time.

I would also like to thank the rest of the co-authors of the papers that are part of this thesis: Helene Møller Nielsen, Thomas Holm Sandberg, and Anne Sofie Korsager. I am very grateful for your help and contribution.

I am thankful to Jens Brøndum Frøkjær for allowing me to have a place in the Radiological Department at Aalborg University Hospital when I needed it.

Thank you to all my current and former colleagues at the Medical Informatics (MI) group at the Department of Health Science and Technology, especially my

colleagues in the Medical Image Analysis (MIA) group. My officemates deserve a special mention: Lasse and Pernille, thank you for sharing this Ph.D. experience with me from the beginning; we have lived through many moments and situations together. Hans Christian, Sisse, Clara, and Diana, although we have shared the office for less time, I have nice memories of our time together.

Finally, I would like to thank my family and friends for encouraging me during these three years. The most special thanks goes to my boyfriend Lars for believing in me and always walking by my side no matter how difficult the path is.

TABLE OF CONTENTS

CHAPTER 1. INTRODUCTION

In the last 40 years, medical imaging modalities, such as computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET), have improved the diagnosis of many diseases. Medical imaging provides clinicians an inside view of the human body in a noninvasive way. Moreover, it provides a more detailed view of the anatomy affected by the disease, enabling a more accurate, rapid diagnosis and precise treatment options. Therefore, medical imaging has become the standard approach to assessing all major medical conditions and diseases.

Chest imaging is often used as part of the diagnosis, to assess disease progression, for treatment planning and as a screening method for lung diseases. The most common chest image technique is X-ray because it is cheap and easy to perform. It is used as a primary diagnostic method, often to exclude some pathologies. However, X-ray is limited in the diagnosis of some diseases due to the superimposition of different structures. Therefore, imaging methods, such as CT or MRI scans, which provide more information in 3D are often used.

Humans are good at recognizing objects and patterns in an image. Radiologists are the experts who inspect medical images, and they can recognize a disease by the changes that appear in the lung parenchyma. They also delineate anatomical structures and tumors for diagnostic purposes. These tasks are time-consuming and subjective. Automatic and semi-automatic computer methods have been developed to help radiologists to identify and quantify diseases. Usually, computer methods first segment the organ of interest to use it for treatment planning, for example, in image-guided radiotherapy, or for further analysis of the disease. A common approach to analyzing lung diseases is texture analysis, which can use the differences in the intensities of scans to identify and quantify diseases.

Chronic obstructive pulmonary disease (COPD) is a lung disease in which medical imaging plays a key role in monitoring the evolution. The preferred imaging technique is high-resolution computed tomography (HRCT) scans, which can acquire images with less than one millimeter resolution. The major conditions associated with COPD are emphysema and chronic bronchitis. Radiologists can identify signs of chronic bronchitis as thickening in the airways in inspiratory HRCT scans or as air trapping in expiratory HRCT scans. To identify emphysema, radiologists look at the whole lung in the inspiratory HRCT scans, searching for areas with low-intensity values inside the lung parenchyma. Automatic methods will aid radiologists by providing an objective, time-saving and quantitative evaluation of COPD.

This thesis presents automatic methods that may support radiologists in the assessment of COPD. The thesis is based on three studies; the first study aims to establish the relationship between airway wall thickness and air trapping. Both descriptors can be quantified in HRCT scans using image analysis methods, and their relationship is investigated by applying statistical models. The second study presents a method to segment lungs from patients with COPD. An accurate segmentation of the lungs makes it more convenient to conduct further investigations. The focus of the third study is to analyze and classify textures to identify emphysema lesions. In this thesis, the lungs are segmented as a whole, omitting the segmentation of their lobes. The lung segmentation is used as a first step in the identification of emphysema lesions and is intended to be performed in the full lung and not at specific anatomical locations.

CHAPTER 2. BACKGROUND

This chapter gives an overview of the background for the thesis. It aims to provide a description of chronic obstructive pulmonary disease (COPD), the role of images in the diagnosis of COPD and the state of the art of how the diagnosis and treatment of lung disease can benefit from image analysis and the methods developed.

2.1. COPD OVERVIEW

COPD is a worldwide health issue that is caused mostly by tobacco consumption, although long-term exposure to dust, chemical particles, and fumes has also been demonstrated to be a risk factor [1]. COPD is in the top five causes of mortality and is expected to become the third leading cause of death in 2030 [2]. COPD is an irreversible disease, but it can be prevented and treated to control the progression of the disease. It is a multicomponent disease that includes airway inflammation, obstruction and structural changes due to parenchymal destruction [3]. Airway inflammation and obstruction have been closely related to chronic bronchitis and lung parenchymal destruction with emphysema, see Figure 1.

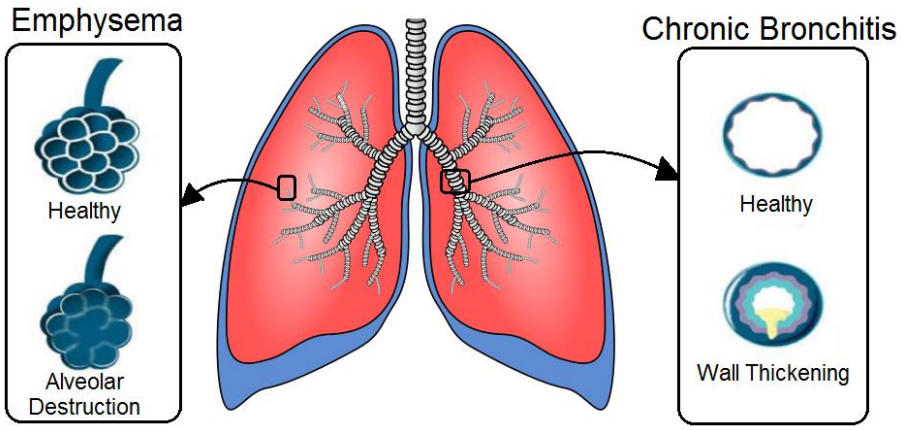

Figure 1: Overview and main manifestations of COPD. Image adapted from [4].

Chronic bronchitis is the most common representation of airway diseases. It is characterized by inflammation and irritation, with an increase of mucus in the bronchi that causes coughing and sputum production [5]. In COPD patients, the symptoms of chronic bronchitis are associated with thickening of the airway walls [6].

Emphysema is a destruction of the lung parenchyma, specifically a loss of elasticity and increased compliance of the alveoli [5]. Emphysema can be categorized into three types: centrilobular, paraseptal and panlobular. Examples of centrilobular emphysema and paraseptal emphysema can be seen in Figure 2A and 2B, respectively. It is common in patients with severe disease that both types of emphysema co-habit [6,7].

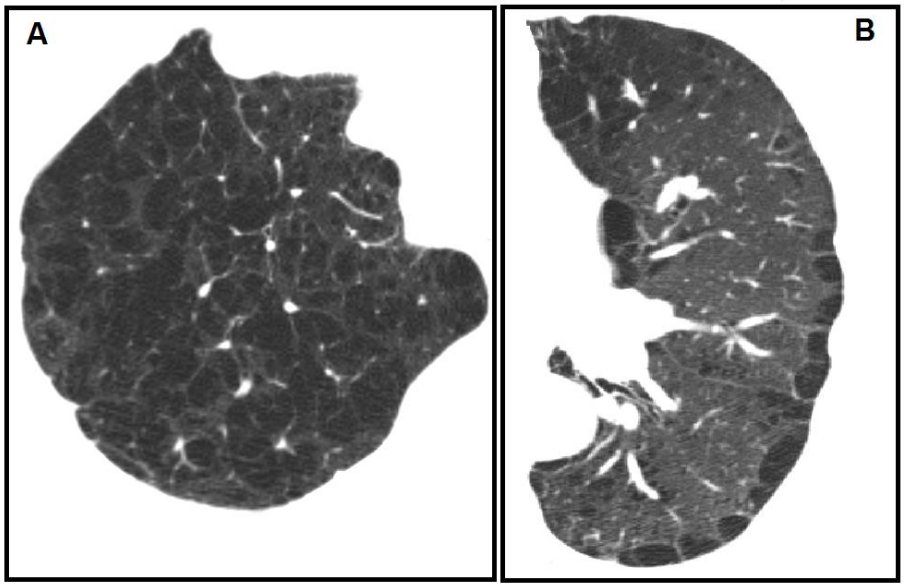

Figure 2: Examples of emphysema patterns for the different types of emphysema; A) centrilobular emphysema, B) Paraseptal emphysema. Emphysema can be seen as dark areas surrounded by normal lung tissue (gray areas). White pixels represent vessels and airway walls.Scans from the Frederikshavn dataset in study III.

A pulmonary function test (PFT) is required to verify the diagnosis of COPD and to assess its severity; the most common PFT is spirometry. Because the diagnosis of COPD is defined as a chronic airway obstruction, it cannot be established without this PFT. To diagnose airflow limitations, the ratio between the forced expiratory volume in the first second (FEV_1) and the forced vital capacity (FVC) should be less than 0.7, with FEV_1 <80% [8]. The severity classification of airflow limitation is

categorized into four groups, 1-4, ranging from mild to very severe. This GOLD stages have served to classify COPD for many years [3]. However, despite being an objective measure of airflow limitation, spirometry alone cannot be used to assess COPD severity. FEV_1 poorly correlates with COPD symptoms, such as dyspnea [9], and it does not provide information about the extent of the airflow limitation [10]. Therefore, to classify patients with COPD, more information than the values of airflow limitation is needed; thus, a combined COPD assessment is recommended. The combined assessment includes lung function, symptoms, dyspnea score and exacerbation history to stratify patients into four categories, A-D, where A represent the least severe and D the most severe [3,11].

In addition to the tests that are required to stratify the patients according to the GOLD guidelines, additional investigations are recommended to more precisely determine the disease severity and to gain a better understanding of its extent. These investigations include lung volume and diffusing capacity and imaging. Lung volume can be obtained by a test called body plethysmography, which measures the static volumes of the lung by measuring changes in pressure in a closed system during different respiratory maneuvers. It provides information on the functional residual capacity (FRC_{pleth}), specific airway resistance (sRaw), total lung capacity (TLC), residual volume (RV), and inspiratory capacity (IC) [12,13]. The diffusing capacity for carbon monoxide (DLCO) test provides information about the gas exchange between the lungs and the bloodstream, which occurs in the alveoli. DLCO can detect emphysema in patients with airflow obstruction. A significant relationship between DLCO and emphysema lesions in COPD patients has been demonstrated in several studies [6,14–16].

Imaging diagnostics are available, including chest X-ray and computed tomography (CT) scans. However, chest X-ray may only be used for acute pulmonary changes and some comorbidities; it is not useful to diagnose COPD due to the poor resolution, which prevents the identification of changes in the lung parenchyma [11]. In contrast, CT scans, specifically HRCT scans (see Figure 3), provide a detailed image of the lungs, where changes, such as alveoli enlargement, which occurs in emphysema, can be seen [5]. However, CT scans are not routinely ordered in the assessment of COPD due to the cost and radiation exposure of the patient [17]. Although image quality is directly linked to the radiation dose, several studies have shown that it is possible to obtain chest CT scans with acceptable image quality at a low radiation dose. It is possible to adjust the radiation dose and the exposure time based on the patient size and disease [18].

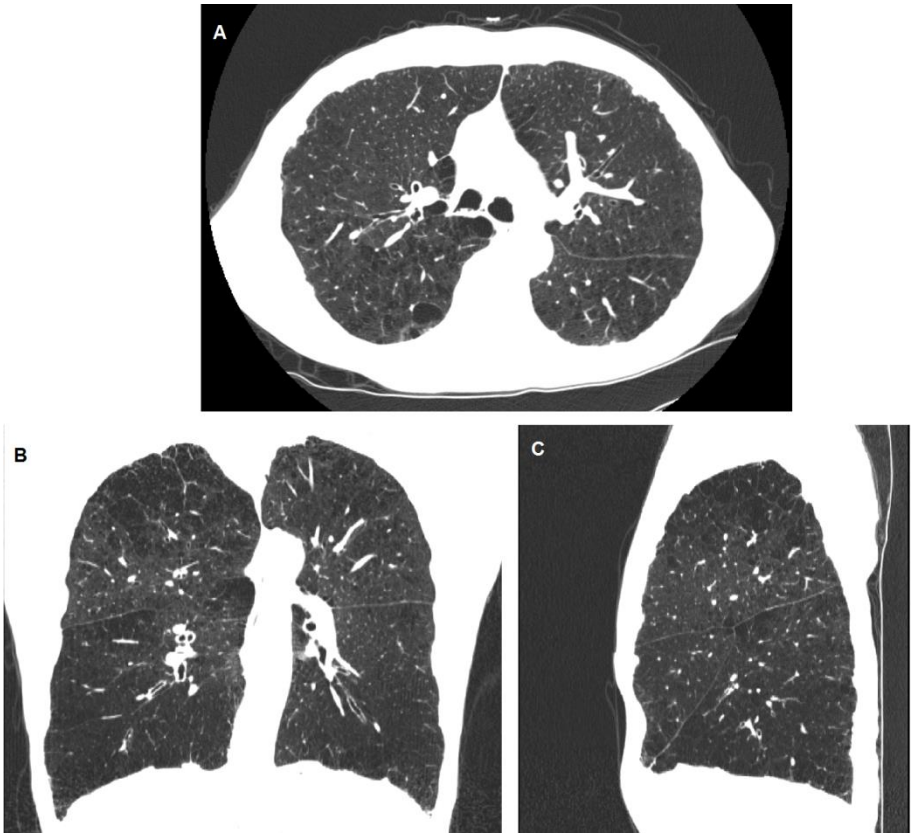

Figure 3: An example of a chest HRCT scan from a subject with COPD. A) axial view, B) coronal view, and C) sagittal view. Scan from study II.

2.2. COPD QUANTIFICATION USING IMAGING IN CHEST CT SCANS

As stated in section 2.1, CT scans can capture the bronchial tree and lung parenchyma with a high level of detail. Moreover, HRCT scans produce chest images quickly with a resolution of less than one millimeter, which for an adult, typically results in a scan with approximately 300 axial slices. These scans with very fine resolution enable the identification of small lesions and changes that occur in the airways and the lung parenchyma. Therefore, the use of CT scans has increased to assess COPD manifestation, such as emphysema, air trapping and airway thickening [7,19,20].

The assessment of CT lung images is usually performed visually by expert radiologists who identify emphysema as low attenuation areas (LAA) in the lung parenchyma. Although radiologists are good at identifying diseases and assessing severity, the quantification of volumetric diseases such as emphysema is challenging, subjective, time-consuming and prone to errors due to intra-observer and inter-observer variability [21–24]. Therefore, automatic and semi-automatic methods to quantify lung disease using CT are needed for a faster and more reliable assessment of the disease and to overcome the limitations of visual assessment.

2.2.1. Airway Quantification

Bronchial wall thickness is one of the most common manifestations of chronic bronchitis in COPD patients. Therefore, measurement of the airway wall is important to assess structural changes and to adjust treatment. Usually, airway wall measurements are performed manually by pulmonologists or radiologists. However, this process is time-consuming and has poor reproducibility [20]. Chest CT scans enable the noninvansive and repeated assessment of the airway wall thickness. The most common methods used to measure airway walls automatically are the full-width at half maximum (FWHM) [25], model-based, integral-based, phase congruency, contour matching, and geometric deformable models [26,27]. The parameters that are usually measured by these methods in the segmental or subsegmental branches are the bronchial lumen diameter, bronchial wall thickness, and total bronchial area [28], see Figure 4.

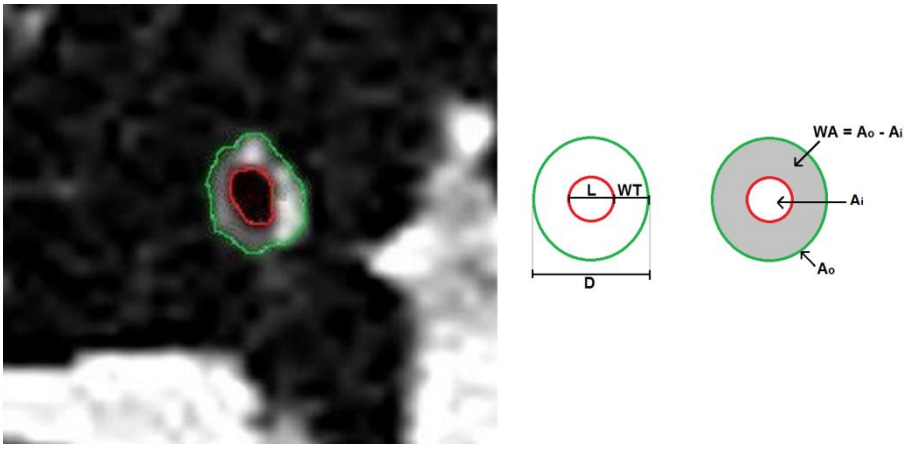

Figure 4: Airway wall thickness measurements. On the left, a cross-sectional view of the airway from the apical bronchus in an HRCT scan from study I. On the right, representation of the measurements. D=bronchial external diameter; L=bronchial lumen diameter; WT=bronchial wall thickness; Ao=airway outer area; Ai=airway inner area; WA=bronchial wall area.

Airway obstruction in patients with COPD usually occurs in the small airways, typically smaller than 2 mm. Therefore, it is difficult to identify airway obstruction in CT scans because these airways are not visible. However, Nakano et al. [29] demonstrated that thickening of large airways might be an alternative for assessing small airway abnormalities. Thus, measurement of wall thickening by CT could be a predictor of small airway obstruction. Alternatively, small airway obstruction can be quantified by measuring air trapping [30]. Air trapping appears in expiratory CT scans as LAA, see Figure 5, and it can be measured as LAA<-856 Hounsfield Unit (HU) [31]. However, air trapping can be affected by emphysema areas. Therefore, the measurement of air trapping needs to be corrected to account for emphysema [32,33].

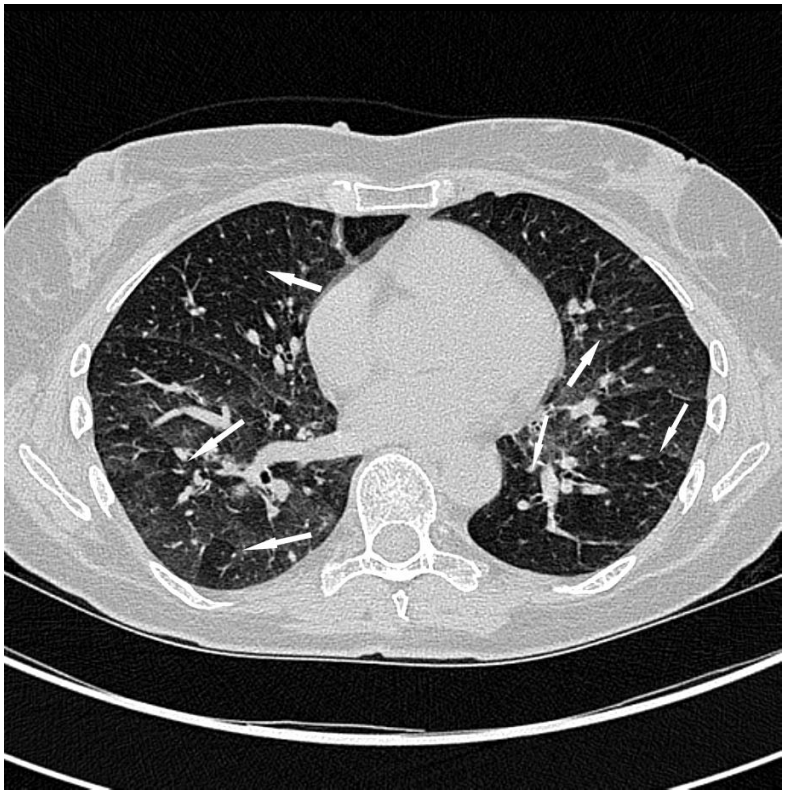

Figure 5: Expiratory HRCT scans from a COPD patient. This subject shows large areas of air trapping, which are indicated by white arrows. Scan from study I.

Based on these approaches for quantifying airway wall thickness and air trapping, study I of this thesis aimed to investigate the relationship between these two obstruction biomarkers by applying statistical methods. To measure the wall thickness in the bronchi, study I used the FWHM method, which is based on rays moving from the lumen center in all directions. The inner wall of the airway is assumed to be located where the intensity is half way between the local minima in the lumen, and the outer wall of the airway is considered to be at half way between the local maxima within the lung parenchyma [32,34], see Figure 1Figure 6. Measurements of the inner wall area, outer wall area, and bronchial wall area were computed from the airway delineations given by the FWHM method.

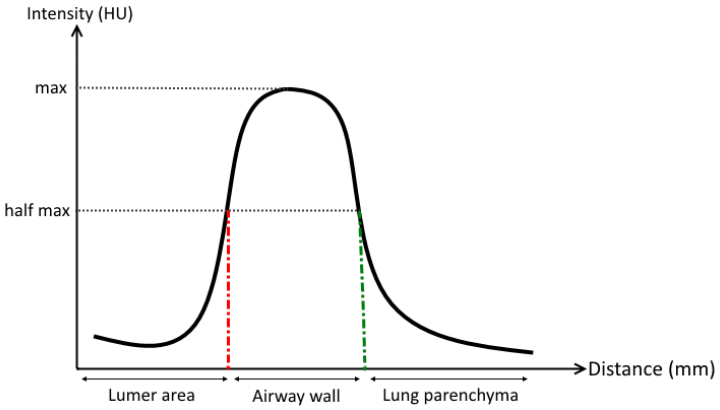

Figure 6: Illustration of the full-width at half maximum (FWHM) method. The red line represents the boundary of the inner wall of the airway; the green line represents the boundary of the outer wall of the airway. The thickness of the airway is the difference between the two boundaries.

Statistical analysis is used in the studies of this thesis to answer questions about the relationship between the quantified measurements of the COPD manifestations. In the case of study I, statistical methods were used to describe the association between the measurements of the airway wall thickness and air trapping and to model the relationship between these two measurements and PFTs.

2.2.2. Emphysema Quantification

The most common approach to quantify emphysema for many years has been based on a threshold [35]. Müller et al. showed in 1988 that emphysema identified using a threshold of -910 HU correlated well with emphysema detected using a histologic sample for the same subject [36]. Additional studies have investigated different thresholds to find the best correlation with emphysema lesions. Although some

variations are accepted for individual lobes, a threshold of -950 HU is commonly used as a reference to quantify emphysema in CT scans with full inspiration [36,37], see Figure 7.

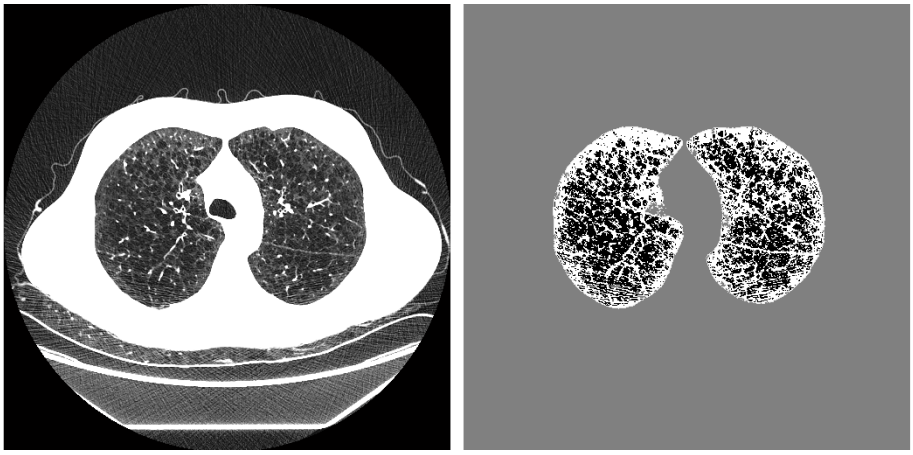

Figure 7: Example of emphysema quantification using a threshold of -950 HU from a scan in study III. On the left, original HRCT scan; on the right, results of the thresholding inside the lung mask.

Nevertheless, the density-based method is sensitive to noise and the scan parameters [38]. Therefore, additional approaches using image analysis methods have been proposed to automatically identify changes in the lung parenchyma. Several of these approaches use texture analysis to detect emphysema and, in some cases, the emphysema type. However, one major problem of texture analysis is that it is susceptible to noise derived from the surrounding anatomical structures [39]. To avoid this effect, texture analysis is applied to previously segmented lungs. In section 2.3, a review of lung segmentation methods is presented, which introduces the state- of- the- art for study II of this thesis.

Emphysema is quantified in CT scans by measuring certain characteristics extracted from the lung parenchyma. These characteristics are represented as feature vectors in a vector space, where each dimension belongs to a specific characteristic. Although there is no agreement with respect to the definition of texture, it can be explained as a pattern that has a specific characteristic [40]. Many studies have used texture features to quantify emphysema, mostly by assessing changes in the intensity level [41,42]. The most common methods are the first- and second-order statistics, which include gray-level co-occurrence matrices (GLCM), gray-level run-length matrices (GLRLM), and intensity level histograms [23,43–48]. Chabat et al. [43] used 13 texture parameters derived from the first- and second-order to differentiate

between two types of emphysema and bronchiolitis. Similarly, in [44], first-order, second-order, and shape features were computed to identify emphysema in patients with mild and severe disease. A similar approach was used in [23], where second-order features were obtained to detect centrilobular emphysema and nodularity automatically. A technique that extracts first-order, second-order, and fractal features based on an adaptive multiple feature method (AMFM) was proposed in [46]. Other examples of texture features used to characterize the lung parenchyma affected by emphysema have been proposed in [49–56]. For example, Sørensen et al. [49] classified in 2D the three types of emphysema using local binary patterns (LBP) as texture features. A later study [51], which aimed to identify subjects with COPD, they used texture features in 3D based on Gaussian filter bank (GFB) due to the difficulty in extrapolating LBP to 3D. Another alternative was introduced in [52] using a combination of Gabor filters (CGF), which encode local intensity information given by LBPs.

Machine learning methods have been applied to classify image features into healthy or emphysematous tissue. This is an automatic method to assist the visual interpretation of radiologists in assessing emphysema in COPD patients. Traditional classifier methods, such as Bayesian classifiers, artificial neural networks, and support vector machines, have been broadly used to classify emphysema and its types [57,58]. However, these types of classifiers require annotated training data to classify unknown CT scans. These annotations are usually performed by clinical experts and are time-consuming and not feasible for longitudinal studies. Therefore, more recent approaches use different types of annotations, for example, those derived from PFTs [59–61], to classify emphysema. This new approach is utilized in study III of this thesis to identify emphysema in non-annotated HRCT scans. The proposed classifiers use global labels extracted from PFT instead of manual annotations, and they classify different textural features computed from the segmented lung parenchyma. These classifiers are a subtype of multiple instance learning (MIL) classifiers, which are explained in more detail in section 2.4. Figure 8 shows an overview of the methodology used in study III. The textural features computed are GLCM and GFB. GLCM is based on the occurrence of a pair of gray-level pixels or voxels at a determined distance and orientation in the HRCT scan. GLCM aims to represent the changes in intensities in the pair of voxels. Texture features, such as energy, entropy and homogeneity among others, are extracted from the results of the computed occurrences in all the distances and orientations. In contrast, GFB uses a convolution of the HRCT scans with a Gaussian function. GFB aims to represent the structures presented in the image, i.e., edges. After the convolution, texture features, such as gradient magnitude, Laplacian of Gaussian or Gaussian curvature among others, are computed.

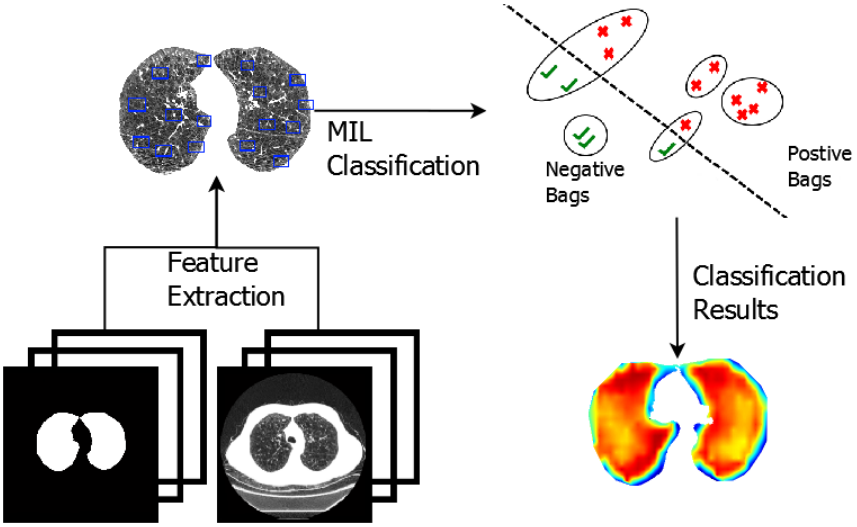

Figure 8: Simplified version of the method used in study III. Texture features are extracted from the lung parenchyma. Two MIL classifiers are trained and tested on previously unseen scans.

2.3. LUNG SEGMENTATION

Segmentation in medical images is used to isolate organs of interest or lesions in the organs for further analysis. Automatic lung segmentation is a challenging task due to the large variability in volume produced by differences in pulmonary inflation. In addition, some diseases make the segmentation task very challenging, such as pleural plaques or ground-glass opacities. These diseases appear in a CT scan with different intensity than the rest of the lung tissue; they have an intensity similar to the tissue surrounding the lungs, which can lead to an inaccurate delineation of the lung. Moreover, for an automatic method, the task of segmenting lungs with severe or very severe pathologies remains challenging. It is important to have a precise segmentation of the organ or lesion of interest because an error in the segmentation can result in an inaccurate quantification of the disease. Therefore, a lung segmentation method is presented in study II to provide an accurate segmentation for further analysis in study III to identify emphysema.

In chest CT scans, the anatomical parts that require segmentation are the lungs, airways, vessels and lung lobes [62]. The segmentation of the vessels, lung lobes, and airways is out of the scope of this thesis. Information on the segmentation of these anatomical structures can be found in [26,35,63–69]. A more detailed lung segmentation analysis from previous studies will be given below. Based on the

review by Mansoor et al. [70], lung segmentation methods can be categorized as follows. Although some specific methods will be presented, most studies combine several methods or use the methods as part of a pipeline that includes pre-processing and/or post-processing.

Thresholding-based methods use the differences in intensity between the lungs or the bronchial tree that appear as black regions surrounded by other tissues with brighter intensities. These methods use a threshold based on HU, which is applied to a whole scan to create a binary image. Armato et al. [71] used thresholding of LAA to segment the lungs. To refine the segmentation, they used morphological operations and eliminated the trachea and main bronchi, the anterior junction line, and the diaphragm.

Region-based methods are similar to thresholding-based methods, but they include information between pixels. The most popular method is region growing, which based on a starting point called seed that is situated inside the lung parenchyma, segments the lungs by adding the neighbor pixels that fulfill a similarity criterion. Van Rikxoort et al. [72] used region growing to segment lungs. However, the performance of the method was not accurate in unhealthy subjects. Therefore, they applied multi-atlas segmentation as a refinement of the region growing segmentation. Other region-based methods include watershed and graph-cuts. Watershed finds the segmentation boundaries by following the gradient until it reaches a local minima. Chen et al. [73] developed a watershed method to identify the lungs, the background, and the trachea. Then, they used connected components to smooth the lung segmentation and removed the background and trachea. Graph-cut uses the information between neighboring pixels; thus, when the contrast between two neighbor pixels is high, they are more likely to be assigned to different classes. In [74–77], the graph-cut method was used as a refinement of a coarser lung segmentation. The graph-cut was used for energy minimization of an anatomical framework based on thresholds and region-based [74], shape prior model [75], multiple sub-graphs built from mesh surfaces, and atlas-based [77].

Shape-based methods incorporate prior shape knowledge of the lungs. The most common shape methods are atlas-based, snakes, active contours and level sets. Atlas-based uses a template of the lungs as prior shape knowledge. First, the template is registered to the image that needs to be segmented; then, the labels from the template propagates to the target image. Sluimer et al. [78] proposed a voxel classification based on multi-atlas registration to segment pathological lungs. Snakes, active contours, and level sets use energy functions to determine the contour of the lungs. Snakes and active contours must be initialized with a prior shape contour. The level-set method was used in [79,80] to identify the lung boundaries.

Neighboring anatomy-guided methods use the information of the surrounding anatomical structures, such as the rib cage, heart, liver and spine, to find the optimal

boundary where the lungs should be segmented. Sun et al. [81] used the identification of the chest cage to initialize the active shape model to segment the lungs.

Machine learning-based methods learn from the data by using features extracted from image patches to identify structures and diseases patterns. These methods use training data to classify pixels or voxels from unknown data into a class label, such as soft tissue, normal lung tissue or unhealthy lung tissue. Pathological lungs were segmented in [82] using a machine learning approach based on texture patterns and a discriminative classifier.

In study II, lung segmentation based on a combination of shape-based and region-based methods is used. Thus, the segmentation method uses multi-atlas, graph-cut, and region growing techniques. The multi-atlas and graph-cut methods to segment the lung parenchyma follow the method presented in [83–85], where the combination of the two approaches was used to segment other organs and tissues in the body. In study II region growing is added to the multi-atlas and graph-cut methods to segment and eliminate the main airways.

The graph-cut method consists of a combination of the graph and the cut. The graph consists of a set of voxels, called nodes, and a set of labels linked to the voxels, called terminals. In the case of lung segmentation, the graph contains two terminals: the lung parenchyma (source, s), and the background (sink, t). In the graph, all edges have a cost, and there are usually two types of edges, the n-links and the t-links. The n-links are the edges that link the voxels of the image, and the t-links are the edges that connect the voxels with the terminals. The cost of the n-links is generated by the gap between close voxels, and the cost of the t-links is given by the allocation of a label to the voxel. The cut of a graph with two terminals consists of dividing the graph into two subsets, one belonging to s and the other to t. The minimum cut is based on finding the minimum cost through all the cuts of the graph, see Figure 9. This approach is also known as maximum flow [86].

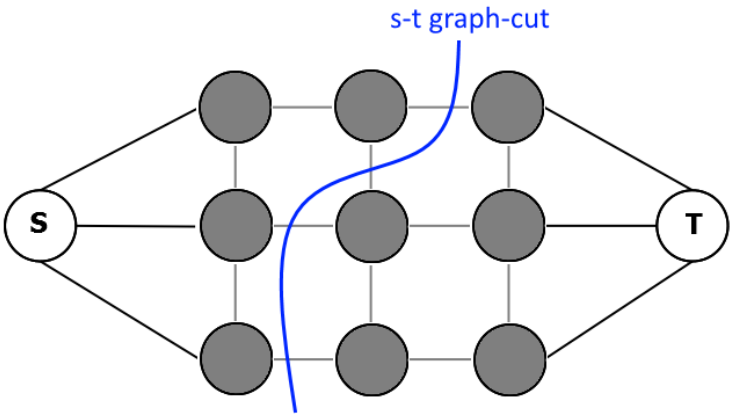

Figure 9: Illustration of the graph-cut method with nine nodes and two terminals. S=source; T=sink; black lines represent the t-links; gray lines represent the n-links; the blue line represents the minimum cut applied on the graph.

In study II, the graph-cut is built based on the association potential and interaction potential. The association potential combines spatial prior knowledge obtained from the registration of multiple atlases with the target image and intensity information, which provides a probability of the voxels being inside or outside the lungs. The interaction potential provides information of the costs for the n-links and t-links from the target image. The segmentation is completed by eliminating the segmented trachea, and main bronchi by region growing. The aim of eliminating the trachea and main bronchi is to achieve an accurate segmentation of the lungs in a difficult area, such as the hilum. Therefore, a coarse airway tree segmentation is conducted. For this purpose, the airway tree does not need to be segmented accurately; the trachea and the airway tree containing the major airways are sufficient. Region growing is used where the seed point is settled in the trachea, which is automatically identified. The region growing stops when major leakages in the bronchi occur. An example of lung segmentation from study II is shown in Figure 10.

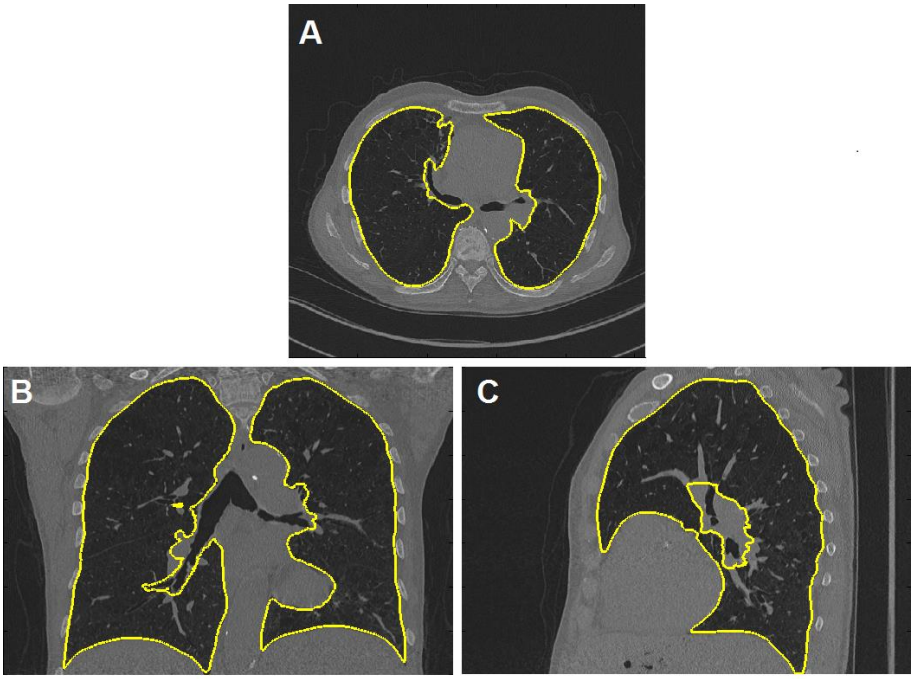

Figure 10: Result of the lung segmentation (yellow delineations) proposed in study II using shape-based and region-based methods. A) axial view, B) coronal view, and C) sagittal view.

2.4. MULTIPLE INSTANCE LEARNING

Supervised machine learning systems learn from data or given examples. A supervised classifier requires a vector of feature values, called instances, and labels representing the categories where each feature belongs, called bags [87]. In medical imaging, classifiers are typically used to identify patients as suffering from a disease or not and to identify diseases. For example, a classifier learns that high blood pressure and a large amount of protein in the urine (instances) in pregnant women after week 20 indicate a high risk of preeclampsia (bag). The supervised classifier can classify an unknown pregnant woman as having a risk or not of suffering preeclampsia. Supervised methods can also identify diseases (bags), but they require examples of the representation of the disease (instances), which are provided as delineations in the images. Traditionally, annotations of diseases are performed manually by radiologists or clinicians, which is very time-consuming and subjective.

MIL classifiers are an alternative to supervised classifiers when the data only have labeled bags available. MIL classifiers are ruled by the *standard* assumption, where a bag is considered positive if and only if it contains at least one positive instance

[88]. Other alternative assumptions have been proposed, see e.g. [89]; however, the standard assumption is used in this thesis. MIL methods can be categorized into two approaches: instance-level and bag-level [60,90]. The instance-level approaches build an instance classifier based on the relation between the labels of the bags and the instances of these bags in the training dataset. The instance classifier classifies instances and then combines the instance labels into a bag label to classify a previously unseen test bag. The bag-level approaches treat bags as a whole; they assume that bags from the same class have similar characteristics and apply supervised classifiers to the bags. In study III, a popular instance-level classifier, miSVM, and a bag-level classifier, MILES, were used to identify emphysema in HRCT scans using only global labels. A representation of the miSVM is showed in Figure 11. A new version of these two classifiers was proposed because miSVM and MILES may suffer from false positives by enforcing the MIL standard assumption too strictly. For example, in MILES, defining the similarity between a bag and a prototype instance as the maximum similarity between that bag's instances and the prototype might be too sensitive to noise. Consider a situation where the task is to learn a concept given positive and negative bags of instances. Both positive and negative bags have instances close to the concept, but the instances of positive bags, on average, are closer to the concept. Due to the maximum operator, a true positive bag and a true negative bag with a single noisy instance may have the same representation, despite the differences in their distributions.

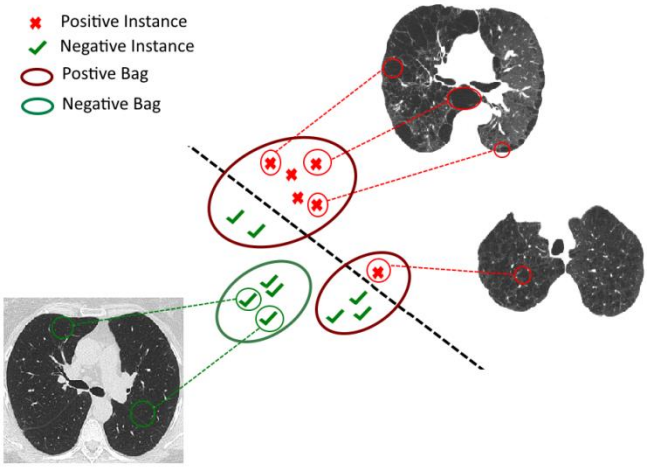

Figure 11: Example of miSVM. In study III, the bags refer to the patients and the instances to healthy or emphysematous tissue.

CHAPTER 3. THESIS OBJECTIVES

COPD is a worldwide problem that is most commonly caused by tobacco, with main manifestations of chronic bronchitis and emphysema. COPD is diagnosed using a combination of tests, including PFTs, questionnaires, and imaging. HRCT scans allow radiologists to visually identify emphysema and the phenotypes of chronic bronchitis, such as airway wall thickness and air trapping. HRCT scans are used not only to verify the diagnosis of COPD but to quantify the extend of the lesions and assess disease progression. However, the visual assessment of HRCT scans is subjective, time-consuming and results in errors due to inter- and intra-observer variability, which can affect the reproducibility of a diagnostic test and lead to a lack of individualized treatment and sometimes to overmedicated patients. Therefore, the motivation for this thesis is to bring objectivity to the detection and quantification of lung conditions derived from COPD, such as emphysema and chronic bronchitis, using HRCT scans.

Automatic and semi-automatic image analysis methods may bring objectivity to the current problem of intra- and inter-observer variability of visual assessment, as one of the main limitations of visual scoring is the observer dependence. Therefore, the objectives of this thesis are to:

- Investigate methods to quantify chronic bronchitis phenotypes, such as air trapping and bronchial wall thickness, in patients with COPD.
- Develop an approach to accurately segment lungs affected by COPD.
- Develop a method to quantify and identify the distribution of emphysema in patients with COPD.

CHAPTER 4. PAPER CONTRIBUTIONS

This chapter presents an overview of the three studies that were conducted as part of this Ph.D. thesis. The studies aim to develop a solution to expert variability and subjectivity of the current assessments. Therefore, the following studies attempt to address the objectives presented in Chapter 3.

4.1. STUDY I: PAPER A

Chronic bronchitis is one of the most significant manifestations of COPD. It is characterized by inflammation and narrowing of the airways. In HRCT scans, chronic bronchitis can be identified by quantifying the air trapped in the alveoli and by looking at the thickness of the airway walls. Study I aimed to investigate how the airway wall thickness is related to air trapping and how these two manifestations of airway obstruction influence PFTs, in particular, spirometry.

Study I included 21 subjects diagnosed with COPD who had a pair of inspiratory and expiratory HRCT scans and PFTs performed. This study was a retrospective study in which the HRCT scans were not conducted for the purposes of the study but as part of the clinical routine. Therefore, the PFTs were performed several months before the HRCT scans. In fact, some of the patients did not have some of the PFTs performed, as indicated in paper A.

To quantify the airway wall thickness, two bronchi, the apical bronchus of the right upper lobe and one bronchus from the sixth-generation in the superior lower lobe of the left lung, were manually selected by a pulmonologist in the inspiratory scans. The selected bronchi in the axial slices of the inspiratory scans were analyzed using the free open-source software “Airway Inspector” [91]. This software uses the FWHM method to analyze the wall area and to measures different parameters.

Air trapping was quantified as a percentage of LAA in the expiratory scans using a combination of two thresholds to avoid areas affected by emphysema. The quantification of air trapping was performed inside the lung area. The lungs were segmented using a semi-automatic region growing method.

Spearman correlation and multi-regression analysis were conducted to investigate the relationships between the measurements of the wall thickness and air trapping with the PFTs. The findings of the study are described in paper A.

4.2. STUDY II: PAPER B

In general, automatic identification and quantification of emphysema and phenotypes of chronic bronchitis, such as air trapping, rely on differences in intensities inside the lung parenchyma. Moreover, the lungs must be accurately segmented to obtain a precise disease quantification. The lungs have a well-delineated shape. However, the hilum region, where the bronchial tree enters into the lungs, is a very difficult area to segment due to its variability in shape. Therefore, study II introduced a method for automatic lung segmentation in patients with COPD using HRCT scans, where the segmentation had a particular emphasis on the hilum region of the lungs.

The segmentation method presented in study II was based on multi-atlas and graph-cut approaches which have been successfully used in previous studies to segment other organs and tissues [83–85]. The method proposed in study II combined information about the shape of the lungs from multi-atlas, intensity information of the voxels using graph-cut and airway shape information from a region growing method. Figure 12 presents an overview of the methodology used in study. The graph-cut method segmented the lung parenchyma using intensity and neighborhood information provided by the association potential and interaction potential, respectively. Concurrently, the main airways were segmented from the target image. Finally, the segmentation was completed by extracting the trachea and the main airways from the segmentation result provided by the graph-cut.

A novel multi-atlas was presented in study II. The multi-atlas was built using 12 HRCT scans from non-COPD subjects. Additionally, 14 HRCT scans from COPD patients with different degrees of COPD severity were used to evaluate the proposed segmentation. Moreover, manual segmentation of these scans was performed by an experienced radiologist for validation and comparison purposes. The segmentation presented in study II was compared to two segmentation methods: multi-atlas segmentation using majority voting and multi-atlas registration and graph-cut. Three quantitative measurements were used to evaluate the agreement between the manual segmentation and the three methods. Furthermore, statistical analysis was performed to evaluate the differences between the three segmentation methods.

A thorough description of the method and the findings of the study is presented in paper B.

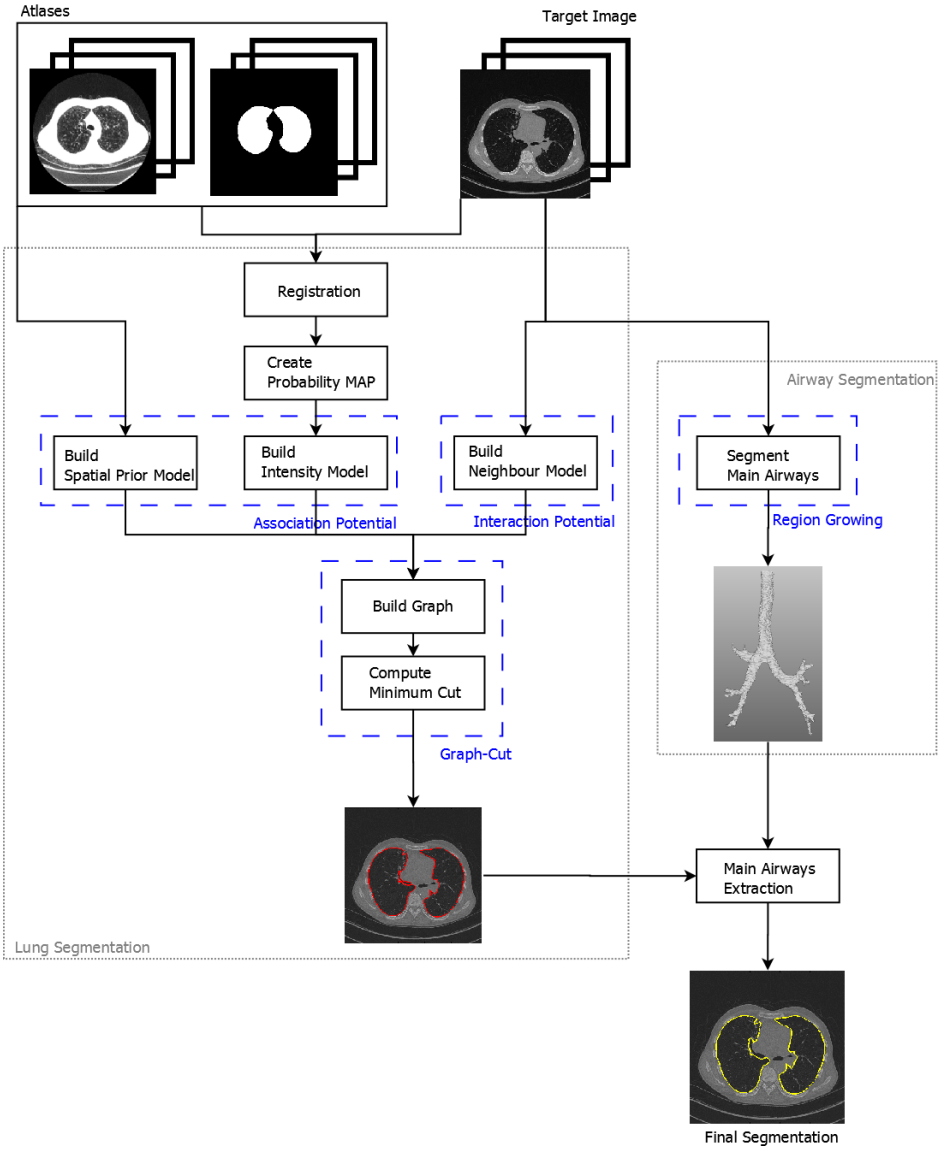

Figure 12: Overview of the methodology proposed in study II for segmenting lungs from COPD patients.

4.3. STUDY III: PAPER C

Emphysema is usually quantified visually by radiologists, which, as mentioned previously, is subjective and results in inter- and intra-observer variability. Therefore, automatic methods to identify and quantify emphysema are proposed as objective methods. In general, the methods proposed in other studies have used supervised classifiers, which can identify emphysema in unseen scans after training. However, these supervised classifiers learn using annotated data, and the annotations are usually performed manually, which is a time-consuming and subjective process. Study III focused on quantifying emphysema automatically without using manual annotated HRCT scans.

In study III, two versions of MIL classifiers, miSVM and MILES, were presented. Both classifiers are sensitive to producing false positives; therefore, in paper C, a more robust version of these classifiers was presented by adapting the standard assumption. The classifiers used textural features to characterize emphysema tissue in the lung parenchyma. Two types of features were used in study III, co-occurrence features and Gaussian filter banks.

Two datasets acquired from different hospitals in Frederikshavn and Aalborg were used in study III. One of the datasets contained eight COPD patients and eight non-COPD subjects, and the other dataset contained 72 COPD patients. The classifiers learned from weak labels extracted from PFTs instead of from manual annotations. The PFTs used were spirometry and DLCO, which were binarized to positive/negative and high/low respectively. The classifier performance was evaluated at the bag level and instance level. The bag-level performance was evaluated based on the AUC, and the instance-level performance was evaluated by an additional measurement introduced in study III called Separability. Based on this evaluation, the best classifier was used to validate the results of the classifier when identifying emphysema lesions. All the experiments in study III were performed using 4-fold cross-validation. The percentage of emphysema quantified by the best classifier trained using weak labels extracted from spirometry and DLCO was compared against the results obtained by a method using a threshold of LAA and the manual annotations made by two experienced radiologists. Statistical analysis was used to assess the relationships between the results of the quantitative methods and the PFTs and the relation between the results of the proposed classifiers and the manual annotations made by the experts.

A full description of the method and the experiments, and the findings from study III are described in paper C.

CHAPTER 5. PAPERS

5.1. PAPER A

Quantitative High-Resolution CT Analysis of Air Trapping and Airway Thickening in Patients with COPD

Isabel Pino Peña, Morten Vuust, Helene Møller Nielsen, Ulla Møller Weinreich, Jesper Carl, Lasse Riis Østergaard.

Published in Jacobs Journal of Pulmonology
http://jacobspublishers.com/images/Pulmonology/J_J_Pulmonol_1_2_010.pdf

5.2. PAPER B

Automated lung segmentation with main airway extraction in patients with chronic obstructive pulmonary disease

Isabel Pino Peña, Thomas Holm Sandberg, Morten Vuust, Ulla Møller Weinreich, Jesper Carl, Anne Sofie Korsager, Lasse Riis Østergaard.

Submitted for publication

5.3. PAPER C

Automatic Emphysema Detection using Weakly Labeled HRCT Lung Images

Isabel Pino Peña, Veronika Cheplygina, Sofia Paschaloudi, Morten Vuust, Jesper Carl, Ulla Møller Weinreich, Lasse Riis Østergaard, Marleen de Bruijne.

Submitted for publication

CHAPTER 6. DISCUSSION AND CONCLUSIONS

6.1. DISCUSSION

The papers presented in this thesis investigate methods to assess COPD patients by automatically quantifying the most common manifestations of COPD, namely, emphysema and chronic bronchitis. The objective of this Ph.D. thesis is to investigate and develop methods to bring objectivity to the assessment of COPD to reduce intra-and inter-observer variability.

HRCT scans are the imaging method used in this thesis to quantify COPD. Historically, the method used to assess the evolution of COPD has been spirometry. However, spirometry poorly correlates with patient symptoms, i.e., dyspnea [92]. Moreover, spirometry cannot discriminate between emphysema and small airway diseases. In contrast, HRCT scans provide detailed information about anatomical and structural changes in the lungs. Moreover, HRCT scans may detect emphysema even before a change in lung function occurs. Some studies have shown that emphysema quantification based on CT scans can identify patients with a high risk of rapid worsening COPD and lung cancer, even when these subjects present normal spirometry [93]. However, HRCT and CT imaging have been limited in the clinic for the diagnosis and monitoring of COPD. The main reason for these limitations is the radiation exposure during the scan acquisition [94]. In general, there is a tradeoff between the radiation dose and the quality of the image; a lower radiation dose increases the noise in the image. Nevertheless, advances in the technology and adjustments based on patient size and clinical indications enable high-quality images at low radiation doses [18,95].

6.1.1. Airway analysis

In this thesis, several approaches are introduced to automatically quantify chronic bronchitis and emphysema. First, chronic bronchitis was investigated by studying its manifestations, namely, airway wall thickness and air trapping. Previous studies showed that although airway obstruction occurs in the small airways, which are usually not visible on CT scans, the obstruction is well correlated well with the wall thickness of the larger bronchi, such as the apical bronchus. The apical bronchus is easily identified in the axial views of CT scans [14]. Free open-source software is available to measure airway walls, such as the software used in study I to quantify the thickness of the bronchi. However, in clinical practice, measuring different

bronchi to assess whether there is thickening of the airways is more time-consuming than looking at the expiratory scans to determine if there is air trapping in the lungs. Therefore, in study I, the relationship between the airway wall thickness and air trapping was investigated to determine how these two manifestations of airway obstruction were related with spirometry. Spirometry was used in the validation of study I because it is the mandatory PFT in the diagnosis of COPD and is the most commonly used PFT to evaluate disease severity. The study showed that air trapping alone could predict spirometry; therefore, measurement of the wall thickness can be omitted.

The study presented some limitations. Air trapping was quantified by the percentage of LAA based on thresholds from previous studies [96–98], which is accepted as a reliable method to quantify air trapping. However, other studies [99–101] have used the expiratory to inspiratory ratio of mean lung density as a more consistent measurement of air trapping. Therefore, the use of both methods is desirable to support the findings of the study. The lungs were segmented using a semi-automatic region growing method in 2D. However, a more robust and automatic lung segmentation method in 3D is desired for more reliable and faster segmentation. The greatest limitation of the study was the amount of data. It was a retrospective study, and only 21 COPD patients that had undergone HRCT scans and PFTs could be included.

6.1.2. Lung segmentation

A robust lung segmentation was presented in paper B, which described an approach that combines shape and intensity information from the lung and the main airways. Although lung segmentation has been a hot topic in recent years, it remains a challenging problem. Many of the proposed methods in the literature perform well in healthy and moderately pathological lungs. However, these methods produce weaker results in severe cases of lung disease, such as interstitial lung disease and pleural effusion.

Automatic lung segmentation is a difficult task due to the differences in shape caused by lung inflation and effects of diseases. Furthermore, there are areas in the lung, for example, the hilum, that are difficult to segment, even in COPD patients, whose phenotypes do not affect the shape of the lungs. Therefore, study II focused on that region. It is important to segment only the lung parenchyma, without the airways, if the segmentation is part of a pipeline for further analysis, i.e., disease quantification. The atlas-based method is based on manual segmentation of non-COPD subjects. The atlas-based method produces an overall accurate shape of the lungs, but it often deviates slightly from the boundary of the lungs. To correct these deviations, study II used a combination of the atlas-based method and graph-cut in

which the graph-cut added intensity information of the neighbor voxels from the segmentation provided by the multi-atlas. Graph-cut successfully corrected the errors introduced by the multi-atlas registration. However, it added small areas to the segmentation from the hilum region that do not belong to the lung parenchyma because graph-cut relies on the intensity of the lung, which has nearly the same intensity as the airways in a CT scan. Therefore, the graph-cut fails to accurately segment the lung parenchyma. To solve this overestimation introduced by the graph-cut, in study II, the segmentation approach was refined by adding an automatic 3D region growing method to segment the trachea and the main airways of the bronchial tree.

A comparison between simple multi-atlas segmentation, a combination of multi-atlas and graph-cut and the proposed method, which includes main airway extraction, was performed to evaluate the performance of the method. The three methods were compared with manual delineations made by an expert radiologist. The radiologist was asked to delineate the lung parenchyma freely; thus, no specific conditions in the hilum area were introduced. The process was performed to demonstrate how the hilum area is a difficult area to segment, even by experts. Due to these manual segmentations, the results of study II are more difficult to elucidate. Although the proposed method performed better than the other two methods, as shown by the qualitative analysis, the quantitative analysis does not indicated an improvement in the multi-atlas and graph-cut method.

The limitations of this study are based on the size of the data. Both the atlas and the validation of the segmentation rely on manual segmentations made by experts, which are very time-consuming. Therefore, a limited number of results are provided in the datasets. Moreover, only one radiologist was available to perform the manual delineations, so some potential variability was not identified due to the lack of more manual annotations to perform comparisons. Another limitation is the time that the algorithm requires to segment a new subject. In a clinical environment, if the segmentation is part of a pipeline for the identification of a disease in the lung parenchyma, it needs to be a quick step to allow precise and fast diagnosis.

6.1.3. Emphysema quantification

Study II laid the foundation for study III, which used the proposed segmentation method to segment the HRCT scans used in study III. The focus of study III was to identify and quantify emphysema. Previous studies have presented different methods to quantify emphysema. However, these studies used manual annotations of emphysema to train supervised classifiers. Manual annotations are time-consuming and need to be performed by experts. Therefore, study III aimed to quantify emphysema using HRCT scans without manual annotations. Weak labels were used

instead of manual annotations to train the classifiers. Thus, the classifiers have a global annotation for the whole scan but not for emphysema areas. The weak labels were extracted from two PFTs: spirometry and DLCO. Spirometry was successfully used as a weak label in [51,60] to classify subjects as COPD or healthy.

In this study, two datasets acquired from different hospitals in Frederikshavn and Aalborg were used. The datasets were combined in to obtain a homogeneous group. Experiments were set-up using two types of textural features and two types of classifiers. The unsupervised classifiers presented in this study were newer versions of two MIL classifiers. miSVM and MILES were adapted to be more precise in avoiding false positives. For MIL classifiers, a bag is considered positive if there is one positive instance. In study III, a bag represents the full scan, and the instances are small patches along the lung parenchyma.

The results of the experiments were validated by correlating with the PFT values and by comparing with the manual annotations of two expert radiologists and a traditional method based on LAA. The two experts annotated a specific number of slices per scan for a full dataset. They were asked to annotate the emphysema lesions that they could find in the lung parenchyma. No information about how the automatic method classified emphysema was given to obtain manual annotations as performed for clinical purposes. The annotation process was blinded for the two radiologists. The results highlight the problem of inter-observer variability, with a Dice coefficient of 0.34. Therefore, the PFTs were used as a reliable measurement to validate the results of the proposed method.

The data were the main limitation of this study. Both datasets were acquired from different hospitals with different protocols, which may have affected the classification performance. The datasets had different sizes and groups. One dataset did not contain controls. Moreover, the available controls were not healthy subjects but non-COPD persons. Therefore, their scans could add some errors to the classification.

6.2. CONCLUSIONS

This thesis has presented work using HRCT scans as a tool to automatically quantify airway obstruction and emphysema. It has been shown that air trapping computed from expiratory scans can be used to quantify obstruction due to chronic bronchitis. Emphysema has been successfully quantified using inspiratory scans without manual annotations. The emphysema quantification provided better results than the density-based method that is commonly used by medical doctors to quantify emphysema. Moreover, a lung segmentation method adapted from [84,85,102] is presented to accurately segment the lungs, even in difficult locatios, such as the

hilum region, which other studies do not consider. The work performed in this thesis is expected to provide objectivity and to reduce the variability in the assessment of COPD manifestations.

6.3. FUTURE PERSPECTIVES

HRCT scans are the most sensitive imaging method to assess COPD in vivo. In recent years, many investigations have proposed automatic and semi-automatic methods to quantify chronic bronchitis and emphysema. However, in clinical practice, few automatic or semi-automatic methods are used, and the assessment relies on the experience and subjectivity of radiologists. In a way, this happens because the differences in the image acquisition of scanners ad scanning protocols. One way to address these problems is to investigate the use of transfer learning. Transfer learning aims to improve the process of learning new tasks based on previous experience obtained from a similar problem.

In the future, methods to detect the evolution of emphysema in HRCT before it is perceptible to the human eye are desirable. Follow-up scans from the same population are needed, preferably from several years after the first scan.

The methods presented in this thesis can be adapted and extended to assess other lung diseases, such as cystic fibrosis and interstitial lung disease. These methods can help clinical experts other than radiologists, e.g., oncologists for the assessment of parenchyma changes due to radiation pneumonitis.

LITERATURE LIST

[1] Eisner MD, Anthonisen N, Coultas D, Kuenzli N, Perez-Padilla R, Postma D, et al. An official American Thoracic Society public policy statement: Novel risk factors and the global burden of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2010;182:693–718. doi:10.1164/rccm.200811-1757ST.

[2] Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006;3:2011–30. doi:10.1371/journal.pmed.0030442.

[3] Global Strategy for the Diagnosis Management and Prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease (GOLD). 2016.

[4] British Lung Foundation. COPD (Chronic obstructive pulmonary disease) n.d. https://www.blf.org.uk/support-for-you/copd (accessed August 1, 2016).

[5] Shaker SB, Dirksen A, Bach KS, Mortensen J. Imaging in chronic obstructive pulmonary disease. COPD 2007;4:143–61. doi:10.1080/15412550701341277.

[6] Friedlander AL, Lynch D, Dyar L a, Bowler RP. Phenotypes of chronic obstructive pulmonary disease. COPD 2007;4:355–84. doi:10.1080/15412550701629663.

[7] Takahashi M, Fukuoka J, Nitta N, Takazakura R, Nagatani Y, Murakami Y, et al. Imaging of pulmonary emphysema: a pictorial review. Int J Chron Obstruct Pulmon Dis 2008;3:193–204. doi:10.2147/COPD.

[8] Celli BR, MacNee W, Agusti A, Anzueto A, Berg B, Buist AS, et al. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004;23:932–46. doi:10.1183/09031936.04.00014304.

[9] Oga T, Tsukino M, Hajiro T, Ikeda A, Nishimura K. Analysis of longitudinal changes in dyspnea of patients with chronic obstructive pulmonary disease: an observational study. Respir Res 2012;13:1–8. doi:10.1186/1465-9921-13-85.

[10] O'Donnell D. Assessment of bronchodilator efficacy in symptomatic COPD: Is Spirometry Useful? Chest 2000;117:46–7. doi:10.1378/chest.117.2_suppl.42S.

[11] Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease GOLD executive summary. Am J Respir Crit Care Med 2013;187:347–65. doi:10.1164/rccm.201204-0596PP.

[12] Goldman MD, Smith HJ, Ulmer WT. Whole-body plethysmography. Eur. Respir. Soc. Monogr., vol. 31, 2005, p. 15–43. doi:10.1007/s10405-009-0343-z.

[13] Criée CP, Sorichter S, Smith HJ, Kardos P, Merget R, Heise D, et al. Body plethysmography - Its principles and clinical use. Respir Med 2011;105:959–71. doi:10.1016/j.rmed.2011.02.006.

[14] Nakano Y, Muro S, Sakai H, Hirai T, Chin K, Tsukino M, et al. Computed tomographic measurements of airway dimensions and emphysema in smokers. Correlation with lung function. Am J Respir Crit Care Med 2000;162:1102–8. doi:10.1164/ajrccm.162.3.9907120.

[15] Nambu A, Zach J, Schroeder J, Jin GY, Kim SS, Kim Y-I, et al. Relationships between diffusing capacity for carbon monoxide (DLCO), and quantitative computed tomography measurements and visual assessment for chronic obstructive pulmonary disease. Eur J Radiol 2015;84:980–5. doi:10.1016/j.ejrad.2015.01.010.

[16] Grydeland TB, Thorsen E, Dirksen A, Jensen R, Coxson HO, Pillai SG, et al. Quantitative CT measures of emphysema and airway wall thickness are related to DLCO. Respir Med 2011;105:343–51. doi:10.1016/j.rmed.2010.10.018.

[17] Coxson HO, Rogers RM. Quantitative computed tomography of chronic obstructive pulmonary disease. Acad Radiol 2005;12:1457–63. doi:10.1016/j.acra.2005.08.013.

[18] ICRP. Managing patient dose in multi-detector computed tomography. vol. 102. 2007. doi:10.1016/j.icrp.2004.12.002.

[19] Coxson HO, Lam S. Quantitative assessment of the airway wall using computed tomography and optical coherence tomography. Proc Am Thorac Soc 2009;6:439–43. doi:10.1513/pats.200904-015AW.

[20] de Jong P a, Müller NL, Paré PD, Coxson HO. Computed tomographic imaging of the airways: relationship to structure and function. Eur Respir J 2005;26:140–52. doi:10.1183/09031936.05.00007105.

[21] Barr RG, Berkowitz E a, Bigazzi F, Bode F, Bon J, Bowler RP, et al. A combined pulmonary-radiology workshop for visual evaluation of COPD: study design, chest CT findings and concordance with quantitative evaluation. COPD 2012;9:151–9. doi:10.3109/15412555.2012.654923.

[22] Choromańska A, Macura KJ. Role of computed tomography in quantitative assessment of emphysema. Pol J Radiol 2012;77:28–36. doi:10.12659/PJR.882578.

[23] Ginsburg SB, Lynch D a, Bowler RP, Schroeder JD. Automated texture-based quantification of centrilobular nodularity and centrilobular emphysema in chest CT images. Acad Radiol 2012;19:1241–51. doi:10.1016/j.acra.2012.04.020.

[24] Mascalchi M, Diciotti S, Sverzellati N, Camiciottoli G, Ciccotosto C, Falaschi F, et al. Low agreement of visual rating for detailed quantification of pulmonary emphysema in whole-lung CT. Acta Radiol 2012;53:53–60. doi:10.1258/ar.2011.110419.

[25] Kim N, Seo JB, Song KS, Chae EJ, Kang SH. Semi-automatic measurement of the airway dimension by computed tomography using the full-with-half-maximum method: a study of the measurement accuracy according to the orientation of an artificial airway. Korean J Radiol 2008;9:236–42. doi:10.3348/kjr.2008.9.3.236.

[26] Pu J, Gu S, Liu S, Zhu S, Wilson D, Siegfried JM, et al. CT based computerized identification and analysis of human airways: a review. Med Phys 2012;39:2603–16. doi:10.1118/1.4703901.

[27] San José Estépar R, Reilly JJ, Silverman EK, Washko GR. Three-dimensional airway measurements and algorithms. Proc Am Thorac Soc 2008;5:905–9. doi:10.1513/pats.200809-104QC.

[28] Lynch D a, Al-Qaisi M a. Quantitative computed tomography in chronic obstructive pulmonary disease. J Thorac Imaging 2013;28:284–90. doi:10.1097/RTI.0b013e318298733c.

[29] Nakano Y, Wong JC, de Jong P a, Buzatu L, Nagao T, Coxson HO, et al. The prediction of small airway dimensions using computed tomography. Am J Respir Crit Care Med 2005;171:142–6. doi:10.1164/rccm.200407-874OC.

[30] Stern EJ, Frank MS. Small-Airway Diseases Expiratory CT of the Lungs: Findings at Expiratory CT. AJR Am J Roentgenol 1994;163:1631–7.

doi:10.2214/ajr.163.1.8010242.

[31] Lynch DA. Progress in Imaging COPD , 2004 - 2014. J COPD Found 2014;1:73–82. doi:10.15326/jcopdf.1.1.2014.0125 1.

[32] Mets OM, de Jong P a, van Ginneken B, Gietema H a, Lammers JWJ. Quantitative computed tomography in COPD: possibilities and limitations. Lung 2012;190:133–45. doi:10.1007/s00408-011-9353-9.

[33] Matsuoka S, Kurihara Y, Yagihashi K, Hoshino M, Watanabe N, Nakajima Y. Quantitative assessment of air trapping in chronic obstructive pulmonary disease using inspiratory and expiratory volumetric MDCT. Am J Roentgenol 2008;190:762–9. doi:10.2214/AJR.07.2820.

[34] Dournes G, Laurent F. Airway Remodelling in Asthma and COPD: Findings, Similarities, and Differences Using Quantitative CT. Pulm Med 2012;2012:670414. doi:10.1155/2012/670414.

[35] Sluimer I, Schilham A, Prokop M, van Ginneken B. Computer analysis of computed tomography scans of the lung: a survey. IEEE Trans Med Imaging 2006;25:385–405. doi:10.1109/TMI.2005.862753.

[36] Litmanovich D, Boiselle PM, Bankier A a. CT of pulmonary emphysema - current status, challenges, and future directions. Eur Radiol 2009;19:537–51. doi:10.1007/s00330-008-1186-4.

[37] Wang Z, Gu S, Leader JK, Kundu S, Tedrow JR, Sciurba FC, et al. Optimal threshold in CT quantification of emphysema. Eur Radiol 2013;23:975–84. doi:10.1007/s00330-012-2683-z.

[38] Mendoza CS, Washko GR, Ross JC, Diaz AA, Lynch DA, Crapo JD, et al. Emphysema Quantification in a multi-scanner HRCT cohort using local intensity distribution. IEEE Int. Symp. Biomed. Imaging, vol. 148, 2012, p. 474–7. doi:10.1109/ISBI.2012.6235587.

[39] van Ginneken B, Hogeweg L, Prokop M. Computer-aided diagnosis in chest radiography: Beyond nodules. Eur J Radiol 2009;72:226–30. doi:10.1016/j.ejrad.2009.05.061.

[40] Materka A, Strzelecki M. Texture Analysis Methods – A Review. Eur COST B11 Progr 1998:1–33. doi:10.1.1.97.4968.

[41] Aggarwal N, K. Agrawal R. First and Second Order Statistics Features for Classification of Magnetic Resonance Brain Images. J Signal Inf Process

2012;03:146–53. doi:10.4236/jsip.2012.32019.

[42] Castellano G, Bonilha L, Li LM, Cendes F. Texture analysis of medical images. Clin Radiol 2004;59:1061–9. doi:10.1016/j.crad.2004.07.008.

[43] Chabat F, Yang G-Z, Hansell DM. Obstructive lung diseases: texture classification for differentiation at CT. Radiology 2003;228:871–7. doi:10.1148/radiol.2283020505.

[44] Park YS, Seo JB, Kim N, Chae EJ, Oh YM, Lee S Do, et al. Texture-based quantification of pulmonary emphysema on high-resolution computed tomography: comparison with density-based quantification and correlation with pulmonary function test. Invest Radiol 2008;43:395–402. doi:10.1097/RLI.0b013e31816901c7.

[45] Uppaluri R, Hoffman E a, Sonka M, Hartley PG, Hunninghake GW, McLennan G. Computer recognition of regional lung disease patterns. Am J Respir Crit Care Med 1999;160:648–54. doi:10.1164/ajrccm.160.2.9804094.

[46] Xu Y, Sonka M, McLennan G, Guo J, Hoffman E a. MDCT-based 3-D texture classification of emphysema and early smoking related lung pathologies. IEEE Trans Med Imaging 2006;25:464–75. doi:10.1109/TMI.2006.870889.

[47] Prasad M, Sowmya A, Wilson P. Multi-level classification of emphysema in HRCT lung images. Pattern Anal Appl 2007;12:9–20. doi:10.1007/s10044-007-0093-7.

[48] Owrangi AM, Etemad-Rezai R, McCormack DG, Cunningham I a, Parraga G. Computed tomography density histogram analysis to evaluate pulmonary emphysema in ex-smokers. Acad Radiol 2013;20:537–45. doi:10.1016/j.acra.2012.11.010.

[49] Sørensen L, Shaker SB, Bruijne M De. Quantitative Analysis of Pulmonary Emphysema Using Local Binary Patterns. IEEE Trans Med Imaging 2010;29:559–69. doi:10.1109/TMI.2009.2038575.

[50] Sørensen L, Lo P, Ashraf H, Sporring J, Nielsen M, De Bruijne M. Learning COPD sensitive filters in pulmonary CT. Lect Notes Comput Sci (Including Subser Lect Notes Artif Intell Lect Notes Bioinformatics) 2009;5762 LNCS:699–706. doi:10.1007/978-3-642-04271-3_85.

[51] Sørensen L, Nielsen M, Lo P, Ashraf H, Pedersen JH, De Bruijne M. Texture-based analysis of COPD: A data-driven approach. IEEE Trans Med

Imaging 2012;31:70–8. doi:10.1109/TMI.2011.2164931.

[52] Nava R, Escalante-Ramirez B, Cristobal G, San Jose Estepar R. Extended Gabor approach applied to classification of emphysematous patterns in computed tomography. Med Biol Eng Comput 2011;18:1492–501. doi:10.1016/j.str.2010.08.012.Structure.

[53] Dharmagunawardhana C, Mahmoodi S. Quantitative analysis of pulmonary emphysema using isotropic Gaussian Markov random fields. Int Conf Comput Vis Theory Appl 2014:44–53. doi:10.5220/0004728900440053.

[54] Blechschmidt R a, Werthschützky R, Lörcher U. Automated CT image evaluation of the lung: a morphology-based concept. IEEE Trans Med Imaging 2001;20:434–42. doi:10.1109/42.925296.

[55] Gangeh MJ, Sørensen L, Shaker SB, Kamel MS. Multiple Classifier Systems in Texton-Based Approach for the Classification of CT Images of Lung. MICCAI, 2011, p. 153–63. doi:10.1007/978-3-642-18421-5_15.

[56] Zulueta-Coarasa T, Kurugol S, Ross JC, Washko GG, San José Estépar R. Emphysema classification based on embedded probabilistic PCA. Conf. Proc. 35th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. IEEE Eng. Med. Biol. Soc., vol. 2013, 2013, p. 3969–72. doi:10.1109/EMBC.2013.6610414.

[57] Lee Y, Seo JB, Lee JG, Kim SS, Kim N, Kang SH. Performance testing of several classifiers for differentiating obstructive lung diseases based on texture analysis at high-resolution computerized tomography (HRCT). Comput Methods Programs Biomed 2009;93:206–15. doi:10.1016/j.cmpb.2008.10.008.

[58] Helen R, Kamaraj N. An Efficient Lung Emphysema Detection in CT Datasets using Combined GA and Support Vector Machine. Eur J Sci Res 2012;84:286–303.

[59] de Bruijne M. Machine learning approaches in medical image analysis: from detection to diagnosis. Med Image Anal 2016. doi:10.1016/j.media.2016.06.032.

[60] Cheplygina V, Sørensen L, Tax DMJ, Pedersen JH, Loog M, De Bruijne M. Classification of COPD with multiple instance learning. Proc - Int Conf Pattern Recognit 2014:1508–13. doi:10.1109/ICPR.2014.268.

[61] Sørensen L, Loog M, Lo P, Ashraf H, Dirksen A, Duin RPW, et al. Image dissimilarity-based quantification of lung disease from CT. Lect Notes

Comput Sci (Including Subser Lect Notes Artif Intell Lect Notes Bioinformatics) 2010;6361 LNCS:37–44. doi:10.1007/978-3-642-15705-9_5.

[62] M Sonka , J Tschirren , S Ukil , X Zhang , Y Xu , J M Reinhardt , E J van Beek , G McLennan EAH. Pulmonary CT Image Analysis and Computer Aided Detection. IEEE Trans Med Imaging 2007:500–3. doi:10.1109/ISBI.2007.356898.

[63] van Rikxoort EM, van Ginneken B. Automated segmentation of pulmonary structures in thoracic computed tomography scans: a review. Phys Med Biol 2013;58:R187–220. doi:10.1088/0031-9155/58/17/R187.

[64] Lassen B, van Rikxoort EM, Schmidt M, Kerkstra S, van Ginneken B, Kuhnigk J-M. Automatic segmentation of the pulmonary lobes from chest CT scans based on fissures, vessels, and bronchi. IEEE Trans Med Imaging 2013;32:210–22. doi:10.1109/TMI.2012.2219881.

[65] Doel T, Gavaghan DJ, Grau V. Review of automatic pulmonary lobe segmentation methods from CT. Comput Med Imaging Graph 2015;40:13–29. doi:10.1016/j.compmedimag.2014.10.008.

[66] Fabijańska A. Segmentation of pulmonary vascular tree from 3D CT thorax scans. Biocybern Biomed Eng 2015;35:106–19. doi:10.1016/j.bbe.2014.07.001.

[67] Montadoun M, Berger P, de Dietrich G, Braquelaire A, Marthan R, Tunon-de-Lara JM, et al. Assessment of Airways with Three-dimensional Quantitative Thin-Section CT: In Vitro and in Vivo Validation. RadioGraphics 2007;242:563–72. doi:10.1148/radiol.2422060029.

[68] van Ginneken B, Baggerman W, van Rikxoort EM. Robust segmentation and anatomical labeling of the airway tree from thoracic CT scans. Med Image Comput Comput Assist Interv 2008;11:219–26. doi:10.1007/978-3-540-85988-8_27.

[69] Nakamura M, Wada S, Miki T, Shimada Y, Suda Y, Tamura G. Automated segmentation and morphometric analysis of the human airway tree from multidetector CT images. J Physiol Sci 2008;58:493–8. doi:10.2170/physiolsci.RP007408.

[70] Mansoor A, Bagci U, Foster B, Xu Z, Papadakis GZ, Folio LR, et al. Segmentation and Image Analysis of Abnormal Lungs at CT: Current Approaches, Challenges, and Future Trends. Radiographics 2015;35:1056–

76. doi:10.1148/rg.2015140232.

[71] Armato III SG, Sensakovic WF. Automated Lung Segmentation for Thoracic CT: Impact on Computer-Aided Diagnosis. Comput Radiol Surg 2004;11:1011–21. doi:10.1016/j.xacra.2004.06.005.

[72] van Rikxoort EM, de Hoop B, Viergever M a., Prokop M, van Ginneken B. Automatic lung segmentation from thoracic computed tomography scans using a hybrid approach with error detection. Med Phys 2009;36:2934. doi:10.1118/1.3147146.

[73] Chen H, Butler A. Automatic Lung Segmentation in HRCT Images. Int. Conf. Image Vis. Comput., 2011, p. 293–8.

[74] Massoptier L, Misra A, Sowmya A, Casciaro S. Combining Graph-Cut Technique and Anatomical Knowledge for Automatic Segmentation of Lungs Affected By Diffuse Parenchymal Disease in HRCT Images. Int J Image Graph 2011;11:509–29. doi:10.1142/S0219467811004202.

[75] Nakagomi K, Shimizu A, Kobatake H, Yakami M, Fujimoto K, Togashi K. Multi-shape graph cuts with neighbor prior constraints and its application to lung segmentation from a chest CT volume. Med Image Anal 2013;17:62–77. doi:10.1016/j.media.2012.08.002.

[76] Sun S, Sonka M, Beichel RR. Graph-based 4D Lung Segmentation in CT Images with Expert-Guided Computer-Aided Refinement. Int. Symp. Biomedial Imaging From Nano to Macro, 2013, p. 1312–5. doi:10.1109/ISBI.2013.6556773.

[77] Shimizu A, Nakagomi K, Narihira T, Kobatake H. Automated Segmentation of 3D CT Images Based on Statistical Atlas and Graph Cuts. MICCAI, 2011, p. 214–23. doi:10.1007/s11263-006-8711-1.

[78] Sluimer I, Prokop M, van Ginneken B. Toward automated segmentation of the pathological lung in CT. IEEE Trans Med Imaging 2005;24:1025–38. doi:10.1109/TMI.2005.851757.

[79] Lee J, Seo JB, Kim N, Park SO, Lee H, Shin YG, et al. Novel Level-set based Segmentation Method of the Lung at HRCT Images of Diffuse Interstitial Lung Disease (DILD). In: Pluim JPW, Dawant BM, editors. SPIE, vol. 7259, 2009, p. 725941–725941 – 8. doi:10.1117/12.811327.

[80] Qi Y, Dong K, Yin L, Li M. 3D Segmentation of the Lung Based on the Neighbor Information and Curvature. 2013 Seventh Int Conf Image Graph

2013:139–43. doi:10.1109/ICIG.2013.34.

[81] Sun S, Bauer C, Beichel R. Automated 3-D segmentation of lungs with lung cancer in CT data using a novel robust active shape model approach. IEEE Trans Med Imaging 2012;31:449–60. doi:10.1109/TMI.2011.2171357.

[82] Birkbeck N, Sofka M, Kohlberger T, Zhang J, Wetzl J, Kaftan J, et al. Robust Segmentation of Challenging Lungs in CT Using Multi-stage Learning and Level Set Optimization. In: Suzuki K, editor. Comput. Intell. Biomed. Imaging, New York, NY: Springer New York; 2014, p. 185–208. doi:10.1007/978-1-4614-7245-2.

[83] van der Lijn F, den Heijer T, Breteler MMB, Niessen WJ. Hippocampus segmentation in MR images using atlas registration, voxel classification, and graph cuts. Neuroimage 2008;43:708–20. doi:10.1016/j.neuroimage.2008.07.058.

[84] Fortunati V, Verhaart RF, van der Lijn F, Niessen WJ, Veenland JF, Paulides MM, et al. Tissue segmentation of head and neck CT images for treatment planning: a multiatlas approach combined with intensity modeling. Med Phys 2013;40:071905. doi:10.1118/1.4810971.

[85] Korsager AS, Fortunati V, van der Lijn F, Carl J, Niessen W, Østergaard LR, et al. The use of atlas registration and graph cuts for prostate segmentation in magnetic resonance images. Med Phys 2015;42:1614–24. doi:10.1118/1.4914379.

[86] Boykov Y, Kolmogorov V. An experimental comparison of min-cut/max-flow algorithms for energy minimization in vision. IEEE Trans Pattern Anal Mach Intell 2004;26:1124–37. doi:10.1109/TPAMI.2004.60.

[87] Domingos P. A few useful things to know about machine learning. Commun ACM 2012;55:78. doi:10.1145/2347736.2347755.

[88] Dietterich TG, Lathrop RH, Lozano-Pérez T. Solving the multiple instance problem with axis-parallel rectangles. Artif Intell 1997;89:31–71. doi:10.1016/S0004-3702(96)00034-3.

[89] Foulds J, Frank E. A review of multi-instance learning assumptions. Knowl Eng Rev 2010;25:1. doi:10.1017/S026988890999035X.

[90] Amores J. Multiple instance classification: Review, taxonomy and comparative study. Artif Intell 2013;201:81–105. doi:10.1016/j.artint.2013.06.003.

[91] Estépar RS, Washko GG, Silverman EK, Reilly JJ, Kikinis R, Westin CF. Airway Inspector: an Open Source Application for Lung Morphometry. First Int. Work. Pulm. Image Process., 2008, p. 293–302.

[92] Gallego M, Samaniego J, Alonso J, Sánchez a, Carrizo S, Mar'\in J. Disnea en la EPOC: relación de la escala MRC con la disnea inducida en las pruebas de marcha y de ejercicio cardiopulmonar máximo. Arch Bronconeumol 2002;38:112–6. doi:10.1016/S0300-2896(02)75167-3.

[93] Sin DD, Leipsic J, Man SFP. CT in COPD: just a pretty picture or really worth a thousand words (or dollars)? Thorax 2011;66:741–2. doi:10.1136/thx.2011.161430.

[94] Milne S, King GG. Advanced imaging in COPD: Insights into pulmonary pathophysiology. J Thorac Dis 2014;6:1570–85. doi:10.3978/j.issn.2072-1439.2014.11.30.

[95] Leipsic J, Nguyen G, Brown J, Sin D, Mayo JR. A prospective evaluation of dose reduction and image quality in chest CT using adaptive statistical iterative reconstruction. Am J Roentgenol 2010;195:1095–9. doi:10.2214/AJR.09.4050.

[96] Schroeder JD, McKenzie AS, Zach J a, Wilson CG, Curran-Everett D, Stinson DS, et al. Relationships between airflow obstruction and quantitative CT measurements of emphysema, air trapping, and airways in subjects with and without chronic obstructive pulmonary disease. AJR Am J Roentgenol 2013;201:W460–70. doi:10.2214/AJR.12.10102.

[97] Jain N, Covar RA, Gleason MC, Newell JD, Gelfand EW, Spahn JD. Quantitative computed tomography detects peripheral airway disease in asthmatic children. Pediatr Pulmonol 2005;40:211–8. doi:10.1002/ppul.20215.

[98] Regan E a, Hokanson JE, Murphy JR, Make B, Lynch D a, Beaty TH, et al. Genetic epidemiology of COPD (COPDGene) study design. COPD 2010;7:32–43. doi:10.3109/15412550903499522.

[99] Mets OM, Zanen P, Lammers J-WJ, Isgum I, Gietema HA, Ginneken B, et al. Early Identification of Small Airways Disease on Lung Cancer Screening CT: Comparison of Current Air Trapping Measures. Lung 2012:629–33. doi:10.1007/s00408-012-9422-8.

[100] Lee YK, Oh Y-M, Lee J-H, Kim EK, Lee JH, Kim N, et al. Quantitative assessment of emphysema, air trapping, and airway thickening on computed

tomography. Lung 2008;186:157–65. doi:10.1007/s00408-008-9071-0.

[101] Bommart S, Marin G, Bourdin A, Molinari N, Klein F, Hayot M, et al. Relationship between CT air trapping criteria and lung function in small airway impairment quantification. BMC Pulm Med 2014;14:29. doi:10.1186/1471-2466-14-29.

[102] Van Der Lijn F, De Bruijne M, Klein S, Den Heijer T, Hoogendam YY, Van Der Lugt A, et al. Automated brain structure segmentation based on atlas registration and appearance models. IEEE Trans Med Imaging 2012;31:276–86. doi:10.1109/TMI.2011.2168420.

ISSN (online): 2246-1302
ISBN (online): 978-87-7112-820-8

AALBORG UNIVERSITY PRESS