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Detection of emphysema in patients with COPD

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Master Thesis

Biomedical Engineering and Informatics

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Synopsis:

Chronic Obstructive Pulmonary Disease (COPD) is characterized by airflow limitations which involves chronic bronchitis and emphysema. Quantification of the emphysema severity is done by physicians or radiologist and typically consists of visual scoring of chest tomographic (CT) images which is subject to inter-observer variability. The purpose of this project was to study an objective automatic method using texture analysis for the detection and quantification of emphysema in patients with COPD.

The proposed method segmented the lungs using region growing and texture features were extracted after applying co-occurrence matrix algorithm to the segmented images. These texture features were used to train and test the support vector machine (SVM) classifier to distinguish between normal lung tissue and emphysematous lung tissue. This classifier was trained and evaluated using the leave-one-out algorithm with a data set of 9 non healthy patients and 2 healthy patients.

In order to validate the results of the proposed method, a comparison between them and the visual scoring of two radiologist and one physician were computed. The statistical method used for measuring the level of agreement was the quadratic weighted kappa which gave as results a fair agreement between experts and the proposed method.

The proposed method described here can quantify emphysema severity avoiding the problem of the inter-observer variability. Therefore, this method can be taken into consideration as an approach to automatic quantify emphysema lesions in patients with COPD.

Preface

This report was written for the 4th semester M.Sc. project during the period of February 4th to June 4th 2013 at Aalborg University in the field of Biomedical Engineering and Informatics, under the supervision of Lasse Riis Østergaard. The project presents an automatic texture-based method for quantifying emphysema severity using HRCT images in patients with COPD.

With special thanks to Ulla Møller Weinreich from the Department of Pulmonary Medicine at Aalborg Hospital and Lars Pilegaard Thomsen from the Department of Health Science and Technology at Aalborg University for their contribution with the HRCT data and their support on this project.

All citations in this report refer to the bibliography section at the end of the report. References are organized following the Harvard method, [Author's last name, year of publishing].

This report was written by:

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CHAPTER

1 Introduction

Chronic Obstructive Pulmonary Disease (COPD) is one of the fastest-growing health problems in Europe and USA. It has a prevalence of 65 million people in severe stages of the disease and it was the fifth leading cause of death worldwide in 2005 although its incidence is increasing and it is expected to be the third leading cause of death worldwide in 2030 [Global Initiative Chronic Obstructive Lung Disease, 2013*a*], [World Health Organization, 2011]. COPD is characterized by slowly progressive and non-reversible airflow obstructions in the airways. The disease is commonly detected in adults above 40 years old who have been long-term smokers, but it can also occur from the long exposure to pollution or chemical fumes [National Heart and Blood Institute, 2012*b*].

COPD usually comprises chronic bronchitis and emphysema. Emphysema refers to a destruction of the alveolar walls with loss of elasticity in the alveoli tissue [Widmaier et al., 2011]. Emphysema is visible on Computed Tomography (CT) images as low attenuation areas. Nevertheless, High Resolution Compute Tomography (HRCT) is preferred due to its ability to detect emphysema lesions smaller than 5mm [Shaker et al., 2007]. Nowadays, the quantification of the emphysema extent using HRCT is done by visual scoring which is dependent on the skills of the observer. Some long-term studies have shown that different radiologists and physicians tend to disagree in the quantification of the emphysema when they evaluate CT from the same patients which highlights the problem of the inter-observer variability. Besides, visual assessment is very time consuming and expensive in for example, long-term studies [Ginsburg et al., 2012].

Automatic quantification of emphysema provides objectivity and reliability. Therefore, many automatic methods have been proposed for quantifying emphysema. The most common method used during many years is based on the Hounsfield Unit (HU) value. It aims to detect low attenuation areas (LAA) using a fixed threshold where the values below the threshold are identified as emphysema. This method provides a solution of the inter-observer variability, however, it is limited because researchers can not agree on the best threshold value due to its dependence of the scanner models [Ginsburg et al., 2012].

The quantification of emphysema using texture-based models are more precise due to these methods take into consideration the spatial relationship between gray-level intensity values. Texture analysis has been used for quantify emphysema in different studies which evaluate texture features obtained from local binary patterns, co-occurrence matrix or run-length descriptor, among others [Sørensen et al., 2010], [Nagao et al., 2003], [Yao et al., 2011].

This project will work with a texture-based model in order to detect and quantify emphysema using HRCT in patients with COPD. This model is chosen because it is believed that quantification of emphysema using texture features correlate better with the assessment from the experts than only using LAA [Gietema et al., 2011]. The purpose of the project is to study a reliable automatic method for quantifying emphysema severity in order to avoid the inter-observer variability.

CHAPTER

2 Background

This chapter will go through the background knowledge for the project. It will start with describing the anatomy of the lung and the Chronic Obstructive Pulmonary Disease. It will continue by focus on emphysema and the quantification of emphysema using computed tomography.

2.1 Lung Anatomy

The lungs are one of the main parts of the respiratory system together with the airways, blood vessels and the muscles which enable the breathing, as seen in Figure 2.1 [National Heart and Blood Institute, 2012*a*]. The lungs are located in the thorax which is composed of the vertebral column, ribs, sternum and intercostal muscles and it is separated from the abdomen by the diaphragm. The right lung is divided in 3 lobes and the left lung in 2 lobes. Both lungs are surrounded by a thin tissue layer called pleura. The pleura consists of an external pleural membrane lining the inner surface of the thoracic wall and the membrane lining the outer surface of the lung, both membranes are separate by the intrapleural fluid [Widmaier et al., 2011].

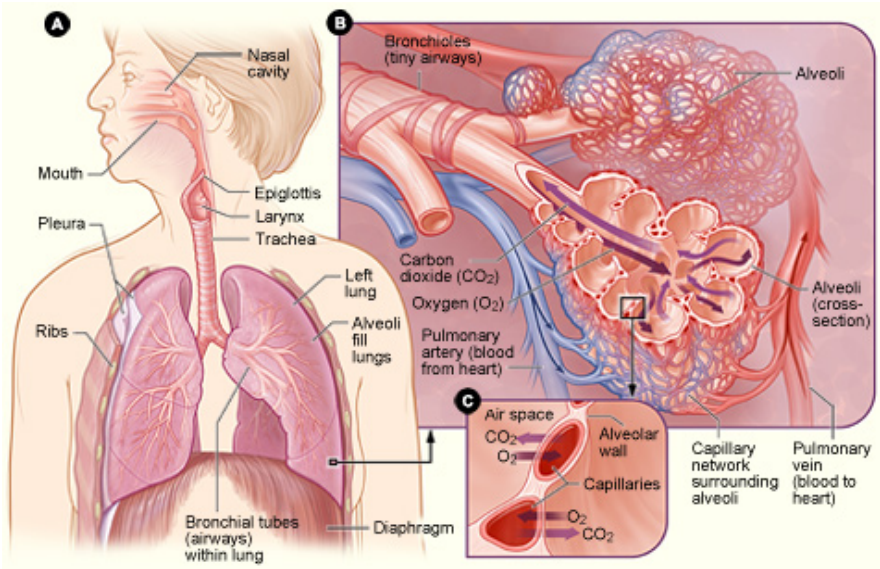

Figure 2.1: A) shows a general overview of the respiratory system. B) shows an enlarged of the respiratory zone. C) shows a magnified view of gas exchange between the capillaries and alveoli. [National Heart and Blood Institute, 2012*a*].

The inhaled air passed through the upper airways and the conducting zone until it arrives to the respiratory zone where the gases are exchanged with the blood. The conducting zone includes the trachea, bronchi and bronchioles and its function is to defend against infections, dust, etc using protective mechanisms such as cilia, mucus and macrophages. The respiratory zone contains alveoli which are tiny air sacs separated by alveolar walls. The alveolar walls contain capillaries and a very small interstitial space. In the alveoli the oxygen is absorbed into the blood and the carbon dioxide passed from the blood to the alveoli to be exhaled [Widmaier et al., 2011], [WebMD, 2009].

2.2 Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease (COPD) is characterized by persistent airflow limitation which is often progressive and related with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases [Global Initiative Chronic Obstructive Lung Disease, 2013*a*]. 65 million people are diagnosed with a moderate to severe COPD worldwide and from 4-10% of adults suffer from it in Europe. COPD constituted the fifth cause of death with the 5% of all deaths worldwide during 2005 which corresponds to 3 million people. Mortality increased more than 60% over the last 20 years and it is estimated that in the next 10 years deaths caused by COPD will go up more than 30%. An estimation shows that in 2030 COPD will be the third cause of death worldwide [World Health Organization, 2011].

2.2.1 Diagnosis

The main diagnosis test of COPD is a breathing test called spirometry [National Heart and Blood Institute, 2012*b*]. This test measures:

- Force vital capacity (FVC): it is the maximum volume of air powerfully exhaled after full inspiration.
- Force expiratory volume in one second (FEV_1): it is the volume of air exhaled during the first second of the FVC performs.
- The FEV_1/FVC ratio.

Airflow obstruction is considered when $\frac{FEV_1}{FVC} < 0.7$ and $FEV_1 < 80\%$ of the predicted value. Spirometry is also used for classifying the severity of the COPD, it is seen in Table 2.1:

Classification of severity of airflow limitation in COPD		
Severity	FEV_1/FVC	FEV_1 predicted
Mild	< 0.7	$\geq 80\%$
Moderate	< 0.7	50 - 79%
Severe	< 0.7	30 - 49%
Very severe	< 0.7	$< 30\%$

Table 2.1: Classification of COPD severity using spirometry [Bousquet and Khaltaev, 2007].

Other test, such as CT scans are performed for diagnosing COPD since they are used to detect emphysema which is one of the most common manifestation seen in COPD.

2.2.2 Symptoms and Risk Factors

The main risk factor for COPD is tobacco smoke and most of the patients diagnosed with COPD had been long-term smokers. However, COPD can be produced by long exposition to urban air pollution, dusts and chemicals fumes from workplaces or passive smokers. Most of the people who suffer COPD are above 40 years old. There are a genetic factor called alpha -1 antitrypsin deficiency (AAT) that can cause COPD in people under 40 years old [National Heart and Blood Institute, 2012*b*], [Currrie et al., 2007]. AAT is a protein made in the liver and secreted into the circulatory system to help protect the lungs. It is a major inhibitor of proteases secreted by neutrophils during inflammation [Mayo Clinic, 2012].

COPD may not cause symptoms until significant lung damage has occurred. Common symptoms of patients with COPD are dyspnea, chronic cough usually with sputum, fatigue when doing mild activity, exacerbation and weigh loss [WebMD, 2009]. In order to assess these symptoms two questionnaires are done, one is the COPD Assessment Test (CAT) and the other is the Modified British Medical Research Council (mMRC).

According to the spirometric classification, exacerbation history and symptoms, patients are classified as shown in Figure 2.2.

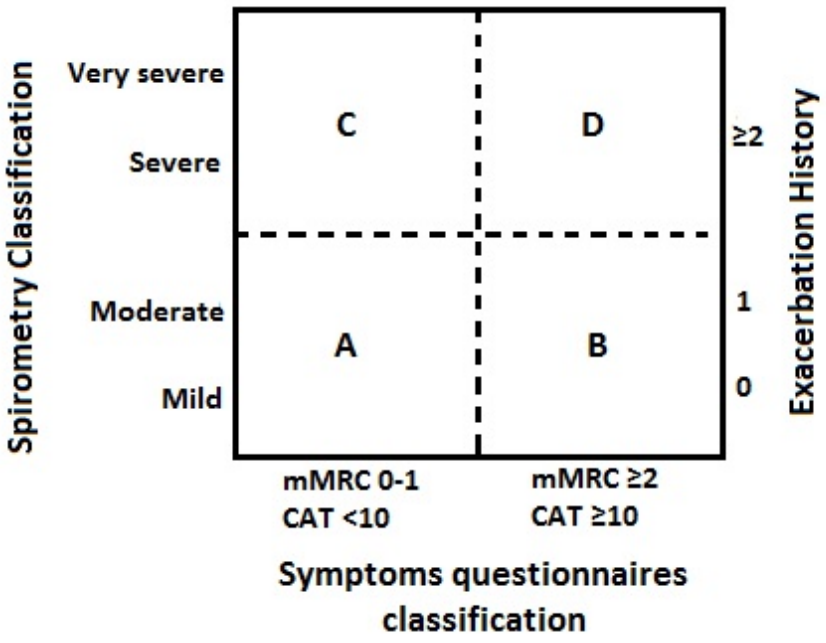

Figure 2.2: Graphic of the combined assesment of COPD. [Global Initiative Chronic Obstructive Lung Disease, 2013*b*].

2.2.3 Treatment

Although COPD is a treatable disease, there is not a cure for it. Thus, the treatments focus on alleviate the symptoms and monitor the disease in order to not get worse. Patients with COPD have to stop smoking in order to stop increasing the lung damage. Treatments depend of the severity of the disease in each patient but usually the treatments consist of bronchodilators, steroids, anti-inflammatory medications and in more severe cases also oxygen therapy. During exacerbation periods antibiotics are required. Non-pharmacological management is recommended such as pulmonary rehabilitation and exercise training [National Heart and Blood Institute, 2012*b*], [Currrie et al., 2007].

2.3 Emphysema

The chronic airflow obstruction that patients with COPD suffer is caused by a combination of small airways disease, chronic bronchitis, and parenchymal destruction, emphysema [Global Initiative Chronic Obstructive Lung Disease, 2013*a*]. Emphysema is defined as a lung condition characterized by the destruction of the alveolar walls leading to a loss of elastic tissue and an increase in compliance, as seen in Figure 2.3 [Widmaier et al., 2011]. When the air spaces are greater than 1cm they are called bullae.

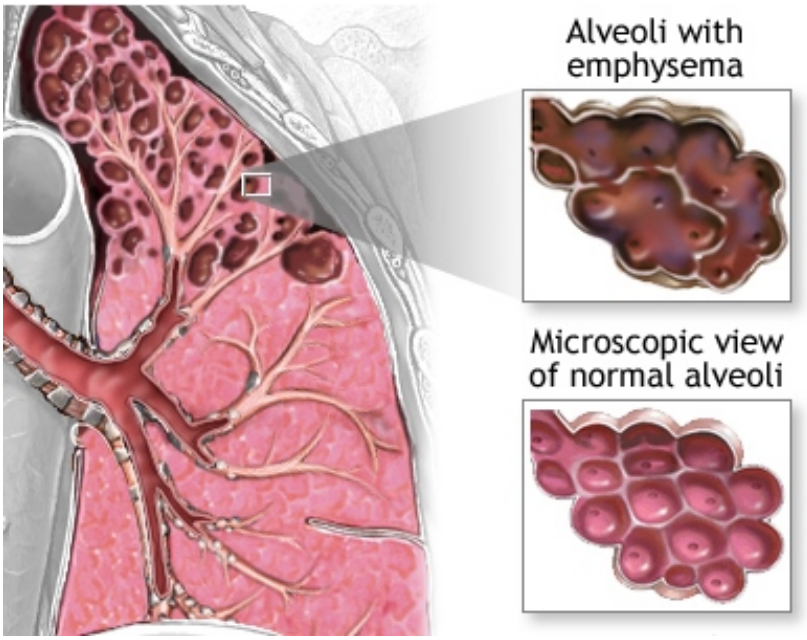

Figure 2.3: Emphysematous lung showing the alveoli destruction and a view of a healthy alveoli tissue. [a.d.a.m. medical encyclopedia, 2011].

There are three different types of emphysema [Shaker et al., 2007]:

- **Centrilobular emphysema (CLE)**: the destruction is limited to the central part of the secondary lobule.

- **Paraseptal emphysema (PSE)**: it presents distension and destruction of the whole lobule and it affects mostly to the secondary lobule adjacent to the inter-lobar septa and pleura.

- **Panlobular emphysema (PLE)**: this type is associate with AAT deficiency.

Centrilobular and paraseptal usually are differently distributed although both can co-exists in severe stages. Centrilobular is typically located in the apex of the upper lobe but spreads down as the disease become worse. On the other hand, paraseptal and panlobular emphysema are more predominant in the lower lobes. The centrilobular is the most common emphysema in smokers and during the mild stage. Usually it does not cause pulmonary dysfunction [West, 1998].

Alveolar wall destruction in emphysematous lungs is the result of an imbalance between protease and antiprotease in the lung. This imbalance is produced because tobacco smoke activates the alveolar macrophage increasing the number and recruits neutrophils into the lung. The activation of the alveolar macrophages release elastase and stimulate the release of elastase from neutrophils which leads to destruction of the alveolar wall. The oxidants in cigarette smoke and free radicals released by neutrophils inactivate the AAT which is the main elastase inhibitor, it is seen in Figure 2.4 [West, 1998] [Barnes et al., 2009].

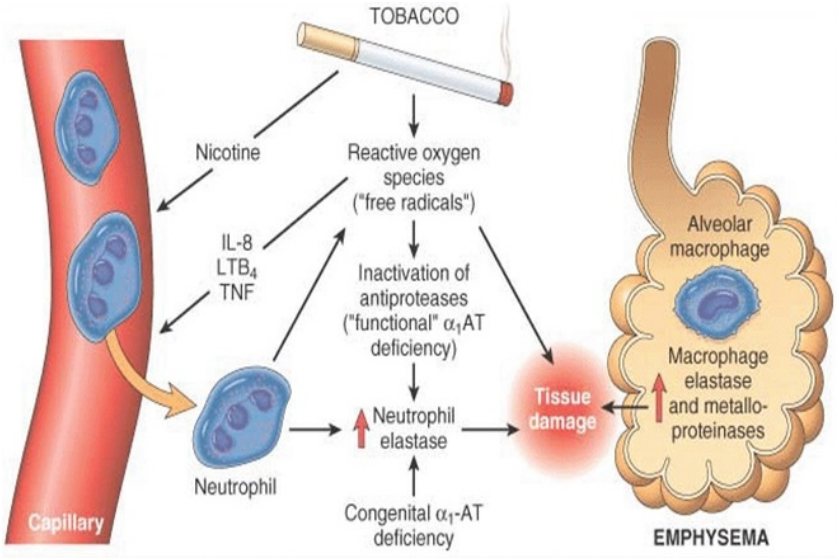

Figure 2.4: Description of pathogenesis of emphysema [Adnan, 2011].

2.4 Computed Tomography for Quantifying Emphysema

One of the most common imaging tests used for diagnosing emphysema in patients with COPD is Computed Tomography (CT) scan. CT usually is used for diagnosing and quantification of emphysema. Although emphysema can be visible in conventional CT scan of 5 - 8 mm thickness, High Resolution Compute Tomography (HRCT) is the imaging method used because it is easier to detect smaller lesions in HRCT with slice thickness of 1 - 2 mm (Figure 2.5) [Litmanovich et al., 2008]. HRCT shows small areas of lung destruction as dark regions without visible wall and easily detected when surrounded by normal lung parenchyma

[Stem and Frank, 1994]. Using HRCT mild emphysema such as centrilobular lesions < 5mm can be detected [Shaker et al., 2007].

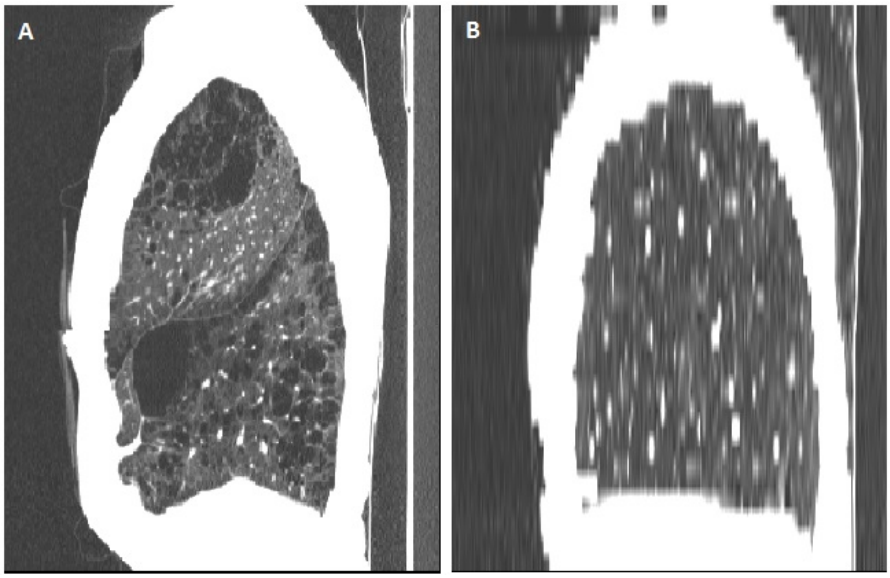

Figure 2.5: Patients diagnosed with emphysema showed in A) HRCT of 1,5mm slices and in B) CT of 5mm slices.

Nowadays, emphysema extend is assessed by visual score but this is subject to intra-and inter-observer variability. Usually classification of emphysema is done in categories, such as, absence of emphysema, 0-25%, 25-50%, 50-75% and >75%. Visual rating can be done in the whole lung or in upper, mid and lower parts [Mascalchi et al., 2012]. Many studies have shown good correlations between visual scores of CT and pathological samples but due to the intra-and inter-observer variability these evaluations can not be used for long-term studies. For that reason, objective quantitative analysis using HRCT is preferred as assessment of emphysema [Mets et al., 2012].

2.5 Previous work in Emphysema Quantification

Many studies of emphysema quantification using CT scans have been carried out in order to find an automatic method which can replace the subjective visual scoring. Emphysema in CT scans appears as an area with low attenuation coefficients. Emphysema has almost the same value as air [Sluimer et al., 2006]. For this reason, the most used technique to quantify emphysema severity is to use Hounsfield Unit (HU) values given in the CT. Emphysema severity is quantified as the low attenuation area (LAA) in the lung with a HU lower than a certain threshold. After applying the HU threshold the lung is classified in normal lung if the voxels are above of the threshold or in emphysematous lung if the voxels are below the threshold [Reilly, 2006]. Gevenois et al. [1995] found that with a threshold value of -950HU there was no difference between the radiological and pathological area of emphysema, although there is not a common agreement between all the studies in which one is the best threshold value. This method is subjective to noise, reconstruction filter and scanner models [Ginsburg et al., 2012].

However, other studies go further and try to describe other patterns of emphysema such as size or spatial distribution of emphysema lesions. Sørensen et al. [2010] formulated a texture classification-based system with the purpose of improving quantitative measures of emphysema by taking in consideration that pixels can be related to the neighbors. It used local binary patterns as texture features and a k-nearest neighbor as a classifier. The results were correlated with a pulmonary function test (PFT) showing a correlation value of 0,79 [Sørensen et al., 2010]. Chabat et al. [2003] describes a texture classification using a 13-dimensional vector that contains statistical moments of the pixel intensity, acquisition-length parameters and co-occurrence matrix descriptors. A bayesian classifier was used to test the performance of the automatic method. The results display that the use of the previous named descriptors can identify different diseases reliably [Chabat et al., 2003].

Nagao et al. [2003] proposed a 3D region growing algorithm for detection of emphysematous lesions. The features are extracted using the region growing method in low-intensity areas. This approach classify the emphysema according with the distribution, concentration and placement using euclidean distance transformation. The results present that emphysema usually are not present close to the bronchi and blood vessels, lesions concentration can be used for assess the severity of the disease, emphysema lesions tend to appear more in the intermediate distance from the hilium and reduction of peripheral bronchiole are very related with severe stages. In this study was concluded that region growing method provides more accurate emphysema quantification than threshold method. [Nagao et al., 2003].

Ginsburg et al. [2012] developed a approach for quantifying centrilobular emphysema as well as centrilobular nodularity. This approach is based on classifying different textures in local region of interest (ROIs) using CT scans. Firstly, a feature extraction is carried out and then these features are classified using multiple logistic regression classifier. Finally a statistical analysis is computed and the results show that the texture-based approach used in this article can discriminate between normal tissue, centrilobular emphysema and centrilobular nodularity [Ginsburg et al., 2012].

There are other approaches based on the morphology of the emphysema as it can been seen in Blechschmidt et al. [2001]. This study aims to be able to quantify emphysematous destruction using a new index which use the size of the bullae. The inter-observer agreement between the result of the automatic approach and the score of the experts shows a coefficient of 0,66 ($p<0,01$) using Spearman correlation [Blechschmidt et al., 2001].

On the other hand, it can be possible to extrapolate and use methods developed in other studies which the focus is not emphysema but pulmonary abnormalities. For example, Yao et al. [2011] developed a computer-aid diagnosis (CAD) of pulmonary infections such as chronic fibrosis, pneumonia or parainfluenza using texture analysis for feature extraction and support vector machine as classifier. In order to obtain the texture features, co-occurrence matrix and run-length algorithm are computed. Support Vector Machine is the classifier used to train and test the CAD. A t-test was conducted for evaluating the statistical independence of the difference between two tissue patterns. The results of this study conclude that texture analysis can be used to distinguish from healthy and unhealthy tissue although clear distinction between some diseases such us pneumonia and parainfluenza can be difficult due to sometimes they can coexist [Yao et al., 2011].

CHAPTER

3 Problem Statement

COPD is a overall problem and represents, with 3 million people, the fifth cause of death. It has a prevalence of 65 million people worldwide but it is estimated to increase in the coming years because of the continued exposure to the risk factors of COPD, mainly tobacco smoke [World Health Organization, 2011].

Most of the patients with COPD suffer from emphysematous lungs and it severity is quantified using CT scans. Emphysema is characterized by enlarged alveolis and destructive changes in their walls [Global Initiative Chronic Obstructive Lung Disease, 2013*a*]. Usually HRCT scans are preferred to asses the emphysema due to its ability to show lesions smaller than 5mm [Shaker et al., 2007]. The previous chapter has presented that quantification of the emphysema is assessed by visual score of the HRCT scans. The emphysema is usually classified in five categories of increasing severity, such as, absence, 0-25%, 26-50%, 51-75% and 76-100%. Visual scoring involves a problem due to the intra-and inter-observer variability and it depends of the experience and ability of the physician. It has been seen in different studies that the results tend to not agree in the severity of the emphysema when different observers have to score the same patients and are blinded to the assessments of each other. [Mascalchi et al., 2012].

Different approaches for automatic scoring have been developed in order to avoid the intra- and inter-observer variability of visual assessment. The most used one through the years have been the so called density mask which applies a threshold to categorize the lung in emphysema or healthy tissue [Gevenois et al., 1995]. However, this method depends on the value of the threshold in which there is not a full agreement among researchers [Friedman, 2008]. Other studies are based in a texture or morphology based concepts which turn out in more precise results for quantifying emphysema.

Therefore, the aim of this project is to study an automatic method based on texture analysis with the purpose of having an objective and reliable procedure to quantify emphysematous lungs in patients with COPD using HRCT scans.

CHAPTER

4 Methods

This chapter describes the data collection and it gives an overview of the method used. Then, the different steps method are explained. It starts with the lungs segmentation process, follow by the texture analysis applied in order to extract the texture features and it ends with a statistical analysis to compare the results of the proposed method and the expert visual evaluation.

4.1 Data Set

The data set used during this project consists of HRCT scans from 24 patients. Data were provided by the Department of Pulmonary Medicine at Aalborg University Hospital in Denmark. The 24 patients were referred to the local pulmonary outpatient clinic for routine assessment where clinical measurements such as $FEV_1\%$ or ∇PO_2 were carried out. HRCT scans were performed 48 hours after the rest of the measurements. HRCT scans were acquired in supine position using 1,25mm slice thickness, no contrast and the patient was asked to hold the breath during the scan [Thomsen et al., 2013].

The HRCT scans, Figure 4.1, were provided as a data set in the anonymous DICOM format. HRCT scans where visually scored for presence and grade of emphysema, bronchial wall thickening and airway diseases by two radiologists and a pulmonary physiologist. Emphysema was graded for three anatomical regions, specifying if the primary site of parenchymal destruction was central or peripheral. The emphysema severity was classify as absence, 0-25%, 25-50%, 50-75% and >75%. The results of the assessments for the 24 patients from the two radiologist and the physiologist were also provided as an excel document.

From the 24 patients that the data set contains, 11 patients were categorized with emphysema, 7 patients with airway diseases, 2 patients as healthy and 4 patients were only evaluated by one radiologist and the physiologist and they could not agree whether the patients had emphysema or airway disease. A patient belongs to one group if at least two of the experts agree in the evaluation. For the purpose of this project the 7 patients with airway disease and the 4 patients which did not have assessment agreement were dismissed because this project only focus in patients with emphysema. From the 11 patients with emphysema, 2 of them had to be dismissed as well, due to their CT scans were acquired using a different protocol. Thus, the control group during the project is formed by 2 healthy patients and the experimental group is constituted by 9 patients.

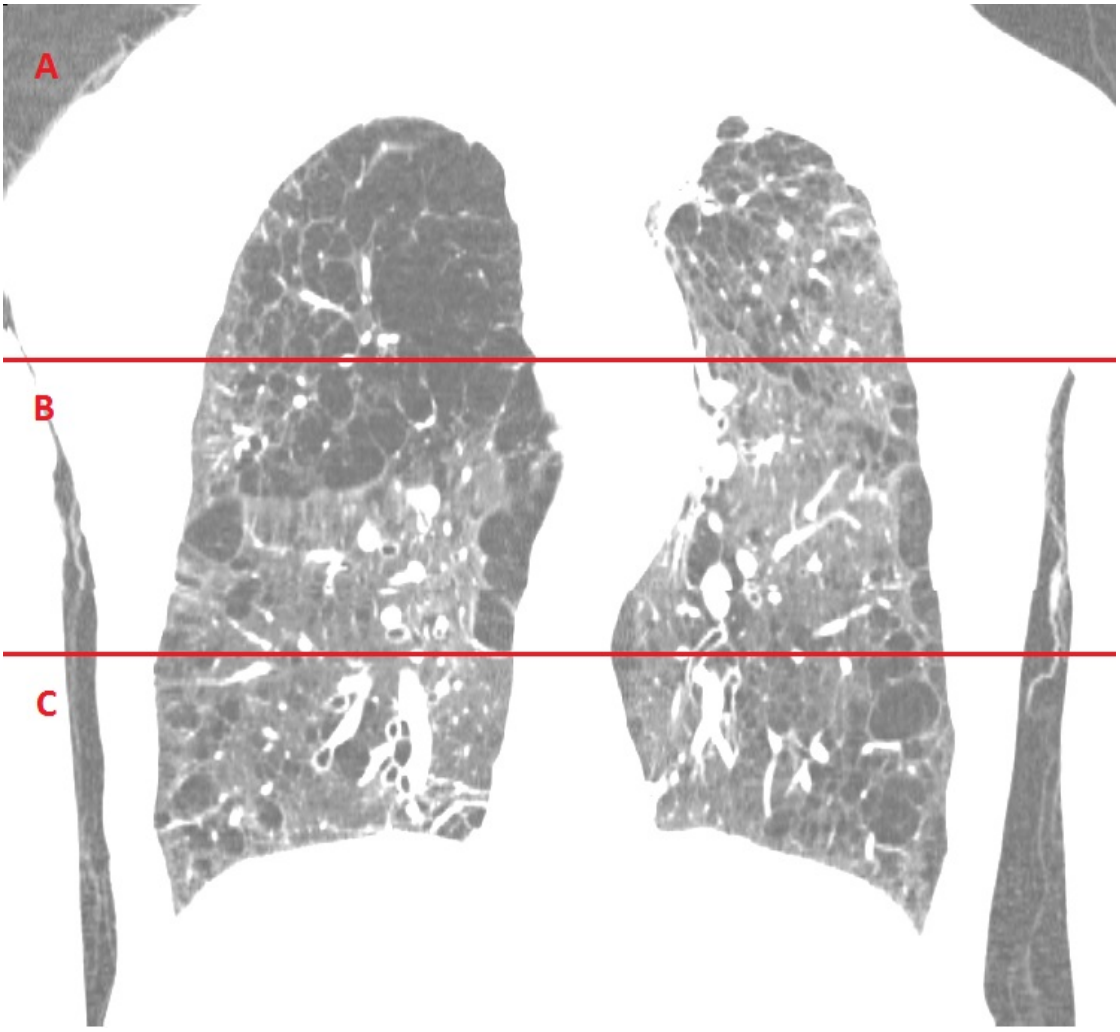

Figure 4.1: Example of data from patient number 8 categorized by the expert with very severe emphysema. Coronal image divided in 3 regions where A belongs to the upper part of the lung, B to the mid part of the lung and C relates to the lower part of the lung.

The data used during this project was not acquired with the purpose of this project and therefore, as seen in the above paragraph, the control and experimental group are very small.

Each HRCT slice has $512x512$ voxels with a voxel size of $0,7365x0,7365x1,25mm$. The number of slices vary from patient to patient, the variation range is from 235 to 276 slices.

4.2 Method overview

Given a HRCT data set, the proposed automatic method first segment the right and left lung in three different sections, secondly it makes an analysis of the texture patterns and then a classifier is trained to distinguish between emphysema and no emphysema tissue. A statistical analysis is finally computed to assess the level of agreement between the results of the proposed method and the opinion of the experts. Figure 4.2 shows a diagram of the proposed method.

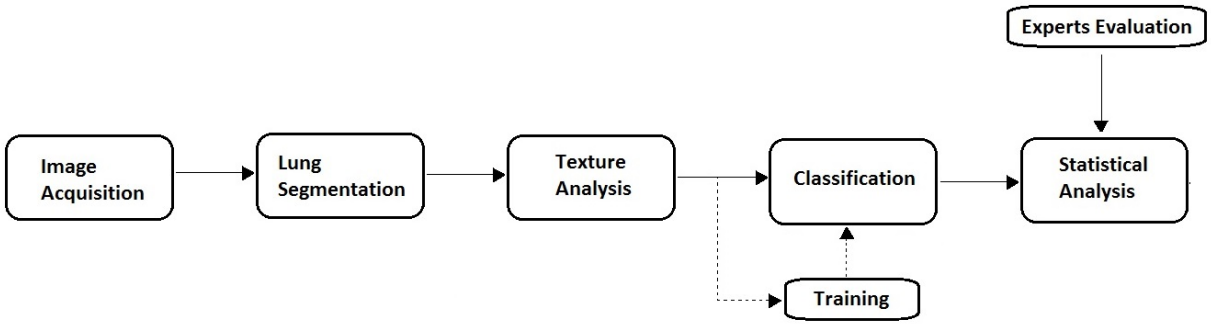

Figure 4.2: Diagram of the image analysis for the proposed method.

In the following sections there will be a description of each module of the diagram, as well as, the procedure used for implementing the theory.

4.3 Lung Segmentation

Lung segmentation is considered as an essential step in any method that analyzes the lungs. There are different ways to segment the lungs depend on the purpose of the study. Some segmentation methods may consider to segment the bronchi and the vessels prior to segment the lungs as in the studies of Chabat et al. [2003] and Yao et al. [2011]. In this first study, firstly the vessels are removed by segmenting them using a morphological segmentation. Then the lungs are segmented using the same technique and finally the ROIS used for extract the textural information are selected manually [Chabat et al., 2003]. In the study by Yao et al. [2011] the region growing is used firstly to segment the trachea and using the position of it to place the seeds for carrying out an automatic segmentation of the right and left lung. A histogram thresholding is used in order to refine the lung segmentation [Yao et al., 2011].

In HRCT, lungs are seen as areas with low attenuation values due to the fact that they are filled with air which has a HU value of -1000. These low HU values give a high contrast between the lungs and the surrounding tissue. The segmentation method used during this project is region growing which uses the variations in intensity values for segmentation of the images. An explanation of the basis of region growing is found in Appendix A.1.

In this project, the segmentation using region growing segments the right and the left lung in three sections in each data set. The three sections belong to the upper, middle and lower part of the lungs. The seeds in each section are placed empirically. Then, by means of a 3D region-growing algorithm, the seeds spread to the whole lung section. The segmentation is

performed in one section at a time first in the right lung and afterward in the left lung. As described in Appendix A.1, it is recommended to choose more than one stop criteria. During this project the absolute gray level difference between the voxels and the seed have to be 18. This value is chosen empirically and it works as a threshold level meaning that the seed will not spread if the voxel value is over the threshold. The second criterion is that the pixel has to be 8-connected to at least one pixel in the same region. The region growing uses 8 connected neighbors in the growing process until the neighbors do not belong to the specified intensity range.

As last step, a morphological operation is used to refine the segmentation. First, a disk-shape structure is created and it is used in the closing process. Closing is the chosen morphological operation due to its ability to fill the holes in the segmented image and to preserve the sharp edges and the original size.

The result of the segmentation is 6 sections with three in each lung. Each segmented section is represented as value 1 and the background is represented with 0 values. In order to check the performance of the segmentation, a superposition of the segmentation and the original image is carried out.

4.4 Texture Analysis

Once the different sections in the lungs are segmented, a texture analysis is performed to extract the texture features. Texture features are used to differentiate between emphysematous and healthy lung tissue. There are diverse methods used to characterize emphysema and different lung diseases using texture analysis such as run-length matrix or histograms as in Ginsburg et al. [2012] and Sørensen et al. [2010]. The run-length matrix is a method which runs of pixels with the same gray-level intensity through a given direction. Computing run-length matrix different textural features can be extracted, these features are related to the size, orientation and attenuation value of the elements in the image [Ginsburg et al., 2012]. Using histogram from the images many parameters can be extracted such as mean gray-level value, variance, skewness or kurtosis [Sørensen et al., 2010].

The texture features in this project are derived from the co-occurrence matrix. Co-occurrence matrix is described in Appendix A.2 and it has been used in different studies to distinguish between healthy and not healthy lungs [Yao et al., 2011], [Chabat et al., 2003].

In this project the co-occurrence matrix algorithm is used in 3D which aims to capture the spatial dependence of gray-level intensities through multiple slices. As in the normal 2D co-occurrence matrix, the 3D co-occurrence algorithm counts the pair of voxels pairs that have the same intensity value. The difference between the 2D and 3D co-occurrence matrix appears in the displacement vector which is defined for the 3D one as $d = (dx, dy, dz)$. The displacement vector represents the distance and direction where the voxel pair is defined. For volumetric data there are 13 different directions, it can seen in Table 4.1.

Directions of displacement vector	
0 1 0	0 degrees
-1 1 0	45 degrees
-1 0 0	90 degrees
-1 -1 0	135 degrees
0 1-1	0 degrees + 45 degrees
0 0 -1	straight up
0 -1 -1	0 degrees + 135 degrees
-1 0 -1	90 degrees + 45 degrees
1 0 -1	90 degrees + 135 degrees
-1 1 -1	45 degrees + 45 degrees
1 -1 -1	45 degrees + 135 degrees
-1 -1 -1	135 degrees + 45 degrees
1 1 -1	135 degrees + 135 degrees

Table 4.1: 13 directions applied for 3D co-occurrence matrix.

In this project, the search is performed in 13 directions and 5 different distances for the voxel pair evaluated. There are 11 subjects in this project with the lungs segmented in 6 sections, thus a total of 4290 co-occurrence matrices are computed. The size of the co-occurrence matrix depends on the range of the gray-level intensity of the evaluated image. The range of intensities of the data set in this project is 8 bits, so, the co-occurrence matrices have a size of 256 by 256.

After obtaining the co-occurrence matrices, the spatial dependence of gray-level values is evaluated by computing the 12 Haralick textural features. The textural features are energy, entropy, correlation, contrast, homogeneity, variance, sum mean, inverse difference moment, inertia, cluster shade, cluster tendency and max probability. They are described in Appendix A.2. For each section, there are a total of 65 co-occurrence matrices, thus, 65 values were obtained for each texture descriptor. Then, the average value of each texture descriptor is computed given as a result a feature vector of 12 Haralick features per section.

4.5 Training and Classification

The Haralick features are used to classify lungs into two classes, normal and emphysema. In this project Support Vector Machine (SVM) is used as classifier method because it has been shown that SVM is one of the most solid classification methods for training and testing data. Besides, Lee et al. [2009] made a study for evaluating the best classifier to classify obstructive lung diseases using texture analysis. The results show that SVM is the most robust method and it performs the best overall accuracy when it is compared with other classifiers such as Artificial Neural Network (ANN), Naive Bayesian classifier and Bayesian classifier [Lee et al., 2009].

SVM is a supervised non-parametric method which aims to divide two categories by a hyperplane. The best hyperplane separating the classes is the one that has the largest margin. The margin is the maximum width between the support vectors which are the points of each data set closest to the hyperplane [Duda, 2000]. An example of a SVM is seen in Figure 4.3.

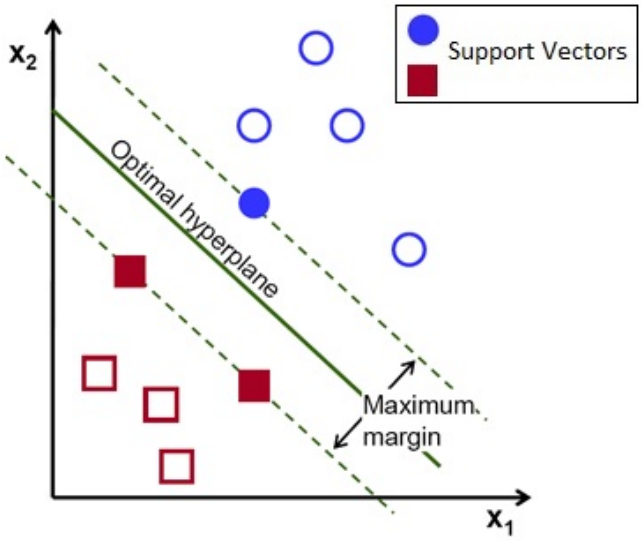

Figure 4.3: Division of two classes using the SVM. Adaptation of [OpenCV, 2011].

As SVM is a supervised method, it needs to be trained before it can be used to classify new data. The kernel function used during this project when training the SVM is the linear kernel which to separate the data uses a hyperplane. During the training process, the SVM classifier learns texture patterns of a normal lung and an emphysematous lung. For training and testing the data the leave-one-out method was used. Therefore, the classifier is trained with all the sections belonging to all the patients except one, then the sections of the patient excluded in the training is used to test the classifier. The SVM returns a 0 if the texture feature belongs to a healthy lung and 1 if the texture feature belongs to a lung with emphysema. This process is repeated for each data set [Duda, 2000].

4.6 Performance Evaluation

Statistical analysis is widely use for validating results in medical studies. The choice of a specific statistic method relies on the data used and the comparison that have to be made. In this project, the purpose of applying a statistic method is to compare the agreement between the results obtained automatically and the results given by the experts. The type of data in both cases are referring to the emphysema severity grade. These data are called ordinal data which is a type of non-parametric qualitative data. It categorizes each observation in a category that has a natural order between categories [Bland, 2000].

There are different statistic methods for measuring the level of agreement between observers (inter-rater agreement). Usually all these methods are based on the rating of the observers agree in a particular case if the observers classify the subject in the same category. The great majority of categorical scales are quite subjective and therefore, perfect agreement is uncommon [Agresti, 1996].

One of the methods that measure the inter-rater agreement using ordinal data is the weighted kappa analysis. Weighted kappa is based on the Cohen's kappa algorithm for nominal data. The weighted kappa is used for ordinal data where the disagreement between closer cate-

gories are less serious than between separate ones. Therefore, the quadratic weighted kappa assigns to each category a different weight [Cohen, 1968]. In this project there are 5 categories labeled with numbers from 1 to 5 where 1 means absence of emphysema, 2 means 0-25% emphysema, 3 means 25-50% emphysema, 4 means 50-75% emphysema and 5 means >75% emphysema. The weight used for each category is 1, 0.937, 0.750, 0.437 and 0 respectively. The comparison is performed using the average of all the lung sections for each patient.

The statistical analysis gives as result the values of the weighted kappa, the standard error and the confident interval. The weighted kappa value express the level of agreement between the observers. The standard error is the value of testing the hypothesis that the underlying value of weighted kappa is equal to a pre-specified value other than zero. Finally, the confident interval shows the 95% confident interval of the weighted kappa value. The value of the weighted kappa can be interpreted as seen in Table 4.2.

Value of Weighted Kappa	
Value	**Strength of agreement**
< 0.20	Poor
0.21 to 0.40	Fair
0.41 to 0.60	Moderate
0.61 to 0.80	Good
0.81 to 1	Very good

Table 4.2: Interpretation of the value of the quadratic weighted kappa [Bland, 2000].

4.7 Data Processing

In this section there will be an explanation of the process of applying the theory from the previous sections. The program used to process the data is MATLAB R2012b and the statistics are computed using MedCalc. MedCalc is a software which computes medical statistics. The version MedCalc 12.5.0.0 in the free trial edition is used in this project.

Before to apply the automatic segmentation of the lungs the data sets need to be crop. Each data set is cropped according to the number of slices which contains the lungs. The rest of slices without lung information are removed with the cropping. Then each slice of the data sets are resize to 128x128 pixels using bilinear interpolation. This step is needed because the heavy computational process of slices of 512x512 pixels.

The segmentation of the lungs is carried out in 3D and it starts dividing the cropped data set in 3 equal sections. Then, automatic region growing is computed for each section in each lung. A total of 6 segments are the results of the segmentation for each data set. The MATLAB code used for the region growing is an adaptation of the code that can be found in *mathworks* [Kellnerd, 2011].

After the segmentation and before to apply the texture analysis, the segmented images are superimposed with the original data and the background is set up to NaN. NaN means not a number and it is a value or a symbol that it is not taken into account when the window size of the co-occurrence matrix are in the edges of the lungs and therefore including these val-

ues. The co-occurrence matrix is computed for each of the 6 segments in 13 directions and 5 distances and 12 textural features are extracted for each distance and direction. A total of 156 features per distance were extracted in each segment, therefore, the mean value of each feature were computed having as result a vector of 12 features per segment. The MATLAB code for calculating the 3D co-occurrence matrix is an adapted version of the one that can be found in *mathworks* [Uppuluri, 2008].

Once, the texture information is obtained the classifier has to be trained. The SVM is the classifier used in this project. First, it is trained with all the data set except one and then the classifier is tested with the data set not used during the training process. The MATLAB code used for build the classifier are two MATLAB functions called svmtrain and svmclassify.

Finally, the results obtained from the classifier are labeled according with same the categorical scale used by the experts. A quadratic weighted kappa analysis is carried out using MedCalc in order to compare the level of agreement between the experts and the automatic method. The analysis was performed in pairs of one expert and the automatic classification, so three quadratic weighted kappa are computed.

CHAPTER

5 Results

In this chapter the results of the proposed method are presented. First, the results from the automatic segmentation as well as a comparison between these results and the original images. The results given by the classifier for distinguish between emphysema and healthy lung. Finally, the results from the statistical analysis are presented which show the agreement between the presented method and the assessment of the two radiologist and the physician .

5.1 Segmentation Results

For all the patients a segmentation of the lung was computed. The lungs were individually segmented using region growing which first, it was applied in the right lung and after in the left lung. Three seeds were set in each lung, thus, the segmentation was done in 3 different parts belongs to upper, middle and lower part according with the division used by the two radiologist and the physician. The results of the segmentation represents the lungs with 0 value (white color) and the background with value 1 (black color). Figure 5.1 shows the result of segmentation of both lungs in the coronal plane of the 3 sections belongs to patient number 7.

An overlap between the segmentation results and the original images is performed in order to validate the segmentation. In Figure 5.2 it can be seen an example of the superposition between the original image and the automatic segmentation carried out by the region growing algorithm in each section. It can be observed that the overlap is matching almost perfectly the boundaries of the lungs in the original image.

Figure 5.1: Lung segmentation of patient 7. Segmentation carried out individually for the right and left lung in 3 different sections, upper, middle and lower.

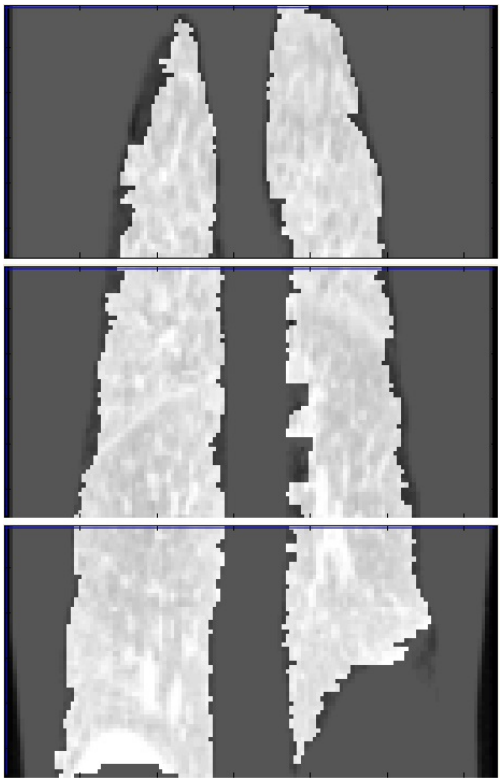

Figure 5.2: Overlap between the automatic segmentation using region growing in patient number 7 and the original image.

5.2 Classifier Results

After segment the lungs a texture analysis is computed in all the sections and 12 textural features are extracted from each section of the lung. These textural features are used to classify the lung in emphysema or healthy. The leave-one-out method was used and therefore, the classifier was trained with all patients except one which was used for test the classifier. The results given by the classifier are presented in Table 5.1 as a percentage of the probability that each region has emphysematous tissue.

Percentage of emphysematous tissue per section			
Data Set	% Section 1	% Section 2	% Section 3
1	78.69	63.84	80.58
4	59.61	77.56	60.57
7	86.60	96.42	78.24
8	84.72	98.61	95.89
10	50.84	71.18	69.16
12	81.75	73.07	62.06
18	70.76	80.76	18.72
20	94.16	96.72	90.98
21	54.99	54.16	70.29

Table 5.1: Classifier results per section for all the data sets.

Since the assessment of the two radiologist and the physician are given as emphysema extent of a lung, the results of the classifier can not be compared straightforward. The percentage in each section given by the classifier is then labeled according with the categorical scale used by the experts in order to be able to compare both results. The categorical scale used labels absence of emphysema as 1, 0-25% of emphysema is labeled as 2, 25-50% of emphysema is labeled as 3, 50-75% of emphysema is labeled as 4 and >75% of emphysema is labeled as 5. The labeled results given by the classifier are seen in Table 5.2.

Quantification of emphysema per section and the whole lung				
Data Set	% Section 1	% Section 2	% Section 3	Average Lung
1	5	4	5	4.6
4	4	5	4	4.3
7	5	5	5	5
8	5	5	5	5
10	3	4	4	3.6
12	5	4	4	4.3
18	4	5	2	3.6
20	5	5	5	5
21	4	4	4	4

Table 5.2: Quantification of emphysema using categorical scale for each section and the average quantification for the whole lung.

Quantification of emphysema severity scored by the twotwo radiologist and the physicians can be seen in Table 5.3.

Quantification of emphysema per section and the whole lung assessed by the experts					
Data Set	Expert	% Section 1	% Section 2	% Section 3	Average Lung
1	Radiologist 1	3.5	5	5	4.5
	Radiologist 2	5	5	5	5
	Physician	4.5	2	1.5	2.6
4	Radiologist 1	5	5	5	5
	Radiologist 2	5	4	5	4.6
	Physician	3.5	2.5	3.5	3.1
7	Radiologist 1	3	3	3.5	3.1
	Radiologist 2	4	3	3	3.3
	Physician	3.5	3	2.5	3
8	Radiologist 1	3.5	5	5	4.5
	Radiologist 2	5	4	5	4.6
	Physician	5	5	4.5	4.8
10	Radiologist 1	3.5	3	2	2.8
	Radiologist 2	4.5	2.5	1	2.6
	Physician	2.5	2.5	2	2.3
12	Radiologist 1	3	3	3	3
	Radiologist 2	2	2	1	2
	Physician	3	2	2	2.3
18	Radiologist 1	4	2.5	2.5	3
	Radiologist 2	1	1.5	0	1.7
	Physician	1.5	1.5	1.5	1.5
20	Radiologist 1	3.5	2	2.5	2.6
	Radiologist 2	4.5	3	2	3.1
	Physician	3.5	3.5	2.5	3.1
21	Radiologist 1	2	2	2	2
	Radiologist 2	3	2	1	2
	Physician	2.5	2.5	2	2.3

Table 5.3: Quantification of emphysema scored visually by two radiologist and one physician.

5.3 Performance Evaluation Results

The statistical analysis is computed in pairs of the proposed method in this project and each of one experts. The results of the statistical analysis are showed in the follow tables where the quadratic weighted kappa results is displayed as well as the standard error and the 95% of confident interval (CI). The weighted kappa value express the inter-rater agreement. The standard error is the value of testing the hypothesis that the underlying weighted kappa value is equal to a some value other than zero. Finally, the confident interval shows the 95% confident interval of the weighted kappa.

The results of the comparison between the visual scoring from the Radiologist 1 and the automatic method are seen in Table 5.4.

Inter-rater agreement between Radiologist 1 and automatic method	
Weighted Kappa	0.182
Standard Error	0.191
95% CI	-0.192 to 0.556

Table 5.4: Quadratic weighted kappa result between Radiologist 1 and automatic method.

The inter-rater agreement between Radiologist 2 and automatic method can be seen in Table 5.5.

Inter-rater agreement between Radiologist 2 and automatic method	
Weighted Kappa	0.219
Standard Error	0.159
95% CI	-0,0929 to 0,531

Table 5.5: Quadratic weighted kappa result between Radiologist 2 and automatic method.

The results of the agreement between the Physician and the automatic method is display in Table 5.6.

Inter-rater agreement between the Physician and automatic method	
Weighted Kappa	0.297
Standard Error	0.129
95% CI	0,0432 to 0,551

Table 5.6: Quadratic weighted kappa result between the Physician and automatic method.

CHAPTER

6 Discussion

The segmentation method used in this project for segmenting the lungs is region growing. Region growing is a method that aims to divide the image in regions according to the gray-level connectivity between pixels. It is a semi-automatic segmentation method but it needs a prior user interaction to suitably place the seeds and to choose the intensity difference between pixels in which the growing process spread out. The results are superimposed with the original images to evaluate the segmentation performance of the region growing method. There is a good matching between the original image and the segmented image. However, the fact that the airways are not segmented apart and therefore included in the lungs segmentation may have an influence in the final results.

Texture features are independent of scanner type and it can be used to quantify emphysema better than only LAA [Ginsburg et al., 2012]. The proposed texture-based system uses co-occurrence matrix as feature extractor. In this project 12 Haralick features were computed from the co-occurrence matrix and used as textural descriptors which describe the spatial dependence of the gray-scale distributions. However, co-occurrence matrix and the Haralick features extracted from it does not take into account shape aspect of the gray-level. It could be solved by adding another descriptors such as features derived from the histograms or run-length parameters but on the other hand, histograms had been shown that are not able to detect mild emphysema [Lee et al., 2009].

The co-occurrence matrix is used for volumetric data, thus, 13 directions are used in this project. This presents an advantage respect to other studies which usually co-occurrence matrix is used in 4 directions, thus, 2D. The co-occurrence matrix is computed in the whole sections where the lungs are divided during the segmentation. Although, it may be considered another approach that could be to select different ROIs instead of characterized the whole lung, it could lead to better results in the classification process.

A big problem during this project is coming from the data set due to it was not acquired with the purpose of this project, hence a very small control group and experimental group are available. Besides, the experts scoring were not provided in a very useful way in order to compare with the results of the proposed method. The proposed method express the probability in percentage of suffering emphysema that a lung has while the experts assessment shows the emphysema extent of a lung. In order to be able to compare more straightforward both results could be if the experts score the patients slice by slice, in that case a percentage of the maximum theoretical score can be computed [Revel et al., 2008].

The classification process performed in this project is carried out using SVM. In this project, the assessment of the patients made by the two radiologists and the physician are taken as a gold standard for comparison purposes, despite of the limitations and the inter-observer variability. The comparison between the results of the classifier and the scoring of the experts does not show the best results for the automatic method. The classifier tend to over estimate the severity of the emphysema. The misclassification in the quantification may be understood in the context of the small data set available.

A statistical analysis is computed in this project for evaluate the agreement between the proposed method and the two radiologists and the physician. The statistical method chosen is the quadratic weighted kappa analysis which give as a result a fair agreement between the experts and the method developed in this project. The experts assessment is being used to validate the method but the fact that visual scoring is depend on the inter-observer variability and the categorical scale used for quantify the emphysema is quite subjective, a perfect agreement when computing the statistical analysis is very rare. It has to be noticed that strong agreement requires strong association, but strong association can exist without strong agreement [Agresti, 1996], thus, if the automatic method rates the patients one level higher than the experts, the strength of agreement is poor even though the association is very strong.

In short, the proposed method can be considered as a method for quantifying emphysema, however, further investigation should be done in order to study if emphysema lesions need to be characterized by other descriptors than only co-occurrence matrix and if the fact to not segment the airways and vessels has a direct effect on the distinction of emphysematous tissue. Besides, a bigger data set acquired and scored by the experts with the purpose of the study is needed in order to validate the results accurately.

CHAPTER

7 Conclusion

The purpose of this project was to study the feasibility of a reliable and objective automatic method for quantifying emphysema in patients with COPD using HRCT scans. The proposed method is based on segmentation, texture analysis and classification of the texture features to assess the emphysema severity. The segmentation process was based on region growing, the texture features were extracted from the computed co-occurrence matrices and a SVM classified the features by distinguishing between emphysema and healthy tissue.

The proposed method during this project has a good prospect of being a reliable method to quantify emphysema. However, the data used for the project was not acquired with the purpose of the project and therefore the results were not in full agreement with the results of the experts. The low rate agreement when the statistical analysis was computed could be explained with the small quantity of data in the experimental and control group as well as the difficulty of not being able to directly compare percentages of emphysema.

Nevertheless, the method explained in this project can differentiate emphysematous and healthy tissue and quantify these textural features to increase the objectivity when assessing emphysema severity in patients with COPD. It can be used as a method to avoid the inter-observer variability of visual scoring by experts.

CHAPTER

8 Perspectives

Despite of the results showed in this project, there are a few other areas and considerations that should be further investigated. Firstly, a data set acquired with the purpose of the project is needed. A bigger experimental group as well as a bigger control group are required. It should be assure that the control group is created by only healthy subjects.

A true gold standard is needed to be able to compare the results of the automatic method with the assessment of the experts. The assessment of the experts needs to be done having in mind the purpose of the project and therefore, having a scores that can be compared directly with the results given by the proposed method.

It is suggested to segment the airways and vessels prior to segmentation of the lungs in order to investigate if it has a direct effect on the distinction of emphysematous tissue. Different descriptors, others than only co-occurrence matrix, should be used to characterize emphysema and to study the influence that different type of descriptors may have for defining accurately emphysema lesions according with its size, distribution or severity.

The presented method can be extrapolated to other areas since quantitative image analysis may yield new relevant information that can be used to improve the diagnosis of different pathologies. Thus, the segmentation and the texture-based methods presented in this project can be used for example, for quantifying lung damage after radiation pneumonitis or detecting tumors in other organs, an example could be the liver. This proposed method can also be used with other types of data, for example magnetic resonance images.

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APPENDIX

A Image Analysis

A.1 Region-based Segmentation

Region-based segmentation aims to divide or group regions regarding common image properties such as intensity values, textures or patterns. In region-based segmentation the regions are considered homogeneous which is used as a criterion. This criterion is used to add pixels to the region in the region growing algorithm or to divide regions which not fulfill the criteria in the region splitting algorithm. Sometimes a combination of both algorithms can been used [Kothari, 1999].

Region growing generates a region in which pixels fit the homogeneity criterion. This approach starts by setting a seed from where neighbor pixels are added to the region consecutively if they have similar properties to the seed points and therefore fulfill the criterion. The algorithm stops when there are no more pixels that fit the criteria. In order to formulate the stopping rule well, it is needed to take into account that criteria such as gray level, texture or color need to be together with additional criteria such as maximum gray level between neighbor pixels, shape or size of the region to be grown [Gonzalez, 2001]. To generate a region growing algorithm is needed to determinate the initial seed point and to decide the criteria.

Usually the seed position is set either manually or automatically by, for example, the maximum level of pixel gray level value. It is also common to use more than one seed if different partitions are required [Kothari, 1999].

The result of applying region growing algorithm is a binary image, usually, with a pixel value of 0 for the background and the segmented object with a pixel value of 1 [Gonzalez, 2001].

A.2 Texture analysis

Texture analysis has been commonly used to detect lesions and distinguish between healthy and non healthy tissue. Texture analysis applies mathematical algorithms to the data from X-ray, CT scans or MR images. Texture features are the result of the mathematical methods which characterize the different objects in the image. Texture analysis can be divided in four groups according to the approach taken for evaluating the pixels in the image [Castellano et al., 2004]. These four groups are:

- **Structural methods**: These methods are based on the primitives for defining the objects in the images and they provided a good description of the image.

- **Model-based methods**: Model-based uses complex mathematical algorithms such us fractal or stochastic. The most used approach is the auto-regressive model.

- **Statistical approaches**: Using these approaches the images are defined by the relation between grey-level values of the pixels. Statistical approaches are the most used method of the four groups and the most common approaches are histogram, absolute gradient, run-length matrix and co-occurrence matrix.

- **Transform methods**: Transform methods apply Fourier, Gabor or Wavelet transform in order to analyze the properties of the images. The wavelet transform is the widely used among the others.

Statistical approaches are the most widely used in medical images, and during this project co-occurrence matrix and a set of features derived from it has been used to characterize emphysema lesions and therefore, to be able to distinguish between emphysematous and healthy tissue.

A.2.1 Co-occurrence Matrix

The co-occurrence matrix extracts statistical information from the image analyzing the grey-level distribution of pairs of pixels. Co-occurrance matrix depends on several parameters listed below [Lemaitre and Rodojevic, 2010]:

- Window size of the connected neighbor pixels where the matrix will be computed.
- The number of gray-levels. It is used to narrow the matrix size.
- Direction and distance in which the matrix is computed.

The co-occurrence matrix is computed in the direction selected for each pixel withing the window size. Then, the number of times that pixels pairs appears specified by the distance is counted, thus, each entry of the matrix correspond to one of the grey-level distribution. An example of co-occurrence matrix computation is seen in Figure A.1.

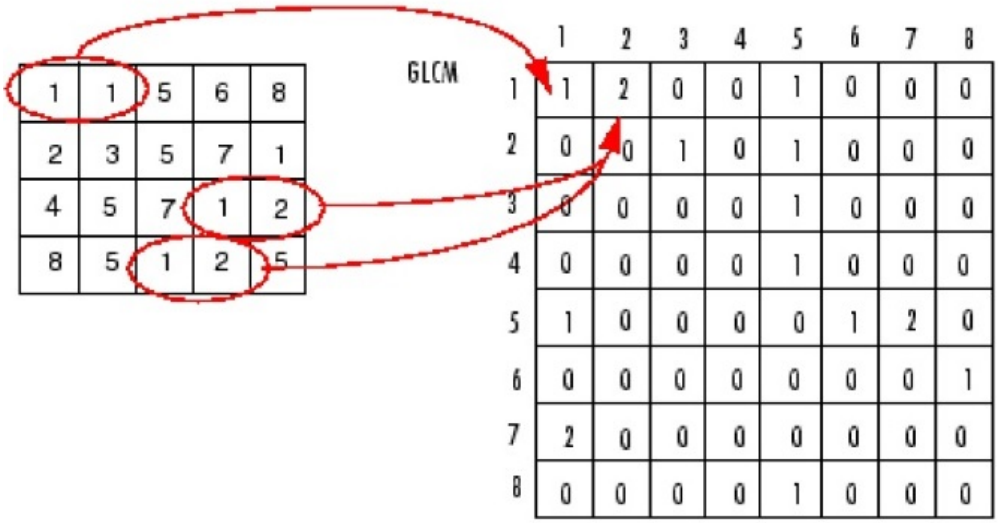

Figure A.1: Example of co-occurrence matrix computation of a 3bits image (I) with 1 distance and 0 degrees.

For a single image there can be many co-occurrence matrices, one for each pair of distances and directions defined. Generally in a 2D image 20 co-occurrence matrices are computed, taking distances of 1 to 5 pixels and directions in 0, 45, 90 and 135 degrees [Castellano et al., 2004], [Chabat et al., 2003].

A.2.2 Haralick Features

After calculating the co-occurrence matrices, different parameters are computed in order to describe the texture of the image. Haralick et al. [1973] developed a set of texture features which use the computed co-occurrence matrix in order to describe the image statistically. 12 of these features are described in Table A.1 where p represents the co-occurrence matrix.

Haralick Features		
Feature	**Type of Measure**	**Formula**
Energy	Uniformity	$\sum_i \sum_j \{p(i,j)\}^2$
Entropy	Randomness	$\sum_i \sum_j p(i,j) \log_2(p(i,j))$
Correlation	Dependence	$\frac{1}{\sigma_x \sigma_y} \sum_i \sum_j (i,j) p(i,j) - \mu_x \mu_y$
Contrast	Intensity	$\frac{1}{(N-1)^2} \sum_i \sum_j (i,j)^2 p(i,j)$
Homogeneity	Spatial closeness	$\sum_i \sum_j \frac{1}{1+(i-j)^2} p(i,j)$
Variance	How data vary from the average value	$\sum_i \sum_j (i,\mu)^2 p(i,j)$
Sum mean	Average	$\sum_{i=2}^{2N} i p_{x+y}(i).$
Inverse Difference Moment	Homogeinity	$\sum_i \sum_j \frac{p(i,j)}{\|i+j\|^2} i\,j.$
Inertia	Intensity	$\sum_i \sum_j i + j^2 p(i,j).$
Cluster Shade	Skewness	$\sum_i \sum_j i + j - \mu_x - \mu_y{}^3 p(i,j).$
Cluster Tendency	Skewness	$\sum_i \sum_j i + j - \mu_x - \mu_y{}^4 p(i,j).$
Max Probability	Probability	$max p(i,j).$

Table A.1: Haralick features description [Haralick et al., 1973], [Albregtsen, 2008].