Longitudinal Analysis of Airways using Registration

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Abstract. Longitudinal investigations of airway abnormalities associated with Chronic Obstructive Pulmonary Disease (COPD) has been very limited so far, partly due to the difficulties in obtaining reproducible measures.
We propose to improve on this by limiting measurements to corresponding branches found using image registration.
The results obtained from scans of 237 subjects show increased intra-subject correlation when measurements are conducted in branches found in each scan compared to similar measurements not limited to corresponding branches. This indicates the method could be useful for longitudinal analysis.
Yearly changes in CT measures showed that airways increase in size and decrease in density with time. Changes were in general not found to be significantly correlated with changes in lung function and neither were there any significant differences between COPD GOLD stages.

Keywords: Airways, Chronic Obstructive Pulmonary Disease, longitudinal, registration, segmentation

1 Introduction

Chronic Obstructive Pulmonary Disease (COPD) is associated with loss of lung tissue, known as emphysema and chronic bronchitis, which is normally described as a narrowing of the air-filled lumen area of the airways and a thickening of the airway walls [5]. The changes cause shortness of breath leading to reduced quality of life, disability and eventually death. Computed Tomography (CT) has become a popular imaging tool to quantify COPD pathology and multiple cross-sectional studies have already shown that CT based measures of both emphysema and airway abnormality are correlated with measures of disease severity such as lung function [1, 4, 9, 16]. As of yet only very few longitudinal studies have attempted to investigate the change over time in airway dimensions [11]. Some

of the reasons for the lack of longitudinal studies are likely that COPD is a very slow developing disease, meaning subjects need to be followed for many years and the lack of reliable automatic approaches for measuring airway dimensions.

Conducting reproducible measurements in the airways are difficult as such measurements in general depend on the position in which they are performed and finding the same position in the following images can be a hard task. For instance in the longitudinal study described in [11], such correspondencies were found manually by locating the anterior, lateral and posterior basal segment bronchus in CT slices. In the end data on 45 out of the 83 subjects participating had to be excluded as the same segment bronchus could not be located in at least three of the yearly scans. The use of modern tools such as three-dimensional segmentation algorithms, centerline extraction and axial reconstruction enable analysis in much more of the airway tree, making the problem of how to do comparable measurements even more complicated.

One way to avoid this problem is to use airway abnormality measures, which are less affected by differences in sampling positions. For instance one can use the assumption that the square root of the wall area and the lumen perimeter are linearly related, when measured in perpendicular slices of the airways, to construct a comparable measure of what the wall area would be if measured where the lumen perimeter is 10 mm. This is the much used PI10 measure [10]. Such approaches probably increase reproducibility, however measurements are likely still dependent on the specific branches included in the analysis.

The airway branches have been given anatomical names down to the subsegmental level within the literature. If such a labeling could be extracted automatically it would enable measurements in correspondingly labeled branches, that would be comparable cross-sectionally as well as longitudinally. Assigning these names is however very difficult in practice, due to biological variation, inspiration effects, pathology, etcetera. So the automatic processes that have been developed usually only proceed down to the 10 segmental bronchi on each side, resulting in 32 labeled branches [2, 15].

Modern segmentation methods on data of reasonable image quality can go significantly deeper than the segmental bronchi and it thus might be possible to match more branches at an intra-subject level. This could be useful in longitudinal studies where the inter-subject variation often is less relevant and particularly important for COPD analysis as it is known to affect the airways further down the tree more [4]. One way to achieve such a matching would be to use image registration. Registration of lung CT images has, for example, been used to track emphysema progression [3] and nodule growth [18], however so far, to the best of our knowledge, it has not been used to investigate airway changes.

The purpose of the work detailed in this paper is thus to investigate longitudinal measurements of airway abnormalities and whether limiting measurements to branches only found in each intra-subject scan, matched with the help of image registration, improves reproducibility.

2 Method

A fully automatic and novel framework for longitudinal analysis of changes in airway wall dimensions and density was developed. It uses state-of-the-art airway and airway wall segmentation and registration methods, described shortly in the following sections. Briefly: the airway lumen was initially segmented using the process described in Sec. 2.1, it was then used as input to the airway wall segmentation method detailed in Sec. 2.2 in order to find the precise shape and position of the airway wall surfaces. The lumen surface returned from this was used to find the airway centerlines using the process described in Sec. 2.3. The airway centerlines were deformed to the center-most image in time using the deformation fields returned by the image registration process described in Sec. 2.4. This common space allowed the centerlines to be matched based on distance and orientation using the method detailed in Sec. 2.5.

2.1 Initial Airway Extraction

The airway segmentation method described in [8] that iteratively extends locally optimally paths to form an airway tree is used in this work. In each iteration, locally optimal paths are defined as paths with minimal cost from the seed-point to the surface of a sphere centered on it. The paths are generated using Dijkstra's algorithm, with a cost function that is based on a kNN classifier trained to classify airway voxels combined with Hessian eigenanalysis to enhance cylindrical structures. A number of criteria taking into account the local appearance of an airway voxel and geometry characteristics are then used to select the most likely path. The paths are then converted into a full lumen segmentation by growing a cylinder around each selected path, using the airway probabilities returned by the kNN classifier.

This airway segmentation method was chosen as it compared very favourably with another region growing based approach [7], which again performed well compared to the state of the art evaluated in the Exact'09 study [6]. One of the advantages of the approach is that it can overcome local occlusions, due to for instance plugging of the lumen due to mucus or pathology.

2.2 Airway Wall Segmentation

The initial lumen segmentation is then used as input to the method described in [14], which builds an optimal surface graph [17] around it with the purpose of both finding the outer airway wall surface and refining the lumen surface returned by the first step. This process begins by converting the initial lumen segmentation into a sub-graph, in which each point on the initial lumen surface is associated with a column of nodes. A column defines the set of allowed positions the point can take in the sought surface. Optimal surface graphs are designed such that the search for the optimal surface can be conducted using maximum-flow/minimum-cut algorithms in polynomial time. The process can be thought of as a refinement or a deformation in which the sub-graph defines the finite set

of possible refined solutions of the initial surface. Since we need to find both the inner and outer airway wall surface the complete graph consists of two subgraphs, one designed to find the inner surface and one designed to find the outer. The optimality of the solution is measured in terms of inner and outer surface cost functions computed from derivatives of the image intensities as described in [13] and smoothness and surface separation priors.

One of the novelties of the algorithm is the way the graph columns are constructed from properly generated greatest ascent and descent flow lines. These guarantee solutions that do not self-intersect and should be very suited for regions with high curvature, such as those found in the branch bifurcation areas.

2.3 Extraction of Branch Centerlines and Generations

The airway centerlines, branches and generations were extracted from the lumen surface generated in the airway wall segmentation process using the front propagation method described in [6]. Starting in the trachea and moving down the branches, the centroid of the front is stored at regular intervals as branch centerline points. Bifurcations are detected and generation count increased as the wavefront becomes disconnected upon hitting the branching points of the lumen segmentation. The method was also used in the Exact'09 study and had thus already been used on a varied data set and on the results of different airway segmentation algorithms.

2.4 Registration

The extracted centerlines were matched within a common coordinate system obtained using registration of the CT images.

Image registration is the process of finding a transformation which maps one image into another. This is usually performed in a pairwise manner, where one image is denoted the moving image and the other the fixed. The transformation maps the coordinates of the fixed image into the moving.

The registration error is generally related to how dissimilar the images are and since the data set consists of subjects scanned five times yearly, we assumed the center-most image in time to be least different from the others and registered this image as the moving image with all the four others.

The images were registered using the mass preserving image registration algorithm described in [3]. Registration based directly on image intensities, such as standard sum of squared differences, is problematic for lung registration because the local image intensity, which in CT images are directly related to the local density, changes with the inspiration cycle. Instead the approach incorporates a tissue appearance model based on the assumption of preservation of total lung mass into a standard deformable image registration framework. This framework uses a composition of a global affine and three free-form B-Spline transformations with increasing grid resolution. A version of sum of squared differences with the mass preservation incorporated is used as a similarity function.

The method was originally evaluated using the average distance between the registered lung vessel trees, and showed a significant improvement compared to standard sum of squared distances, especially in the more difficult cases with large differences in lung volume.

2.5 Matching Airway Branches

Each centerline point was matched to the nearest point on each of the other centerlines of the same subject, measured within the common coordinate system. Such a match was deemed acceptable if the distances to the common center for each of the centerline points was less than δ and the angle the direction of the centerlines formed with the average direction of the centerlines, was less than θ. The airways were then cropped at the position where the deepest acceptable match was found.

Having accurately assigned generation numbers is important as COPD mostly affects the smaller airways, and splitting measurements by generations is a common pathology independent way to only measure relevant airway branches. See for instance the results of the generation based analysis conducted in [4]. Most erroneously assigned generations are due to segmentation errors, where only one of the continuing branches at a bifurcation is found. In these cases one longer branch may be found where it should have bifurcated and split in two and the sub-tree will have its generation count off by one. The matched centerlines were used to correct some of these cases. Beginning at the root of the tree and moving down the centerline the current generation is determined by a majority vote. Missing or spurious branches are detected whenever one of the centerline points have a different generation number than the majority. It is corrected by adding the difference to each of the centerline points in the sub-tree. The process allows a correct identification of the generations, even in situations where errors occur in all the trees from any string of branches from root to leaf, as long as each bifurcation is found in the majority of the cases. See Fig. 1(c) for a visualization of the results of this.

3 Experiments and Results

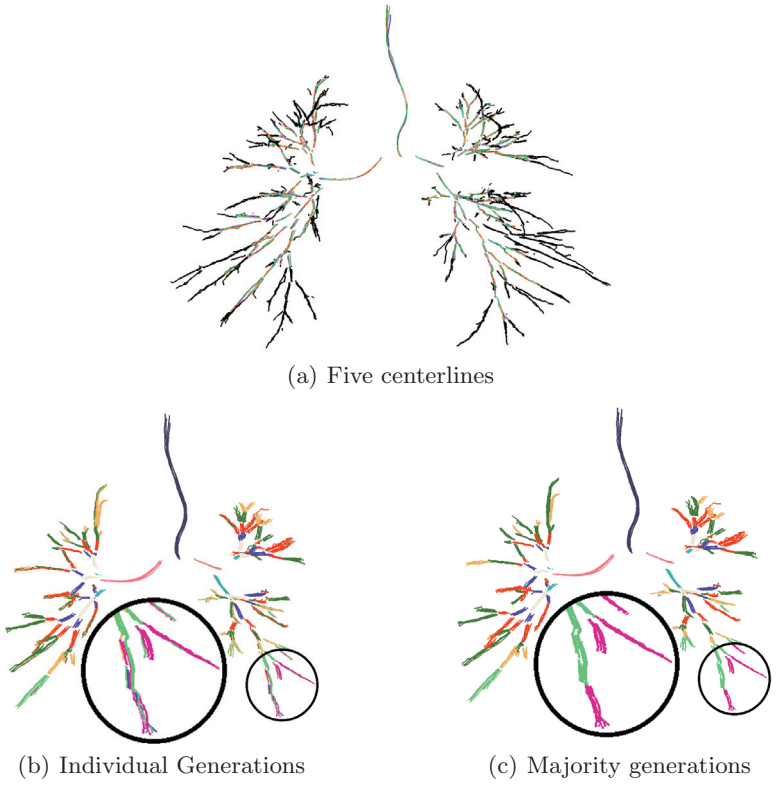
3.1 Data

The material used comes from the Danish lung cancer screening trial [12]. The images were obtained using a Multi Detector CT scanner (16 rows Philips Mx 8000) with a low dose (120 kV and 40 mAs), reconstructed using a hard kernel (D) with a resolution of approximately $0.78mm \times 0.78mm \times 1mm$. 237 randomly selected subjects from the trial were included in the analysis. Data from five yearly CT scans and lung function measurements were available on each.

At baseline, the subjects included in the analysis had a mean value of FEV1 (% predicted) of 96%($\pm$17%) and FEV1/FVC of 0.71($\pm$0.08), totalling 144 without COPD, 61 with mild COPD, 31 with moderate COPD and 1 with severe COPD. 143 men and 94 women with an average age of 58($\pm$5) years.

3.2 Centerline Cropping

A value of 1.7mm for δ and 37 degrees for θ were estimated by visual inspection on a small set of scans that are independent of the data used in the rest of the analysis. Fig. 1 shows a typical result of running the branch cropping method. Notice, in Fig. 1(a) how the five deformed centerlines are so close that they



(a) Five centerlines

(b) Individual Generations

(c) Majority generations

Fig. 1. Fig. 1(a) shows the centerlines deformed to a common space, each tree has a unique color, the cropped parts of the tree where at least one scan is missing a branch are black. Fig. 1(b) shows the trees colored by the generations of the individual trees and Fig. 1(c) shows the corresponding majority generations. The enlarged area within the circles shows branches where generations are corrected. Note that in the last two figures each tree has been slightly offset compared to the others, such that the generations of each individual tree is more easily visible.

more or less appear as one single airway centerline, indicating how well the registration method works on this data. Fig. 1(b) and 1(c) shows the results of the generation correction method. The improvement is most clearly visible in the bottom of the tree, where the many missing branches leads to wrongly detected

generations, most often seen as the same branch being colored with multiple colors in Fig. 1(b).

Fig. 2 shows the amount of branches found in each generation of the airway tree in both the cropped and non-cropped case. The amount of branches in the cropped airways are actually larger in generation 3-5 compared to the non-cropped airways due to the generation correction process. Moreover the number of branches in each generation are roughly doubled in both cases until generation 6, consistent with a bifurcating branching tree. This suggests that the airway trees are roughly complete until this point and that the cropped branches mostly belong to the generations that are already incompletely found. It is also interest-

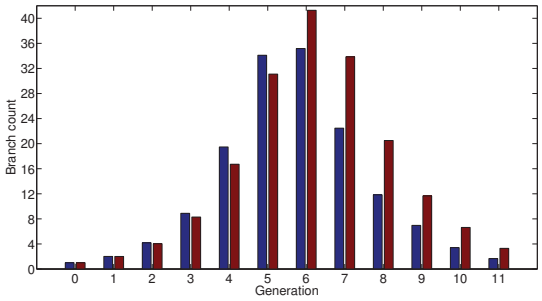


Fig. 2. The average amount of branches in each generation of the cropped (blue) and non-cropped (red) airways.

ing that even with as many as five time points the average number of branches found in the cropped airways far exceeds the number of named branches.

3.3 Measurements

Airway morphology was quantified with four different measures, the Interior Volume (IV) (also called the lumen volume), the complete Airway Volume (AV), that is the sum of the interior and wall volume, the wall volume percentage (WV% $= 100 \times$ (AV-IV)/AV) and the Mean Airway Density (MAD), which is the average density in the complete airway volume. Density based measures have received some attention in the last couple of years as they may be more sensitive to a change in size of the smaller airways due to partial volume effects [13, 16]. IV, AV and WV% on the other hand are three-dimensional extensions of commonly used airway abnormality measures [1, 4, 9, 11, 13, 16].

The measurements were conducted in the un-registered images, by classifying the segmentation into branch generations with the use of the cropped centerlines. This was done by assigning the generation of the nearest centerline point to each segmented voxel as described in [14]. Voxels whose nearest centerline point was

cropped, were simply not included in the measurements. Fig. 3, shows an example of this.

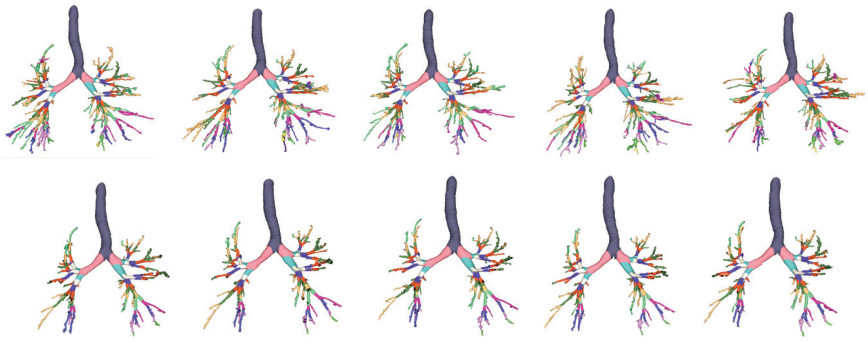


Fig. 3. Lumen segmentation surface in five scans of one subject. Top row shows all the branches, whereas the bottom row only show corresponding branches.

3.4 Reproducibility of Measurements

COPD is a slow developing disease and so airway abnormality measurements can be assumed to change little from one year to the next. The coefficient of determination calculated from the Pearson correlation coefficient of the measures at baseline with the following year can thus be used to estimate reproducibility of the measures. Fig. 4 shows how this looks in each generation for the measures extracted from the cropped and non-cropped airways. It is clear that the crop-

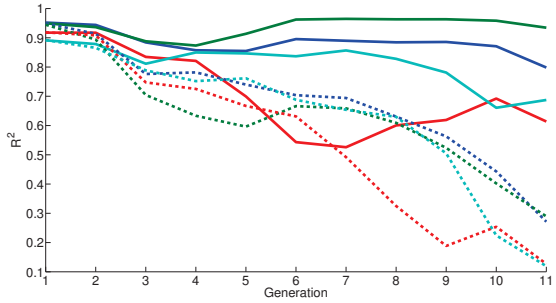


Fig. 4. Reproducibility as the coefficient of determination calculated from measurements at baseline and first year repeat scan. Red, green, dark and light blue is WV%, AV, IV and MAD respectively. The dotted lines are measurements based on the non-cropped airway trees.

ping operation results in more reproducible measures, especially in the smaller branches, with the only exception being WV% measured in generation 6. In general the reproducibility in the non-cropped airways can be observed to fall with generations, the fact that this trend has largely been removed after the cropping operation suggests that a large part of this variability can be attributed to differences in the amount of segmented airway branches.

3.5 Annual Change in Measures

Table 1. Change in measurements per year. Second and third row are Pearson correlation coefficients. Third row are measurements conducted only within subjects diagnosed with COPD at baseline. Note /year has been left out from the units for readability. (*), (***) denote p values less than 0.05 and 0.0001 respectively.

	IV (mm^3)	AV (mm^3)	WV% (%)	MAD (HU)
Mean (± std)	55 (±547)	328 (±1120)(***)	0.026 (±0.51)	-2.9 (±7.4) (***)
FEV1 (%)	-0.04	-0.08	-0.00	-0.12
COPD FEV1 (%)	-0.01	-0.07	-0.03	-0.21(*)

The first row of Table 1 shows the annual change in the measures obtained via the slope of the linear relationship between subject age at the time of the scan and the measurements in the airway belonging to generation 3 and up. IV and WV% showed no significant annual change, whereas AV was found to increase and MAD to decrease, indicating that the airways increase in size and become less dense.

The annual change of the measures was not found to be correlated with the annual change of lung function. However when analysis was limited to the subjects with COPD at baseline, a significant negative correlation could be observed between the annual change in MAD and the annual change in FEV1(% predicted). It should be mentioned though that the result is no longer significant if the level is Bonferroni corrected. The result is however consistent with cross-sectional studies, which found that poorer lung function in general was associated with a higher density [13, 16].

We also tested whether there were any significant differences between the different GOLD stages of COPD severity for any of the measures, but found none.

4 Discussion

The implemented branch matching procedure is simple compared to anatomical labeling approaches [2, 15], but visual inspections indicate that it works well, likely because the registrations are good. That is, the distance between

corresponding branches and their mutual angles within the common coordinate system are generally smaller than the distances and angles to non-corresponding branches.

Compared to recent cross-sectional studies [1, 4, 9, 14, 16], where wall thickness and lumen area or volume have been found to be correlated with poor lung function, it is perhaps surprising that this relationship wasn't reflected in our longitudinal measurements. The lack of correlation can however be explained by the fact that COPD develops slowly, and thus five years might simply be too short to see any significant change in this data set. Moreover both lung function and CT based measurements are still very noisy and the registration based cropping operation described in this paper, is only able to reduce the intra subject variation introduced by differences in the amount of found airway branches. Other variations, such as for instance those caused by changes in inspiration level are still influencing the measurements. It should be mentioned that in the results presented in [11], a significant correlation was found between changes in airway measurements and lung function on a smaller data set. However, that study included more severe COPD cases, with a baseline mean value FEV1/FVC of 0.51 and FEV1(% predicted) of 50%.

An advantage of using image registration over for example branch labeling methods, is that it allows for measuring changes of for instance wall thickness, density, etcetera, local to specific points in the airways. Such changes could be visualized to increase understanding of the disease or combined to form new, possibly more sensitive global measures.

Another option which could be explored would be to measure the airway abnormality changes within the registered volumes. We chose not to do this in the present study, as the changes caused by the transformation could drown any small change caused by COPD. However one advantage of doing this would perhaps be a larger immunity towards inspiration effects.

5 Conclusion

A fully automatic framework for longitudinal analysis of airways was presented, using state-of-the-art airway wall segmentation and image registration methods.

The process of limiting measurements to airway branches found in each repeated scan was shown to increase reproducibility. This indicates that a large part of the intra-subject variation in the measurements can be attributed to differences in the amount of segmented branches and thus that the framework could be useful for longitudinal studies. The number of matched branches exceeds the number of anatomically named branches.

A significant annual increase of AV and decrease of MAD was observed. Annual changes in the CT measures was not observed to be correlated with annual changes in FEV1(% predicted) in the complete data set, nor were there any significant differences between the means of subjects in the different COPD stages. However the change in MAD was seen to be negatively correlated with

the change in FEV1(% predicted) when limited to the subjects with COPD at baseline.

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