

# Three-Dimensional Airway Measurements and Algorithms

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Advances in high-resolution computed tomography (CT) imaging are making a full three-dimensional analysis of the lungs feasible. In particular, airway morphology can be studied *in vivo* and quantitative metrics of airway size and shape can be extracted. The thickening process associated with the inflammatory response in the diseased lung can be quantified by means of image processing techniques that extract the airway lumen and airway wall. In this article, we give an overview of these imaging techniques and their diverse nature. We also offer a comprehensive view of the analysis pipeline for three-dimensional airway trees and a validation framework that is needed to compare different techniques.

**Keywords:** COPD; airway wall thickness; lung imaging; computed tomography

A wide range of lung diseases have some pathologic involvement of the airways. Chronic obstructive pulmonary disease (COPD), for example, is associated with a heterogeneous mixture of emphysema and airway disease leading to incompletely reversible expiratory airflow obstruction. Unfortunately, standard spirometric methods for the assessment of disease severity are insensitive to the relative burden of these two processes. Further, due to the heterogeneous nature of this disease, investigating the mutual interrelation and the potential pathogenetic associations of airspace and airway disease requires large study cohorts. Because of this, image-based tools that facilitate the study of bronchial tree morphometry and identify more homogeneous subsets of disease phenotypes are crucial (1).

Over the last 30 years, X-ray Computer Tomography (CT) has become the most promising clinical image modality for the thorax because of its ease of use and its ability to exploit the marked contrast in X-ray absorption properties between air and tissue. Based on this tissue differentiation, CT has been used for both the assessment of emphysema and airway morphometry. Because of the limited out-of-plane resolution in early CT scan technology, initial image-based investigations of the lungs in subjects with COPD was constrained to the use of single slice data examination at selected airway locations (2–5). As scanner technology evolved and the speed of image acquisition improved such that volumetric data can be easily collected in a single breath hold, three-dimensional analysis of the tracheo-bronchial tree has become a reality. Such data sets provide a new venue for the application of computer vision techniques that automatically analyze the airway tree and report metrics of airway morphometry.

## AIRWAY ANALYSIS PIPELINE

The morphometric analysis of the airway tree can be broken down into three well-defined components. The first is the *detection* of the luminal part of the airway tree, also known as segmentation of the airway lumen. This is accomplished by performing a voxel-by-voxel examination of the data set and discriminating the presence or absence of airway lumen, regardless of the size of the airway. After luminal segmentation, additional post-processing analysis may include extracting the centerline of the airway tree (6) and subsegmental labeling according to a canonical atlas (7).

The second component of the analysis pipeline is the *localization* of the airway wall through the identification of lumen-wall and wall-parenchymal boundaries on the CT image. This falls into the more general problem of computed tomographic measurement of thin-layered structures. After lumen extraction and generation of the airway centerline, the CT airway image may be reformatted such that its long axis is orthogonal to the imaging plane. In this way, overestimation of wall thickness due to obliquity can be minimized. After such reformatting, the remaining challenge is the accurate definition of the inner and outer mural boundaries. Given the comparable size of airway walls and point spread function of the CT scanner, the partial volume effect complicates this analysis. Further, as one attempts to quantify the morphology of more distal small airways, this partial volume effect becomes more problematic and influences image-based assessments of airway wall morphology in a nonlinear fashion. This latter observation has led to the conclusion that the overestimation of image-based measures of wall thickness is progressive and a function of diminishing airway size (8). A final factor that complicates efforts to perform quantitative airway analysis of CT images is the influence of scanner type and imaging protocol on the resultant image data. CT scanner algorithms used for image reconstruction are proprietary, and there is only limited information available that can be referenced to determine the “likeness” of CT imaging protocols. This latter issue is of great concern for multicenter clinical investigations, in which the use of identical scanner brands and reconstruction algorithms cannot be guaranteed.

Therefore, in the absence of using identical imaging parameters for data acquisition, an optimal method for quantitative airway analysis in subjects with COPD would be one that attenuates the effect of scanner brand and reconstruction protocol on measures of airway morphology.

The third component is *validation*. This process is focused on directly comparing CT measures of airway morphology to those obtained on histologic examination. Through this, one can assess the deviation of derived measures of airway wall thickness from a potentially more valid “truth.” Validation has to be a main component of the airway analysis pipeline to assure that different wall localization methods can be adequately assessed against both each other and histologic measurements.

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## AIRWAY LUMEN DETECTION

The airway exhibits a tree-like structure with almost cylindrical branches of decreasing radius. With a central air-filled lumen surrounded by higher density mural tissue, proximal airway walls provide an ideal contrast in composition for image analysis. As the airway tree progresses into smaller, more distal generations, however, the partial volume effect blurs the inner lumen and bronchial wall into an indistinguishable mass with a CT density similar to the lung parenchyma. This latter observation has proven to be a major challenge for quantitative airway analysis.

The vast majority of algorithms that have been published for the detection of the airway lumen are based on so-called "region-growing" algorithms. The simplest region-growing approach works by marching from a seed point inside the lumen to adjacent voxels whose intensity is within a predetermined range expected for air. When such criteria are met, the adjacent voxel is also defined as lumen. The seed point is typically defined inside the trachea automatically, and the region growing algorithm progresses from the larger central airways to the distal small airways.

Due to partial volume effects, which progressively blur lumen and wall attenuation with airway sizes approaching the limits of scanner resolution, the region-growing process tends to stop prematurely when it can no longer find adjacent voxels of low enough attenuation. Similarly, as the blurring of lumen and wall progresses, one may find on visual inspection that airway walls are discontinuous. At such sites, the region-growing algorithm will "leak" into the surrounding lung parenchyma.

Different techniques have been proposed to deal with this problem of segmentation leak. One such method was introduced by Mori and coworkers and is aptly called explosion-controlled region growing. (9). This method iteratively increases the Hounsfield Unit threshold value used to define lumen in adjacent voxels until the total number of growing voxels increases too much in one single evolution step. Only adjacent voxels below this CT attenuation value will therefore be defined as lumen. Other methods based on this concept have been proposed (10, 11). A similar approach proposed by Tschirren and colleagues (12) works by defining local volumes of interest as the region grows and performing an adaptive region growing with fuzzy connectivity inside the defined volume of interest. When a leak is detected, the evolution process is stopped for that volume of interest. Figure 1 shows the region growing evolution process for a sagittal slice.

In summary, factors that may limit airway lumen segmentation are as follows:

- Partial volume effect limits the distal extraction of small airways and may lead to leaks in the propagation process that have to be accounted for.
- CT artifacts like beam hardening and X-ray scattering introduce changes in the measured CT intensity that reduce image contrast and complicate the evolution process due to spatially variant luminal CT intensity.
- Respiratory secretions inside the airway lumen and airway stenosis may stop the evolution process, preventing the extraction of distal airway segments.
- Image noise due to low radiation doses and high body mass indexes also complicates the segmentation process.

Once the airway lumen has been segmented, standard post-processing steps include centerline extraction and airway labeling. The former has been widely studied in the computer vision community and has been applied to virtual colonoscopy and bronchoscopy applications among others. A common

technique to obtain a centerline is based on a thinning process (13) that reduces the segmentation result to a set of pixels or skeleton by removing voxels in an orderly fashion. Alternatively, some proposed methods for airway lumen detection are based on directly extracting the centerline. These approaches track a centerline by using properties of the intensity profile around the lumen, in particular by using the Hessian matrix (14, 15). Although very promising in nature, these approaches have not been widely used due to problems when dealing with branches.

Anatomical labeling of the bronchial tree is another important aspect of airway detection and segmentation. Although the inter-subject variability in airway anatomy, specifically the small airways, complicates this stage, different techniques seem to achieve over 90% accuracy in resolving the right anatomical label up to the fifth generation (7).

## AIRWAY WALL LOCALIZATION

Accurate thickness measurement of sheet-like structures has become increasingly important in clinical applications as well as in fundamental research. Examples of structures that can be modeled as such include airway walls, articular cartilage, and the vertebral cortical shell. A sheet-like structure is defined as being thin-layered with at least three different tissue densities measured by CT. A layer is considered thin if the size of the structure is in the order of the scanning resolution given by the modulation transfer function (i.e., in the order of single number of voxels). One complicating factor in performing measurements on structures of such size is the blurring effect imposed by the scanner point spread function (PSF), also known as *partial volume effect* mentioned previously. When the size of the structure to be measured is comparable to the scanner point spread function spatial extent (2 or more pixel widths), standard methods may result in a quantitative assessment of the PSF rather than the structure itself (8).

The techniques employed to perform automatic airway wall measurements can be broadly classified in two categories: parametric and nonparametric methods. Parametric methods are those that make use of the scanner point spread function (PSF) to infer the location of the wall (16–20). These methods attempt to undo the blurring process imposed by the scanner PSF (i.e., partial volume effect). Typically, the PSF is modeled as a Gaussian function and then the estimation of the PSF reduces to the estimation of the Gaussian standard deviation. The location of the airway wall can then be resolved by means of an optimization technique that matches the measured intensity profile and the expected intensity profile based on the model. The main advantage of parametric methods is that they may allow measurements below the scanner resolution. However, there are technical and practical limitations that preclude their use in a clinical application. The scanner PSF is typically a spatially variant non-Gaussian function (21) that is difficult to model on *in vivo* structures and is not generally assessed using a calibration phantom in the standard radiologic workflow. In addition, the PSF varies among manufacturers, making standardization at multiple sites challenging. Recognition of these limitations has led to significant reluctance to use imaging as a standard way to assess airway wall thickness in lung diseases.

Nonparametric methods do not make use of the PSF of the scanner, but rather attempt to infer the airway wall location by analyzing properties of the reconstructed CT signal that may be invariant to the blurring process imposed by the PSF (3, 22–24). The traditional approach to perform wall thickness detection based on nonparametric methods has relied on the so-called

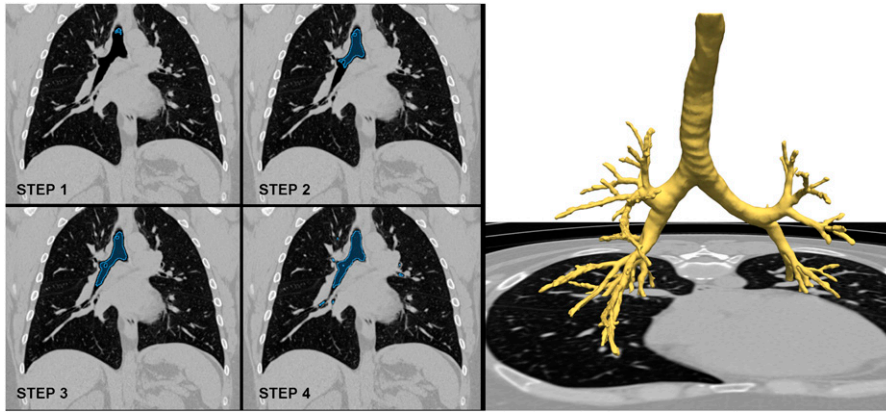


Figure 1. Airway tree detection by means of region-growing techniques. Left, evolution process: voxels of similar intensity and connected to an initial seed point are marked as belonging to the airway lumen. Right, rendering of the full airway tree.

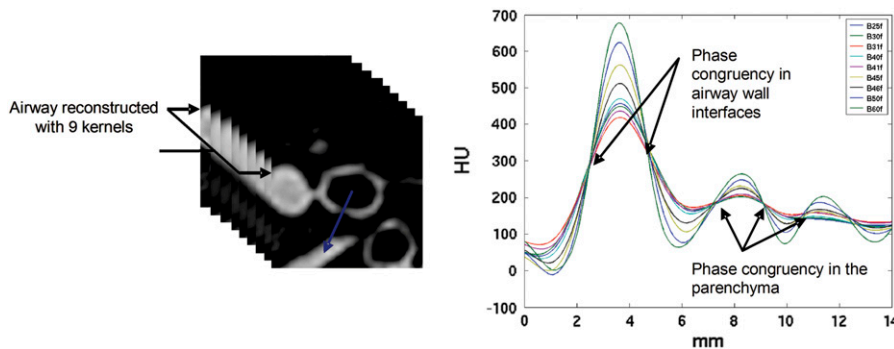


Figure 2. Airway wall localization by means of phase congruency using multiple kernels. The location of the airway wall is expressed as the location where the intensity profiles from multiple reconstruction kernels intersect.

“full width at half max” (FWHM) principle. It is based on the observation that for an ideal step function undergoing a low-pass filtering, the true edge is located at the FWHM location. For an airway model, the ideal step function model is only a good model for the inner and outer wall locations as long as the wall thickness is much greater than the bandwidth of the PSF. Otherwise, it has been shown that, under a Gaussian model for the PSF, FWHM yields an underestimation and overestimation of the inner and outer wall locations, respectively (16).

An alternative approach to the definition of the airway wall location is to use the properties of the second-order derivative operator. A criterion to define the location of the wall may be the location of the inflection point between the valley intensity and the peak intensity. This inflection point is given by the zero value of the second order derivative along the direction of the multi-layered structure (22). This approach is closely related to the edge-detection theory originally proposed by Marr and Hildreth (25).

A recent alternative approach to localize the airway wall is the phase congruency approach (24). Phase congruency is an intrinsic property of a signal that can be used to characterize the

location of transitions (i.e., lumen-to-wall and wall-to-parenchyma); therefore, it can be used as a method for airway measurement. Phase congruency is preserved even when the signal undergoes some sort of *smoothing* such as the one introduced by the PSF of the scanner. One approach to measure phase congruency is by providing different approximations of the signal that is being measured with different spectral properties (i.e., different bandwidths). A way to achieve these approximations from the scanner is to use different PSFs to generate the final CT images. Although some of the components that comprise the PSF are physically constrained and cannot be easily modified, like the scanner geometry, others can be changed even after the acquisition of the raw data. The overall behavior of the PSF can be modified by choosing different reconstruction kernels or algorithms. The reconstruction kernel is a parameter of the reconstruction process that defines how the neighboring samples in the projection space (Radon space) are averaged out before back-projection to compute the final intensity of each pixel location (26). The reconstruction kernel directly affects the spatial frequency characteristics of the reconstructed image, resulting in a visually smoother or sharper image. Figure 2 shows the effect of phase

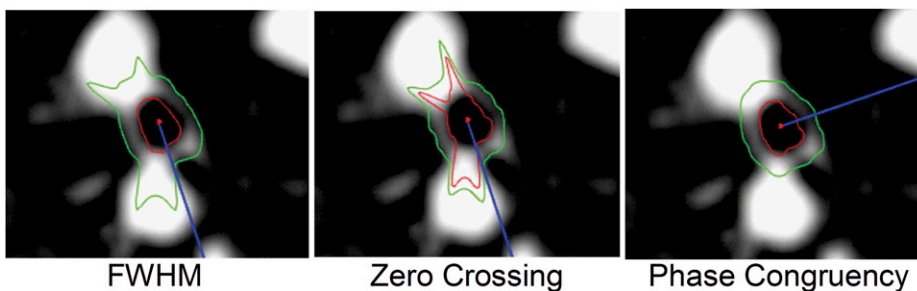


Figure 3. Airway wall localization by means of three nonparametric methods for the same airway. The inner and outer luminal contours are indicated in red and green, respectively. Phase congruency yields a more robust delineation of the airway wall when dealing with adjacent blood vessels.

congruency on an airway reconstructed with nine different kernels. The common crossing point between the intensity profiles from different kernels is an indicator of maximal phase congruency, and therefore it can be used as an estimator for airway wall location. The airway wall location is defined as the location where the intensity profiles corresponding to multiple kernels intersect. Preliminary results show that phase congruency with multiple kernels can achieve a relative error below 5% in the estimation of airway wall thickness for structures that are at least twice the pixel size. Figure 3 shows the localization of an airway wall by means of three nonparametric methods. Phase congruency not only gives a more accurate measurement, but the result is more reliable, yielding a good definition of the airway wall even in locations adjacent to vasculature structures where the edge is not as well defined.

A main shortcoming of nonparametric methods is that they are limited by the range of airway sizes that they can reliably measure based on the limit imposed by the Nyquist theorem. This limitation stems from the intrinsic behavior of nonparametric methods that rely on the local spectral properties of the signal. Airway sizes below the image resolution have spectral components that are irremediably lost. In such cases, parametric methods can potentially yield reliable measurement of structures smaller than the image resolution by using the prior knowledge given by the PSF to recover the blurring imposed by the scanner.

## AIRWAY MEASUREMENTS

The results of the airway detection and localization processes enable the quantification of airway morphometry by means of different measurements of airway size. The measurements can be broadly classified in the following categories according to the dimensionality of the data:

1. One-dimensional (1D)-based measurements. For a given airway location in the bronchial tree, an intensity profile can be cast from the center of the lumen outwards. Based on these profiles, measurements about the lumen radius and wall thickness may be computed (3).
2. Two-dimensional (2D)-based measurements. These measurements use the full extracted wall for a given airway location along the tree centerline. Measurements like luminal and wall area, wall area percentage (ration between wall area and the outer wall area), and inner and outer perimeter can be provided (4, 5, 27).
3. Model-based measurements. The definition of the airway wall is challenging due to limitations in resolution, image artifacts, and surrounding structures like vessels. A way to partially overcome those challenges is by using a model of the airway morphology, for example an ellipse (17). An ellipse can be fitted to the inner and outer wall locations defined in the localization stage. Measurements that can be computed to establish airway morphometry are: ellipse major and minor axis lengths, angle between ellipse axes, ellipse eccentricity, the ratio between axis lengths, and ellipse area.
4. Three-dimensional (3D)-based measurements. The previous set of measurements focus on a given point along the extracted airway tree. The associative information that the airway tree provides can be used to yield the previous set of measurements either on a per-segment or per-lobe basis. Rate of change can be also studied by taking first order (and even higher order) derivatives of the

corresponding measurement along the airway centerline. Rate of change can be useful to reveal different patterns of airway size tapering across different subject populations.

5. Structural measurements. Measurements of a different nature are those that focus not only on the airway morphometry but the airway structure itself. In this sense, measurements based on the CT density of the airway inside the wall might reveal important information about the mural remodeling process.
6. Relational measurements. A widely unexplored area is the possibility of deriving new measurements that try to relate emphysema and airway diseases. For example, areas of emphysema, as defined by one of the multiple image-based criteria, could be related to areas of wall thickening by computing lung density as a function of distance from the bronchial tree.

## VALIDATION

The validation of the different computational techniques involved in airway morphometry is crucial to establish the accuracy and precision of these methods. Validation attempts to bridge the gap between the measurement done using high-resolution (HR)CT and the measurement that could alternatively be achieved by histologic assessments of the same airway. The validation task can be seen as a process that involves different levels in both complexity and scope. A standard for the evaluation of airway localization techniques can be broken down as follows:

1. Computerized airway models. Airway models can be defined analytically and the method response can be computed over those analytical models to evaluate the accuracy of the airway localization algorithms (8). For example, Reinhardt and coworkers (16) reported that the FWHM overestimates airway wall thickness by means of an analytical model. Methods can be also tested against synthetically generated images of different airway sizes that mimic the results obtained by HRCT. In this case, the ground truth for airway wall thickness is accurately established by means of experiment design.
2. CT airway phantoms. Phantoms made of plastic tubes and parenchymal-like materials (16, 17, 24) serve as a good surrogate to establish method accuracy. Partial volume effect and other related scanner artifacts can be properly accounted for by using airway phantoms. These tools do not, however, accurately reflect *in vivo* airway peculiarities such as erratic airway density or the variable body mass surrounding such structures as seen in a clinical cohort.
3. CT airway tissue samples. *Ex vivo* airway tissue samples can be used to obtain CT images that capture the different airway and parenchymal details that cannot be reproduced by means of an airway phantom. The true airway wall thickness can be assessed either by microscopic analysis of the *ex vivo* airway or by means of micro-CT (28).
4. *In vivo* validation. The last step is the *in vivo* validation of airway morphometry methods by means of *in vivo* ultra-high-resolution imaging techniques like optical coherence tomography (OCT). Recent studies like those performed by Coxson and colleagues (29) show the applicability of OCT to establish correlations between CT-based measurement and high-resolution imaging-based measurement.

## CONCLUSIONS

CT technology has radically advanced in the last 20 years; however, the resolution provided by current state-of-the-art scanners is still limited in providing a precise analysis of the airway morphometry, at least at a meaningful histologic level. The variety of airway measurements is conditioned by the capabilities of localizing the airway wall. Without a full characterization of the CT scanner (by means of PSF estimation), methods used for airway wall localization and quantitative measurement are bounded by the scanner resolution. Given such constraints, accurate mural assessment of the small airways where expiratory airflow obstruction is thought to occur is not possible (30). Unfortunately, characterizing the scanner PSF is complex and disrupts the current radiology flow for patient scanning. Recent alternative approaches, like phase congruency, seek to exploit the information carried by several reconstruction kernels to improve airway measurement accuracy without resorting to a full PSF characterization. These new approaches, while increasing post-processing time and storage requirements, would keep patient scanning time and radiation exposure unchanged and may increase accuracy with respect to well-regarded methods like FWHM for airway wall morphometry.

Finally, given the multitude of software packages available for quantitative analysis of CT images, validation of the metrics obtained has become crucial. To facilitate such investigation, consideration should be given to create an open access resource of images with corresponding histologic measures similar to the tissue bank created for the Lung Tissue Research Consortium. While the up-front investment in such an endeavor is not insignificant, the resultant database would serve as a national and international metric for methodologic investigation and could serve as the standard for evaluating image analysis tools for use in multicenter investigations.

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