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EXECUTIVE SUMMARY OF THE THESIS

Automatic measurements of airway dimensions from CT images in health and asthma

TESI MAGISTRALE IN BIOMEDICAL ENGINEERING – INGEGNERIA BIOMEDICA

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1. Introduction

An increase in respiratory diseases has been estimated in recent years and among them one of the most common and widespread is asthma[1]. Asthma is a chronic inflammatory disorder and its distinctive feature is the airflow limitation due to airway obstruction, which may be reversible or permanent depending on the severity of the pathology. In particular, it is observed that this obstruction is due to an increase in the thickness of the bronchial wall together with a narrowing of the lumen of the airways. The combination of these structural changes is called airway remodelling[2]. Investigations of airway remodelling are needed to evaluate disease progression and develop new effective therapeutic treatments to attenuate or reverse these structural changes. In this sense, computed tomography (CT) offers new possibilities in the qualitative and quantitative assessment of airway morphology in a non-invasive way [1]. To obtain information related to the morphology of the airways, CT images need to be processed with appropriate image processing algorithms. Although numerous methods developed for this purpose are present in the literature, a lot of research is still active in this regard due to the difficulty in accurately measuring these morphological parameters and due to the fact that, starting from these measurements, it is possible to perform diagnoses and plan therapeutic treatments, therefore this topic is clinically relevant.

The aim of the thesis is the development of an algorithm for the extraction and accurate measurement of morphological parameters related to the airways visible on CT images.

2. Material and methods

The population considered in this study is composed by five healthy subjects (controls) and five patients with asthma. Each patient was scanned in supine position at maximum inspiration, near total lung capacity (TLC).

The procedure developed in this work of thesis comprises three main phases: the implementation of the algorithm starting from the processing of 3D CT images of healthy subjects; its validation; the application of the algorithm to both asthmatic and healthy subjects to evaluate the airway remodelling occurring in asthma.

2.1 Algorithm implementation

The algorithm was implemented following three main steps: segmentation of the airway lumen; centreline extraction; morphometry analysis.

Segmentation

The algorithm for segmentation was already available in C++ language and, in this work, it has been converted in Python language using the ITK library.

At first, the grey-scale CT images are converted into binary images by applying an optimal thresholding algorithm. Then, the trachea is identified by searching for round elements having the centroid in the central region of the image. The bronchial-tree is segmented using a region growing algorithm within an iterative cycle. At the first iteration, the seed is the segmented trachea whose pixels have an intensity value lower than a given threshold, set to the mean intensity value of the trachea pixels. Then at each new iteration the previous reconstructed tree is given as seed. The result is a 3D binary image depicting the lumen of the airways.

Centerline Extraction

The centreline can be easily extracted using a skeletonization function of the scikit-image package available in Python that is applied to the segmented image after being processed. In particular, the morphological filters of closing followed by an opening has been applied to retrieve an accurate centreline without spurs.

Morphometry Analysis

The morphological parameters segmented and measured in this thesis work are reported in Fig.1

Before proceeding with the measurements, a suitable tree data structure has been implemented to store and organize the measurements, starting from the bifurcation points detected on the centreline. The tree data structure allows to efficiently perform a suitable labelling, to

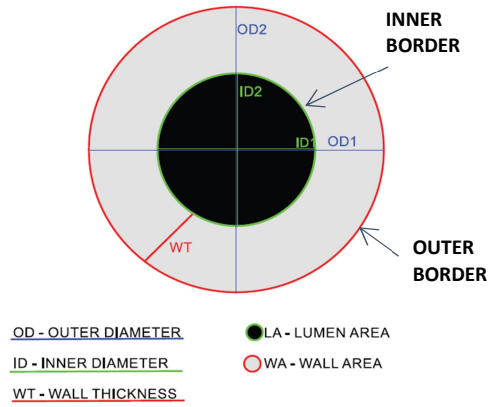

Figure 1: scheme of a cross-sectional view of an airway and the relevant morphological parameters calculated[2]

associate each measurement to its corresponding airway branch and to compare corresponding generations of airways between subjects.

The measurements were retrieved in every detected airways, also in those with an oblique orientation with respect to the axial plane of the image, thanks to the extraction of a 2D section [3] orthogonal to the airways in the point of measurement[5].

Lumen Area

The lumen area is calculated by simply extracting the orthogonal 2D section of the binary 3D image representing the segmentation of the trachea-bronchial tree and then expressed it in mm^2.

Total Area

The total area comprises the lumen area plus the bronchial wall area.

The problem of airway total area segmentation is related to the correct identification of the outer wall border that in this work has been figured out by implementing an iterative dilatation operation process. The dilation is iteratively applied to the segmented airway lumen obtained in the previous step by using a round kernel. At each iteration a new dilatation is performed and the mean intensity value of the corresponding pixels in the original image is calculated. The iterative process is stopped when the mean value decreases by 20% with respect to the previous iteration and the previous iteration is maintained valid for the calculation of the total area.

The hypothesis is the following: in correspondence of the bronchial wall the mean intensity value is comparable to that of the soft

tissue (about 50HU), whereas, out of the bronchial wall, the mean intensity value suddenly decreases as the lung parenchyma is included (about -800HU). So, a mean intensity drop by 20% means that the outer wall border has been crossed and that the parenchyma starts to be comprised in the dilatation.

An example of the iterative process is illustrated in Fig. 2.

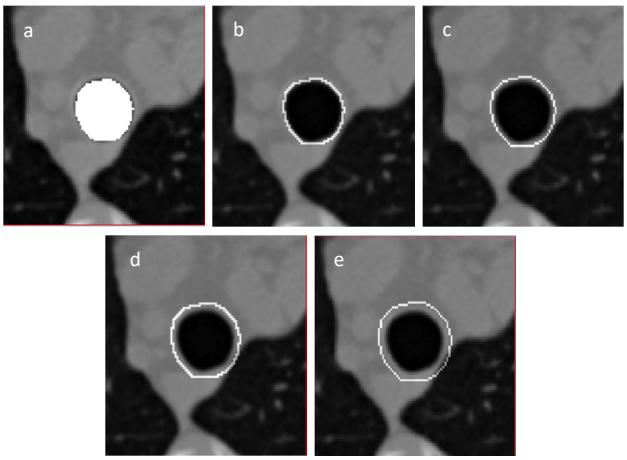

Figure 2: example of the iterative process of dilatation: a) the starting point is the airway lumen already segmented; b) annulus obtained by the difference between the dilated lumen area and the previous one, and in correspondence of the white pixels in the gray-scale image the mean intensity value is calculated; c),d) the iterative process continues, until the parenchyma is reached (e).

Bronchial Wall Area

The bronchial wall area is finally calculated as the difference between the total area and the lumen area. Another parameter taken into consideration is the wall percentage area (WA%), calculated as (BronchialWallArea/TotalArea) * 100.

Wall Thickness

The measurement is performed by tracing a ray segment from the center of the bronchial-wall area. When the ray crosses the inner and the outer white borders, the two crossing points are detected and the distance between them, which is the wall thickness, is calculated. A total of 36 ray segments have been traced, one every 10 degree and for each segment a value of wall thickness is calculated. These 36 values are averaged to obtain a mean value of wall thickness in millimetres.

Outer and Inner diameter

The major and minor inner and outer diameter can be easily retrieved from the lumen area and total area. In the following analysis only the mean diameter is considered, averaging the major and minor diameter. Another parameter considered is the ratio between wall thickness (WT) and the mean outer diameter (OD).

2.2 Validation of the algorithm

The validation is performed by comparing the measurements automatically retrieved as output by the algorithm and the manually traced on the images using the Medical Image Processing and Visualization software (MIPAV). The measurements are obtained in correspondence of 50 points randomly chosen and subsequently compared by calculating the Linear Regression and the R-square and by retrieving the Bland Altman plot.

2.3 Comparison between healthy and asthmatic subjects

The validated algorithm has been used to quantify the structural alterations occurring in the airways due to asthma. To this aim, the airways have been measured in healthy and asthmatic patients and the results were compared between the two groups. The comparison is made between the same generations and it is performed using a t-test, if the data are normally distributed, or a Mann-Whitney test otherwise. The normality test (Shapiro-Wilk) is initially performed. P-values below 0.05 were considered statistically significant.

3. Results and their Discussion

3.1 Qualitative evaluation of the algorithm

The segmentation results are visually evaluated and no leakages of the airways on the lung parenchyma were found. The number of generations reached for each subject has been counted and compared to the one found in other studies. In the present work it was possible to identify up to the 7th generation, found only in 3 of 10 subjects. This generation depth is lower compared to other studies, that can identify up to the tenth generation [4].

We hypothesize that this is due to the pre-processing method applied to the segmented 3D

image to obtain an accurate centreline. In particular the opening filter, which was effective in removing any spurs, leads also to the disconnection of small branch segments from the principal airway tree structure and this may be the cause of a lower depth of generations achieved. An alternative strategy for a correct centreline extraction should be considered, containing some preservation conditions to prevent the removal of the end points of airway segments[1].

3.2 Validation of the Algorithm

Only the lumen area and total area parameters are considered for the validation procedure.
The linear regression analysis shows that data are not dispersed around the line of regression, except for few points in correspondence of the lower values, and the R-squared is equal to 0.98 for both the total and lumen area.
The Bland-Altman plot shows that the difference between the two measurements are dispersed around the zero, with the majority of them lying within the range defined by the upper limit (22.66mm^2 for lumen area and 33.89mm^2 for total area) and the lower limit (-20.40mm^2 for lumen area and -30.91mm^2 for total area) , except for few measurements which are out of the range.

In those points the presence of two airways very close to each other was observed and the algorithm failed in identifying the border of separation. A possible solution could be to apply some filter for the edge enhancement on the original 3D image to make the border of separation more detectable. Alternatively, additional segmentation algorithm can be applied to separate different objects which overlapped on the 2D binary image depicting the orthogonal section of the airway, indeed the measurement calculated by the algorithm due to this error is about the double of what it should be because the two close airways are almost partially overlapped, and considered as one.

The Bland-Altman plot, obtained discarding the outliers, is also evaluated. The range between upper and lower limits significantly reduces and an underestimation of the lumen area is detected (the mean difference of the measured lumen area is equal to -1.8mm^2).

This issue could be solved by improving the iterative region growing algorithm adopted for the segmentation procedure. In particular, at each iteration new pixels are set as seeds if their intensity value is lower than a given threshold. So, in a future development of the work, a more suitable value of threshold could be established to comprise more pixels during the segmentation. Alternatively, another approach adopted by some studies [5], is to calculate the lumen area on the 2D grey-scale image obtained by extracting the 2D airway's orthogonal section directly on the original CT image, implementing an algorithm both for the inner and outer border detection and calculate at the same time lumen and total area.

3.3 Quantitative Analysis of the Airways in Healthy and Asthmatic Subjects

A statistically significant difference between health and asthma is found from the third generation downwards and considering just some morphological parameters (Figure 3).

In particular, Lumen Area (LA) is lower in patients than in healthy subjects at generation three and six (p-value equal to 0.007 and 0.004 respectively). Also, Total Area (TA) is lower in asthmatic at generation zero and three (p-value equal to 0.012 and 0.015 respectively).
Wall Area (WA) seems to be lower in asthmatic than in healthy, even if a large variability of data is found, with significant statistical differences for the first two generations (p-values equal to 0.002 and 0.013 respectively). Nevertheless, if considered in percentage, wall percentage area (WA%) is larger in asthmatic patients for generation three, four and six (p-value equal to 0.00116, 0.0588, and 0.0172 respectively).

The results of LA and WA% are coherent with what was expected. In contrast to those related to WA, which are also in contradiction with some previous studies. Our results can be explaining considering that WA depends on the bronchial size, and so depends on TA [4]. In our work, TA is lower in asthmatics than in healthy subjects, also with a certain statistical significance, so the lower values of WA are consistent.
Instead, WA% is less dependent from the highly variable airway size present among different patients. This represents a valid reason to preferably consider WA% as the most reliable

parameter to investigate the structural changes occurring with the disease.

Considering the wall thickness (WT), a great variability of data is found without any statistically significant differences between the two groups. The mean outer diameter (OD) is lower in asthmatic than in healthy subjects, but no significant difference is found.
The mean inner diameter is lower in asthmatic patients at generation three and five (p-value equal to 0.0014 and 0.045 respectively).
WT/OD is greater in asthmatic patients than healthy subjects from the third generation downwards (p-value=0.0189 at generation 3), with a large variability among the two populations.

WT is not found to be greater in asthmatic than in healthy patients, as expected. Indeed, considering WT/OD, greater values are found in asthmatic patients than in the healthy.

In conclusion, airways structural changes are present in patients with asthma, in particular there is a thickening of the bronchial wall and a lumen narrowing as expected (Fig.3).

3.4 An insight into structure-function relationship in asthma: a comparison between 3He-MRI and CT images

The tool developed in this work can be potentially used to further investigate the structure-function relationship in pulmonary disease.

Among the patients with asthma, we identified one patient with a signal void in the 3He-MR image and in the corresponding CT image, the WA% and LA/TA% are retrieved for the airway close to the region where the abnormality has been identified on 3He-MRI.

The corresponding WA% and LA/TA% are equal to 80,17% and 19,82% respectively. The analogous airway in the healthy subjects is characterized by a mean value of WA% and LA/TA, respectively equal to 73,23% and 26,77%.

These are just representative results about the structure-function relation that exist in the lung, that will be further investigated in future studies.

4. Conclusion

The objective of the present work of thesis was the development of an algorithm for the extraction and accurate measurements of morphological airways parameters. Considering the results thus obtained, it can be concluded that the present algorithm is a valid and innovative tool for quantitative airways' analysis.
Some additional efforts are needed to improve this algorithm considering the lumen area measurements and especially the extraction of the centreline.
The accurate identification of the centreline is paramount to accomplish the further steps and achieve accurate measurements. Indeed, starting from the centreline, the direction necessary to extract the 2D orthogonal section from the 3D image is retrieved. In this work the orthogonal direction is calculated as the difference between the coordinates of the selected point where making the measurement and the one three position ahead in the centreline. Actually, an improvement for a future development could be to calculate the orthogonal direction as the tangent to the centreline in the selected point. This

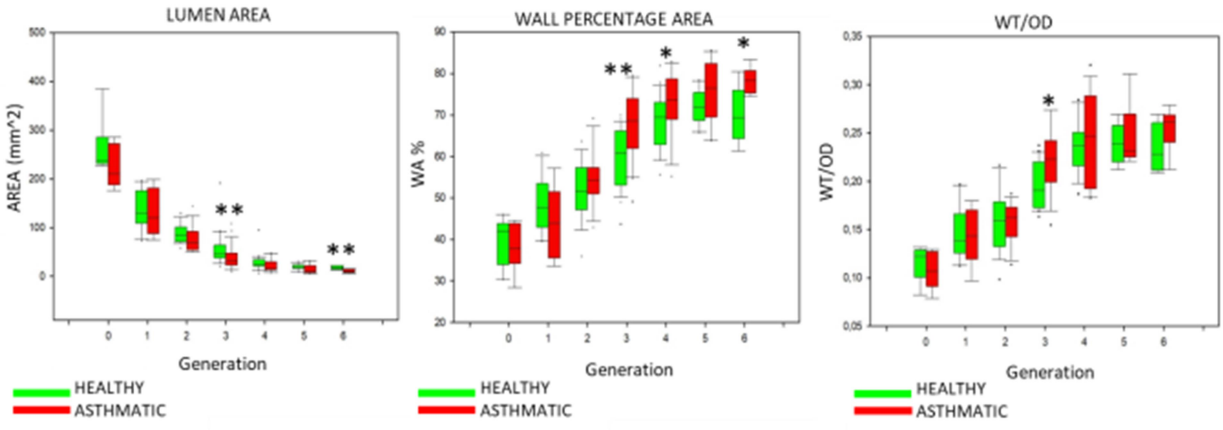

Figure 3: Measurements of most relevant morphological parameters: box-plots and statistical analysis represented as: * P-value ≤ 0.05, ** P-value ≤ 0.01, *** P-value ≤ 0.001

can potentially improve the accuracy in performing the measurements.
Moreover, starting from an accurate centreline it is possible to correctly detect the bifurcation points and create the tree data structure for data organization. A missing part of this work of thesis is the validation of the process of bifurcation points identification from the centerline. A wrong identification of these points leads to a wrong implementation of the tree data structure, so to a wrong identification of the airway generation, and to a consequent erroneous comparison of corresponding generations between healthy and asthmatic subjects. Previous studies validated this step using a gold standard provided by an expert image analyst who performed manual segmentation[5] or alternatively using phantom studies [1].
Concerning the segmentation of the outer wall border, a simple method consisting on an iterative dilatation process has been implemented and successfully validated. Some erroneous measurements are anyway present but mainly derived from error in detecting the corresponding lumen area. The other morphological parameters, as derived from lumen area and total area, can be considered successfully validate too.
The results obtained from the comparison phase can be considered encouraging. Indeed, significant differences are obtained even if the considered images are acquired at the maximum inspiration phase (TLC), while asthma is characterized by an airflow limitation especially during the exhalation phase.
Furthermore, even if in the present work asthma is the pathology taken into consideration, the developed algorithm can potentially be applied to other lung diseases that lead to airways' structural changes detectable on CT images, such as pulmonary fibrosis, and can be potentially used to investigate the relationship structure-function in respiratory diseases.
This method presents anyway some limitations. The number of analysed data was limited, so, the implemented algorithm may not be robust enough to take into account for the large variability of airways among different individuals and different pulmonary diseases.
Moreover, the validation procedure is done through a comparison with manually segmented measurements. This method typically suffers from a relatively large intra- and inter-variability, in particular considering the small airways, and so may not be considered very reliable [1].

The road towards a possible clinical application is long and the developed algorithm needs further investigations and improvements. However, in a long-term perspective this method could support diagnosis, follow-up and treatment definition.

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