Published in final edited form as:

IEEE Trans Med Imaging. 2013 March ; 32(3): 493–510. doi:10.1109/TMI.2012.2223760.

Optimal Graph Search Based Segmentation of Airway Tree Double Surfaces Across Bifurcations

Xiaomin Liu,

Department of Computer Science and Engineering, University of Notre Dame, Notre Dame, IN
46556 USA

Danny Z. Chen,

Department of Computer Science and Engineering, University of Notre Dame, Notre Dame, IN
46556 USA

Merryn H. Tawhai,

Auckland Bioengineering Institute, University of Auckland, Auckland 1010, New Zealand

Xiaodong Wu,

Departments of Electrical and Computer Engineering and Radiation Oncology, The University of
Iowa, Iowa City, IA 52242 USA

Eric A. Hoffman, and

Department of Radiology and Biomedical Engineering, The University of Iowa, Iowa City, IA
52242 USA

Milan Sonka

Department of Electrical and Computer Engineering, the Department of Ophthalmology and
Visual Sciences, and the Department of Radiation Oncology, The University of Iowa, Iowa City, IA
52242 USA

Xiaomin Liu: xliu9@nd.edu

Abstract

Identification of both the luminal and the wall areas of the bronchial tree structure from volumetric X-ray computed tomography (CT) data sets is of critical importance in distinguishing important phenotypes within numerous major lung diseases including chronic obstructive pulmonary diseases (COPD) and asthma. However, accurate assessment of the inner and outer airway wall surfaces of a complete 3-D tree structure is difficult due to their complex nature, particularly around the branch areas. In this paper, we extend a graph search based technique (LOGISMOS) to simultaneously identify multiple inter-related surfaces of branching airway trees. We first perform a presegmentation of the input 3-D image to obtain basic information about the tree topology. The presegmented image is resampled along judiciously determined paths to produce a set of vectors of voxels (called voxel columns). The resampling process utilizes medial axes to ensure that voxel columns of appropriate lengths and directions are used to capture the object surfaces without

interference. A geometric graph is constructed whose edges connect voxels in the resampled voxel columns and enforce validity of the smoothness and separation constraints on the sought surfaces. Cost functions with directional information are employed to distinguish inner and outer walls. The assessment of wall thickness measurement on a CT-scanned double-wall physical phantom (patterned after an *in vivo* imaged human airway tree) achieved highly accurate results on the entire 3-D tree. The observed mean signed error of wall thickness ranged from -0.09 ± 0.24 mm to 0.07 ± 0.23 mm in bifurcating/nonbifurcating areas. The mean unsigned errors were 0.16 ± 0.12 mm to 0.20 ± 0.11 mm. When the airway wall surface was partitioned into meaningful subregions, the airway wall thickness accuracy was the same in most tested bifurcation/nonbifurcation and carina/noncarina regions ($p=NS$). Once validated on phantoms, our method was applied to human *in vivo* volumetric CT data to demonstrate relationships of airway wall thickness as a function of luminal dimension and airway tree generation. Wall thickness differences between the bifurcation/nonbifurcation regions were statistically significant ($p < 0.05$) for tree generations 6, 7, 8, and 9. In carina/noncarina regions, the wall thickness was statistically different in generations 1, 4, 5, 6, 7, and 8.

Index Terms

Airway trees; bifurcations; complex topology; graph search; image segmentation; multiple surfaces

I. Introduction

The parenchyma and the airway tree are two interrelated structures in the lung that contribute to the air flow obstruction that occurs in both asthma and chronic obstructive pulmonary disease (COPD). In order to better understand pathologic processes in these diseases and thereby target new therapeutic interventions, there has been an increasing interest in the use of multi-detector row computed tomography (MDCT) to quantitatively assess the lung, with the hope of categorizing (phenotyping) patients diagnosed as having asthma or COPD into homogeneous subgroups with unique patterns of parenchymal pathology, airway pathology or a mix of the two. Large multi-center studies funded by the National Institutes of Health [including the Severe Asthma Research Project (SARP), COPDGene, and the SubPopulations and Intermediate Outcome Measures In COPD Study (SPIROMICS)] are trying to understand the link between specific phenotypes and genotypes. These studies seek metrics which can be used to detect diseases early and to identify target populations for therapy, as well as metrics which can be followed before and after an intervention with the goal of determining intervention efficacy in shorter periods of observation. Significant advances have been made in the application of advanced image processing tools to evaluate the various components of the lung [1]–[4] including an assessment of the airway wall thickness as a measure of so-called airway wall remodeling in both asthma [5] and COPD [6]. In comparing airway wall thickness assessed by MDCT and airway wall remodeling assessed by the use of endobronchial biopsies [5], some uncertainty was introduced by the inability to directly compare corresponding sample sites. Approaches to the assessment of the airway wall thickness on MDCT images have limited quantitation to the lateral borders of the airway tree segments while the endobronchial biopsy needle sent

down the working channel of the bronchoscope can only sample in a forward direction and thus samples the airway walls in the region of the branch points or “airway carinas.” Since it has long been recognized [7], [8] that deposition of inhaled particles—which might have an influence on regional airway remodeling—is concentrated at the airway branch regions, the inability to evaluate the airway wall at these branch regions is a considerable limitation of current quantitative methods for assessing the airway from MDCT image data sets.

The pulmonary airway is a highly branching tree-structured 3-D object that consists of two inter-related surfaces (inner and outer walls). Airway wall thickness is thought to reflect disease-associated changes that affect lung function. Airway wall thickness can be influenced by inflammatory and cancer-related processes, or the presence of an altered mucus layer. We have recently demonstrated that as the airway wall stiffens, there is an increased susceptibility to alterations in shear forces at the luminal borders that could affect cellular function [9]. Alterations in the airway wall are of great interest to the study of lung pathology. However, wall thickness in the areas of interest is in the order of—at most—a few millimeters, and the wall thickness changes that need to be quantified can be substantially less than a millimeter. Therefore, accurate and unbiased assessment of the airway wall and assessment at both the lateral walls as well as the branch regions is of considerable interest.

Accurate identification of the airway double surfaces in MDCT volumetric images is challenging because of the inhomogeneity of the bronchial lumen and bronchial wall gray levels in such images. A variety of approaches have been reported in this area, most of which focused on segmenting the inner surface or extracting the tree morphology. The earliest attempts of Wood *et al.* and Sonka *et al.* focused on segmenting 3-D canine bronchial trees [10], [11]. Once electron-beam human lung CT images became available, methods for human airway tree detection quickly followed. Sonka *et al.* proposed a combination of a 3-D seeded region growing method [12] (for identifying large airways) and a rule-based 2-D segmentation (for identifying probable locations of smaller diameter airways). A fuzzy-logic approach to airway tree segmentation was introduced by Park *et al.* in [13]. Aykac *et al.* applied gray-scale morphological reconstruction to identify candidate airways and reconstruct a connected 3-D airway tree. After segmentation, the airway branch points were estimated based on connectivity changes in the reconstructed tree [14]. Fetita *et al.* proposed an energy-based 3-D reconstruction of the bronchial tree from multislice CT acquisitions. The growth of a subset of low-order generation airways extracted from CT images was controlled by a robust mathematical morphology operator [15].

While the inner surface of the CT-imaged airways is relatively easy to distinguish, the airway outer wall is juxtaposed with structures of more similar densities and textures. Therefore, the detection of airway outer surface is particularly difficult without the information about the inner surface. Most of the previous methods for evaluating the airway outer surface are limited to 2-D cross sectional images along the centerline, and are not capable of detecting the airway wall surfaces in the bifurcation areas. The traditional full-width half-maximum (FWHM) based method [16] locates the outer wall halfway between the maximum and minimum gray levels along a ray cast from the center of the lumen. Although commonly used as a simple and robust method, the accuracy of FWHM methods

can be influenced by various factors such as airway sizes, shape, and system resolution [17]. A bronze standard based on phase congruency for locating the airway wall position was proposed in [18]. The method yielded more accurate results than FWHM across a range of airway sizes, but was still biased to overestimation of the wall thickness. Another group of model based approaches [17] works by fitting elliptical or cylindrical models to the airway inner and outer walls, but may not produce accurate results on clinical data where the airways are not strictly elliptical.

Recently, new methods were proposed which do not depend on any shape models or prior information of the wall position. For example, 2-D dynamic programming approaches were developed [19], [20] to detect both the inner and outer boundaries in cross-sectional images, utilizing cost functions combining the first and second derivatives. An active contour approach was presented [21] to estimate the lumen and airway wall dimensions, with the outer wall based on the final inner boundary. In another study [22], the airway inner wall was first obtained by the method presented in [15]; then the airway outer surface was segmented by a 3-D segmentation method that locally deformed the lumen mesh under specific force constraints. However, the performance of the approach in bifurcation areas is not clear as the method was only validated in nonbifurcating areas. To the best of our knowledge, only a few methods are known for the segmentation of the airway outer surface and for the measurement of wall thickness across the airway tree bifurcations. Even when such attempts were made [22], they searched for the two surfaces separately or the outer surface depended purely on the inner one. Consequently, such methods may suffer from segmentation errors due to the lack of consideration of the global inter-relations between the sought surfaces.

It is worth noting that none of these previous approaches was able to guarantee the optimality of their solutions. Wu and Chen [23] developed an optimal graph search based algorithm that was extended to multiple surface segmentation by Li *et al.* [24], which can simultaneously search for multiple interrelated surfaces. These graph search based schemes first transform the image segmentation problem to computing a minimum-cost closed set [25], [26] in a derived vertex-weighted directed graph, from which an optimal segmentation is produced. The methods have been successfully applied to nonbranching airway segmentation [24] and MR arterial wall segmentation [24], but they were not extended to segmenting objects with tubular and tree-like topology such as bifurcating airways or blood vessels (Fig. 1). These methods [23], [24] are suitable only for objects that have a relatively simple topology (e.g., cylindrical or spherical). In these cases, a 3-D geometric graph can be built either by unfolding the sought surfaces to terrain-like surfaces or resampling the image along the normal surface directions within a narrow band. These “simple” methods for constructing the 3-D graphs are not directly applicable to objects with complicated structures and when employed may cause severe interferences among the resampled voxel vectors (columns) and/or the resampled voxel columns may fail to intersect (or capture) the sought surfaces.

Yin *et al.* [27] extended the graph search algorithm to segmenting multiple interacting objects (LOGISMOS), and proposed an approach based on the electric lines of force (ELF) to construct noncrossing columns in the interaction areas. Positive electric charges are

assigned to the vertices of the initial surface to simulate an electric field. The paths (columns) from any points outside the surface can be computed by tracing the electric lines of force. While applicable to objects with complicated topologies, the algorithm is computationally expensive for objects with large scale interactions. Similarly, Petersen *et al.* [28] suggested to convolve the initial segmented image with a kernel/filter and construct the columns by tracing the gradient or negative gradient direction in the vector field, which is computationally tractable for large scale problems. The method was applied to airway wall segmentation in CT scans, but no validation was reported for airway bifurcation areas.

To address the above-mentioned drawbacks, we present a new scheme for segmenting tubular and tree-structured objects in 3-D. The main contribution of this paper is that it presents and provides a thorough validation of a new approach for building a graph model to represent a complicated structure such as a branching tree. The previous approach by Li *et al.* [24] either uses a simple graph model to represent the target objects, or assumes such a graph model is available. To represent structures with complicated branching topologies using multi-column graphs, a key difficulty is to determine the lengths of columns so that they can penetrate the sought surfaces without interfering with each other. To overcome this difficulty of segmenting branching structures, we use two approaches—construction of medial axes and performance of surface dilation—to guide and produce an effective image resampling. Our graph search on the resampled images uses task-specific cost functions for airway trees. Consequently, we obtain segmentations of a pair of inter-related inner and outer wall surfaces of 3-D airway tree walls with substantially improved quality. Our method allows for successful identification of the airway double wall surfaces across bifurcations with guaranteed global optimality. Instead of segmenting an airway tree section by section and then linking the resulting pieces together as in a previous effort [24], our approach treats the entire 3-D airway tree as a single object and searches for the complete optimal inner and outer walls simultaneously. It should be pointed out that once the object topology is given, the graph search based techniques [23], [24] guarantee the optimality of the segmentation results with respect to the cost functions used. This nice feature is preserved by the method presented here since we use the same underlying optimal graph search technique although in a much more sophisticated manner applied to a more complex object topology.

Because of the topological complexity, airway bifurcations are the most difficult areas to achieve accurate segmentation and measurement in the airway tree (Fig. 1). As discussed above, it is of clinical importance to improve assessment accuracy on these areas. For example, the experimentally observed local accumulations of inhaled particles within bronchial airway bifurcations may play a crucial role in lung cancer induction [29], [30]. A segmentation of a complete bifurcation should cover the entire “Y” shaped part that connects to the relatively straight branches (which are the nonbifurcation areas). In addition, it is physiologically interesting and likely diagnostically important to focus on specific parts of the bifurcations, such as the carina area between the two sub-branches. For example, wall thickening in or distortion of the tracheal carina may be serious as it may indicate the presence of adjacent lymph node carcinoma around the region where the trachea divides [31]. Hence, we seek to distinguish the bifurcation/carina and nonbifurcation/noncarina

areas of the airway trees, and evaluate the segmentation results separately on both these areas.

We have conducted extensive validation using an MDCT-scanned double surface bifurcating phantom with known wall thickness to optimize the cost function used by our graph search based segmentation. The wall thickness is assessed as a function of airway tree generations. In order to achieve this, two methods were employed to identify the bifurcation and carina areas of the airway trees based on the one-voxel wide 3-D skeleton and 3-D medial sheets, respectively. The wall thickness was measured on the identified bifurcation/nonbifurcation and carina/noncarina points, grouped together and compared for different generations. Once the method's parameters were optimized and its performance established on phantoms, the developed method was applied to determine the variability and consistency of the wall thickness for individual generations of the airway trees across normal subjects.

This paper presents full details of the methodology only outlined in earlier works [32], [33]. A thorough evaluation of the algorithm is reported in a physical phantom derived from human *in vivo* data. Notably, the phantom analysis is different from that in [33] and substantially more sophisticated. The new phantom was scanned within a chest phantom filled with potato flakes to simulate the pulmonary parenchyma on CT scans. The phantom was also scanned with different reconstruction kernels and at different orientations. As another novel contribution, this paper includes analysis of airway wall thickness on a set of 25 CT scans of normal human lungs. Novel results are presented regarding the relations between wall thickness and inner diameter, the wall thickness in bifurcating/nonbifurcating areas, and the wall thickness in different generations demonstrating feasibility of the reported approach *in vivo* and thus facilitating larger phenotyping studies.

II. Graph Search Based Segmentation

The graph search based algorithms [23], [24] solve the image segmentation problem by transforming it to finding a minimumcost closed set [25], [26] in a vertex-weighted directed graph, which can be computed in polynomial time. Our graph search based image segmentation approach consists of the following four major steps.

1. **Presegmentation and meshed surface representation.** A presegmentation is needed to provide basic information on the object's global topological structure. It is not necessary for the presegmentation to be locally accurate. However, it is crucial to preserve the topology of the target object. If the presegmentation does not yield a surface mesh, we also need to transform the volumetric result into a mesh representation.
2. **Image resampling.** Using the outcome of the presegmentation, the image is resampled based on each vertex of the initial surface mesh directly, resulting in a set of vectors (called *columns*) of voxels. In this paper, medial axes [34] are applied to determine the directions and lengths of the resampling voxel columns.
3. **Graph construction.** Each voxel in the columns is considered as a vertex in a graph. The graph has three types of edges (intra-column, inter-column, inter-surface), representing the relations of voxels within the same surface or between

pairs of different surfaces of the object (i.e., the intra-surface and inter-surface constraints). A cost is assigned to each vertex of the graph which reflects certain properties of the sought surfaces. Appropriate cost functions should be adopted according to different image/object types.

4. **Graph search.** Finally, a minimum s - t cut algorithm [23], [24] is applied to the resulted graph to simultaneously search for multiple inter-related surfaces.

For segmenting tubular and tree-structured objects with graph search, the most nontrivial task is to build a vertex-weighted directed graph to model the volumetric image. When constructing this graph model, we need to carefully resample the volumetric image in order to ensure that the following requirements are satisfied. 1) All the sought surfaces must be captured by the graph. 2) The relations among the voxel columns should be consistent with the surface topology specified by the preliminary mesh from the presegmentation. For example, interferences among different voxel columns must be avoided (more on this later).

In the rest of this section, we present a novel image resampling approach which makes sure that the graph constructed from the resampled voxel columns meets these two requirements. We also discuss the graph construction scheme and the design of cost functions for airway wall double surface segmentation.

A. Presegmentation

The airway trees are presegmented using the commercially available PW+ software (VIDA Diagnostics, Coralville, IA). This presegmentation produces only the luminal (inner) wall and is approximate with respect to the positioning of the luminal surface. This approximate segmentation was previously used for double-wall segmentation in airway segments between bifurcations [19]. The bifurcation areas were not previously segmented since no applicable approach was available for this task. The approximate character of the initial tree lumen segmentation is further discussed in Section IV-B. Once a labeled image is generated by the presegmentation, the inner wall surface is transformed into a triangulated mesh using the marching cube algorithm [35].

B. Image Resampling Based on Medial Axes

To segment an optimal surface in the image using the given preliminary meshed surface, our approach performs a resampling of the input 3-D image for every meshed surface vertex along the normal direction of the meshed surface at that vertex, resulting in a column of voxels for each vertex. A linear interpolation kernel was used for resampling. In this process, we seek to avoid two “bad” situations: (1) The length of a voxel column is too short, so that it fails to capture enough information about the sought surface; (2) the length of a column is too long, so that it interferes (intersects) with other columns (see Fig. 2). In situation (1), the graph search algorithm would fail to find the correct surfaces. In situation (2), the graph constructed from the resampling would contain wrong topological relations among the involved columns [see Fig. 3(a)], which is determined by the base graph (i.e., preliminary mesh). Note that presegmentations of some bifurcations may form a sharp angle between two branches, so the columns along the normal directions may not intersect the sought surfaces without interfering with each other.

It should be pointed out that these difficulties did not arise in the problems studied by the papers [23], [24], approaches which were designed for objects with a relatively simple topology (e.g., cylindrical or spherical). In these “simpler” cases, a 3-D geometric graph can be built either by unfolding the sought surfaces to terrain-like surfaces or resampling the image along the normal surface directions within a narrow band. Hence, it is usually sufficient to use one global length for all the voxel columns involved. However, in our problem, due to the complex topology of the target object, the column lengths can be largely different from each other, that is, the length of each column must be determined based on the local features of the object and the relations with the surrounding structures.

To deal with the above two challenges, we follow two approaches: 1) Use the medial axes [34] of the preliminary surface to help avoid column interferences [see Fig. 3(b)], and 2) grow (dilate) the preliminary surface by a certain distance to make sure that the noninterfering columns determined by the medial axes are sufficiently long to reach the sought surfaces. To avoid possible interferences among the resampled columns, we need to determine the proper directions and lengths of the columns. Intuitively, the normal direction at each mesh vertex is appropriate to seek intersections with the desired surface.

A medial axis of the preliminary surface is a set of points each consisting of at least two different nearest points on the surface [34]. At each mesh vertex, the medial axis determines the maximum distance that a column can be extended along the normal direction without any interference with other columns. Although the exact computation of the medial axes is possible in principle, implementation is complicated due to significant algebraic difficulties [34]. Approximate solutions can be obtained using computational geometry techniques [36]. An algorithm for computing an approximate medial axis and the column lengths is summarized as follows.

1. Let S be the set of vertices of the mesh. We compute the Voronoi diagram VD of S and the dual Delaunay triangulation D of S in the 3-D image [36].
2. The points of both the inner and outer medial axes for a vertex $p \in S$ are approximated by the poles v_{p1} , v_{p2} in VD , which are computed as the centers of selected big Delaunay balls (i.e., circumscribed spheres of the Delaunay tetrahedra in D) adjacent to the vertex p .
3. The inner and outer poles v_{p1} and v_{p2} are assigned to each mesh vertex p by selecting the largest poles among the k -nearest neighbors of p (on both sides of the surface, Fig. 4), to reduce the impact of possible noise on the surface [36]. The k -nearest neighbors were identified using $k = 8$. See Fig. 5 for an example of the resulting medial axes.
4. The column lengths are obtained by computing the distances from each mesh vertex p to its corresponding medial axis points v_{p1} and v_{p2} (on both the inner and outer medial axes of the preliminary surface, Fig. 4).

A sought surface may contain very sharp angles at its branches. In such situations, a medial axis could be very close to the branching portions of the surface and consequently the columns computed based on the medial axis could be quite short, giving very little flexibility

to the graph search algorithm. To avoid this problem, we first grow (dilate) the preliminary surface by a certain distance, and then compute the inner and outer medial axis according to the dilated surface. The dilation distance we used in the experiments was three voxels and should in general depend on the size of the objects. The columns are constructed based on the vertices of the dilated surface, with lengths computed based on the medial axes of the dilated surface. In our case, the base graph was moved from the initial surface to the dilated surface. As long as the columns are long enough to penetrate the desired surface, the graph search algorithm is able to identify it within the constructed graph, no matter where the initial surface was.

C. Graph Construction

A graph $G = (V, E)$ has a set V of nodes (or vertices) that are connected by edges in E . In this paper, the nodes in V of G are voxels in the resampled volumetric image, organized by the columns. Each column of nodes is associated with a vertex of the preliminary mesh, and is sampled along the normal direction of the meshed surface at that vertex. The mesh vertices are connected by edges of the mesh. Below we show how to assign edges to connect nodes in G and to enforce two important geometric constraints (e.g., the *smoothness constraint* and the *separation constraint* on the sought surfaces [24]).

For each sought surface (e.g., the inner or outer wall surface), we first construct a subgraph of G that is designed to capture that surface. Specifically, at each mesh vertex v , there are two columns, associated with the inner and outer airway wall surfaces, respectively. Denote these two columns at vertex v by $\text{Col}_i(v) = (n_i(v, 0), \dots, n_i(v, K_{v,i} - 1))$ and $\text{Col}_o(v) = (n_o(v, 0), \dots, n_o(v, K_{v,o} - 1))$, respectively, where $K_{v,i}$ and $K_{v,o}$ are the lengths of these two columns for v . The inner/outer columns $\text{Col}_i(v)$ and $\text{Col}_o(v)$ are both oriented according to the inner surface normal of the original mesh towards two directions (the inner and outer medial axes). The resampled voxels in the inner and outer columns are the same, but the separation constraints impose that the outer surface must be outside of the inner surface. Within every column, say, $\text{Col}_i(v)$, each node $n_i(v, k)$ is connected by a directed (intra-column) edge to $n_i(v, k-1)$ for $k=1, 2, \dots, K_{v,i} - 1$. Between each pair of *adjacent columns* for a sought surface, that is, the columns resampled for two adjacent vertices on the mesh (i.e., the two corresponding mesh vertices connected by an edge in the mesh), a set of edges is assigned to enforce the *smoothness constraint* [24] on that surface. Let v_1 and v_2 be two adjacent vertices on the mesh and suppose $n_i(v_1, k_1)$ is connected to $n_i(v_2, k_2)$ by an inter-column edge. Then the smoothness constraint requires that

$$-\Delta \leq k_1 - k_2 \leq \Delta \quad (1)$$

must be satisfied. With the smoothness constraint, we avoid any dramatic change between the neighboring voxels on the same sought surface, consequently resulting in “smooth” surfaces of the target objects. In the case of our double surface detection, another set of edges, called inter-surface edges, is added to G to impose the *surface separation constraint* [24] between the two sought surfaces. The separation constraint ensures that the two sought surfaces are not unreasonably far away from and also not too close to each other (e.g., they may not be allowed to intersect). The inter-surface edges are between the two subgraphs for

the two sought surfaces, and are assigned between vertices $n_i(v, k')$ and $n_o(v, k'')$ for each mesh vertex v , such that the following separation constraint:

$$\delta^l \leq k' - k'' \leq \delta^u \quad (2)$$

is satisfied, where δ^l (resp., δ^u) specifies the smallest (resp., largest) allowed distance between the two sought surfaces (assume $\delta^u - \delta^l > 0$). We use $\delta^l = 3$ and $\delta^u = 30$ in all reported experiments with the phantom and MDCT data. In (1) is set to 1, because we use a dense mesh to capture every local structure of the airway surface, and the airway surfaces are tubular objects that are locally smooth. The value of δ^l is small enough to make sure that the thinnest airway wall can be detected, and the value of δ^u is large enough to measure the thickest airway wall (the resampling interval $\rightarrow$ the distance between two vertices on the columns is about 0.12–0.30 mm depending on the voxel size).

After the graph G is constructed with the above three types of edges (intra-column, inter-column, inter-surface) between the nodes in the columns, cost values are assigned to each of the nodes in G .

D. Cost Functions

An airway tree has two surfaces: the inner wall and outer wall. The inner wall is quite distinguishable from the airway lumen, but the detection of the airway outer wall is difficult since the outer surface is often surrounded by other adjacent tissue with similar gray-scale intensities in MDCT images. In our graph search based segmentation, a cost function used must reflect the possibility for a voxel (node) to belong to a certain surface. It should also distinguish voxels that belong to different surfaces. For airway wall detection, the two surfaces differ from each other in the direction of intensity changes, i.e., in the orientation of image edges [37]. Since the airway lumen is darker than the airway wall, the intensity increases from low to high at the inner border. Conversely, the intensity decreases from high to low at the outer border when only parenchymal tissue is adjacent. Edge strength associated with the outer wall locations may be very weak. However, even small differences in brightness are utilized by the algorithm for positioning the outer wall. More importantly, even in the presence of nonparenchymal surrounding tissues or adjacent vessels, it is very likely that at least one section of the airway wall will not be immediately adjacent to such structure considering a spherical surrounding of the airway. A combination of this spherical context and the image intensity information is utilized to position the outer wall surface when the airway is touching nonparenchymal structures.

The cost function we use for airway tree segmentation is a combination of the first and second derivative edge detectors and is based on a previously proposed cost function [38]. This is due to the property that the two edge detectors tend to yield the maximum magnitude on one or the other side of the true edge, causing certain overestimate or underestimate of the airway wall position. Thus, a weighted sum of the first and second derivatives works better for the accurate border location. The value of the weight ω is determined by the size of the airway and was computed based on the method in [19], [38]. One notable difference that likely caused differences in the ω values compared to [19] was that the focus was on minimization of the wall thickness errors (or joint positioning of both surfaces) while the

previous work [19] sought minimization of the surface positioning errors for each individual surface. In our problem, the local size is actually the same as the inner column length (i.e., the distance from each point on the presegmented surface to the inner medial axis). The x coordinates of the endpoints of each piece-wise linear intervals are determined as in [19]. The y coordinates of the endpoints are empirically adjusted to provide good performance in phantoms. Fig. 6 illustrates the piecewise linear function of the weight ω used in the validation for a double surface bifurcating phantom. Ideally, a 3-D edge detector should be applied in our situation because of the 3-D nature of the image. However, a comparison test of the 2-D and 3-D edge detectors showed that the 3-D edge detector performs similarly as the 2-D one but with a significant increase of computational overhead. Thus for a better efficiency, the 2-D edge detector is adopted to build the cost function at each node of the graph, as follows:

$$\text{Cost}_{\text{outer}}(v) = \omega \cdot I_t(v) * M_{\text{Sobel}_1} + (1 - \omega) \cdot I_t(v) * M_{\text{Marr}} \quad (3)$$

$$\text{Cost}_{\text{inner}}(v) = \omega \cdot I_t(v) * M_{\text{Sobel}_2} + (1 - \omega) \cdot I_t(v) * M_{\text{Marr}} \quad (4)$$

where M_{sobel_1} and M_{sobel_2} represent two inversely oriented 2-D Sobel templates, M_{Marr} represents the 2-D Marr template (all in 5×5 size), and $I_t(v)$ is a 5×5 gray-scale image template resampled from the input 3-D image around the node v . As we did for resampling the columns, the template is also sampled along the corresponding vertex's normal direction (as illustrated in Fig. 7). Thus, the 2-D image template is centered at the node v and is on a plane orthogonal to the surface. The voxels are sampled at the interval size d_t such that

$$d_t = d_{\text{col}} / 2 \quad (5)$$

where d_{col} is the interval between consecutive voxels in a resampled column. In our experiments, the resampling interval d_{col} is set to be 0.25 voxel unit. This value was chosen empirically to balance between the accuracy and efficiency of the algorithm.

E. Determining an Optimal Solution

To determine an optimal solution for segmenting airway double surfaces in a 3-D image I , the problem is transformed to computing a minimum-cost closed set in a directed graph G' . G' is derived from the graph G (as discussed in [23], [24] and Section II-C). The graph G contains k disjoint subgraphs, each of which corresponds to searching one of k sought surfaces ($k = 2$ in our case). These k subgraphs are connected by inter-surface edges in G . The edges within and between the subgraphs in G enforce the smoothness and separation constraints, respectively, on the k sought surfaces. To transform the segmentation problem to a minimum-cost closed set problem, the cost of each node in G is modified in G' . Denote by $n(v, j)$ and $c(v, j)$ the j th node and its cost in a column $\text{Col}(v)$ for the graph G associated with a mesh vertex v , and the corresponding node and its cost in G' by $n'(v, j)$ and $c'(v, j)$ (in column $\text{Col}'(v)$), respectively. Then the (modified) costs $c'(v, j)$ in G' are assigned as

$$c'(v, j) = \begin{cases} c(v, j), & \text{if } j=0 \\ c(v, j) - c(v, j-1), & \text{if } j>0. \end{cases}$$

Note that with this modification, the sum of the costs for the 0th to the j th nodes in $\text{Col}'(v)$ of G' , $\sum_{i=0}^j c'(v, i)$, is equal to the cost $c(v, j)$ of the j th node $n(v, j)$ in G . As proven by Li *et al.* [24], after some additional modifications of the edges in G' from G , finding an optimal set of k surfaces in the original volumetric image I is equivalent to computing a minimum-cost nonempty closed set in G' , which is solvable in low-order polynomial time. For our problem of segmenting the airway double surfaces, an optimal solution in a resampled 3-D image with n voxels can be computed in $O(T(n, n))$ time, where $T(N, M)$ is the computation time for finding a minimum s - t cut in an edge-weighted directed graph with $O(N)$ nodes and $O(M)$ edges.

III. Performance Assessment on Physical Phantoms

A. Identification of Airway Bifurcations and Carina Regions

For an object with a tree-like topology such as the airway tree, parental generations typically split into two child airways at the site of a bifurcation. Trifurcations can be modeled as a series of two bifurcations in a rapid succession. The region where two child airways separate forms a 3-D V-shape. To assess the accuracy of airway wall segmentation and wall thickness measurement in the segments between successive bifurcations and within the bifurcation regions, subsets of the airway wall surface must be identified to allow performance comparisons. For this purpose, the tree structure can be represented by its 3-D skeleton that holds useful information about the tree topology, branching points, tree segments, etc. The skeleton can therefore be used to define regions of specific properties within airway bifurcations. Two such region labelings are utilized in this work. Consequently, each point of the airway tree surface is labeled with two labels: as belonging to a bifurcation or nonbifurcation region as well as belonging to a carina or noncarina region.

1) Identifying Bifurcation Regions—An airway tree skeleton is computed using a 3-D thinning algorithm by Lee *et al.* [39]. This algorithm iteratively removes the *simple points* from a given object while preserving the object topology (such as the connectivity, holes and cavities of the object, etc.). The output skeleton of this thinning algorithm is a one-voxel wide centerline structure. Next, a tree-labeling process identifies the branching points and nonbranching points in the skeleton using a depth-first search. Each of the branching and nonbranching points is associated with a corresponding generation number.

It is a well-known phenomenon that an object skeleton/medial axis is sensitive to local changes of the object surface—possibly forming undesired skeleton branches. Since it is important to remove such false branches, the length of each branch is determined and the branches that are too short compared to the corresponding local diameter are pruned.

The bifurcation regions are defined as the subset of surface points with smaller than a specified distance from the branching point. To conveniently define surface subsets, spheres of desired diameters are centered at each branching point. To cope with the varying airway sizes, the sphere diameters are set proportional to the corresponding local branch diameters. In Fig. 8(a), the diameter of the sphere was selected twice as large as the local diameter in order to incorporate the entire bifurcation. However, in this situation, some of the branches [e.g., in generations 3–6 of the example in Fig. 8(a)] that are short compared to the local diameter may become partially included in the bifurcations (covered in red).

2) Identifying Carina Regions—The tracheal carina is a cartilage-rich saddle region within the trachea that separates the trachea and the two mainstem bronchi. Carina regions exist at each higher generation bifurcations. The carina regions can be defined as the V-shaped saddle areas described earlier. As illustrated in Fig. 8(b), the carina regions can be well represented by surface points that are within a small distance from the outer medial axis (once such a distance is properly determined with respect to the local diameter). The outer medial axis can be computed as given in [36], see Section II-B. This approach is based on Delaunay triangulation and construction of a Voronoi diagram of the 3-D object surface and generates both the inner and outer medial axes of the object at the same time. Surface points, which are sufficiently close to the outer medial axis, are then forming the carina regions.

B. Experimental Methods—Physical Phantoms

The airway tree is segmented, inner and outer wall surfaces identified, and airway wall thickness determined for each point of the airway wall. The wall thickness is measured between the two segmented (inner and outer) airway surfaces along the normal directions to the inner surface. All points of the segmented airway tree wall are subsequently associated with two labels (bifurcation/nonbifurcation and carina/noncarina) as described above. To allow a generation-specific analysis, the wall locations throughout the entire tree are associated with tree generation information. Generation-specific performance assessment is obtained for both the bifurcation/nonbifurcation and carina/noncarina areas.

To evaluate the performance of our graph search based airway wall segmentation, a typical approach would be to obtain manually-traced independent standard on the same data sets and compare them with our segmentation results. However, this classic approach is not feasible due to the large volume and the complicated structure of the airway trees. Additionally, human experts are not very good at manually determining the exact positions of the airway wall borders/surfaces considering the image ambiguities and location-perception changes resulting from different window-level settings of the viewing displays. Consequently, physical phantoms remain the only reliable way of determining airway wall detection accuracy, despite the problems associated with questions about how realistic such phantoms are with respect to mimicking *in vivo* CT airway tree image data. Therefore, our quantitative assessment of the pulmonary segmentation was performed on a double-surface rapid-prototyped phantom, which was modeled after *in vivo* scanned human airway trees to simulate real airways. The phantom was built to include airways corresponding to all segmented generations and representing the entire range of segmented airway sizes. Due to the way how the phantom was constructed, it was not feasible to build the entire airway tree

and a subtree satisfying the requirement of representing all generations and all size ranges was used for phantom construction.

The 3-D manufactured phantom was imaged by MDCT. It is worth mentioning that no known reliable method exists that allows direct determination of airway wall segmentation accuracy *in vivo*.

A double-wall phantom with predefined wall thickness values was constructed from segmented (PW + software) volumetric MDCT images of a healthy male lung. Segmentations of the airway lumen (to the inner wall) were imported into the CMGUI visualization software (www.cmiss.org), which was used to numerically define the location of densely sampled discrete surface data points on the inner airway surface. A bicubic Hermite finite element mesh was geometrically-fitted to the surface of the outer wall. The bicubic Hermite interpolation function provides both c_0 and c_1 continuity at the mesh nodes, and represents the complex curvilinear airway wall geometry with a minimal number of mesh elements. Geometric fitting involves formulating an objective function that is the summation of the distance from each surface data point to the mesh surface. By successive iterations, the nodal locations and derivatives were calculated to minimize the objective function. The geometrically-fitted model describes the curvature of the airway surface, and the highly curvilinear carina. The surface mesh was converted to a volume by defining a wall thickness at each mesh node, copying and scaling the fitted inner surface mesh to sit at the assumed outer airway wall, and defining connectivity between the inner and outer surfaces to give a volume mesh. The wall thickness was taken from calculations that were initially made during the image segmentation (by PW+). Wall thickness values (mean, SD, minimum, and maximum) in each phantom tree generation are given in Table I. The wall thickness prescribed by the model ranged from a maximum of 2.69 mm in the trachea to a minimum of 0.05 mm.

The volume mesh was exported to a stereolithography (STL) file that was imported to a solid printer. A solid phantom was manufactured from acrylonitrile butadiene styrene (ABS) plastic using a Dimension Elite solid 3-D printer (Stratasys Inc.). The solid structure was composited of 0.25-mm-thick layers of ABS production grade thermoplastic and support material. The support material was dissolved following the manufacturing process. We assume that the minimum wall thickness (due to manufacturing limitations) is 0.25 mm—note therefore that it may not be possible to manufacture wall thickness at the lower range of the desired wall thickness interval. Airways that are oriented with their axial direction parallel to the z-axis of the solid printer (e.g., the trachea) would have the least error in wall thickness, whereas those perpendicular to the z-axis of the solid printer would be limited to multiples of 0.25 mm for the wall thickness.

The ground truth of the wall thickness was determined from the original digital mesh of the double-wall phantom used for fast prototyping of the physical phantom by calculating the orthogonal projection from the vertices of the triangular mesh to the inner wall surface. The phantom was placed inside of an Alderson chest phantom (RSD, Long Beach, CA) simulating the human chest wall for CT scanning. To obtain a realistic phantom image, the rest of the thoracic cavity was filled with potato flakes that approximate the texture and

intensity levels of lung tissues in CT scans (Fig. 9) [40]. The phantom was scanned at three different orientations, each with three reconstruction kernels B30, B35, and B50, which resulted in nine CT scans in total. The phantom consisted of nine generations of airway branches, most of which were not oriented perpendicularly to the scanning plane. The image size of these nine CT scans was $512 \times 512 \times 470$ with the voxel sizes of $0.63 \times 0.63 \times 0.50 \text{ mm}^3$. The processing time on image size $512 \times 512 \times 470$ was 12.1 min on a 3.20 GHz workstation with 4 GB memory.

The performance of our algorithm was tested on all nine CT scans of the phantom. As such, six phantom-based comparisons were performed. Airway wall segmentation accuracy was assessed by comparing the obtained wall thickness measurements with the phantom-blueprint-based independent standard after the MDCT image and the 3-D phantom blueprints were registered. The wall thickness errors were calculated as signed and unsigned differences between the locationally matching computer-determined and phantom-based wall thickness values. The error measurements are jointly reported for all scans with the same reconstruction kernel. The obtained wall thickness errors were statistically compared for different airway locations and for different generations using Wilcoxon rank-sum test, $P = 0.05$ was considered significant. The numbers of airway segments for one phantom scan contributing to the individual generations (from the first to the ninth) were: 1, 2, 2, 4, 6, 2, 2, 2, and 2.

C. Results—Physical Phantoms

As summarized in Tables II and III, the mean signed and unsigned errors of the wall thickness measurements were low for the double surface phantom reconstructed with all three kernels. The errors are reported in both the bifurcation/nonbifurcation and carina/noncarina areas. The close-to-zero average values of the signed wall thickness errors attested to almost no measurement bias. The average signed and unsigned errors of each generation and their standard deviations are given in Figs. 10 and 11, independently considering the wall thickness accuracy in the bifurcation/nonbifurcation and carina/noncarina regions. Note that the averages and deviations in Figs. 10 and 11 were calculated for all airway segments/branches in each generation.

The achieved accuracy did not differ significantly (see below) when comparing the regional bifurcation/nonbifurcation and carina/noncarina accuracy of wall thickness measurements. Note that the difference between Tables II–III and Figs. 10 and 11 is that the averages and deviations in Table II–III were calculated for all surface points in bifurcating/nonbifurcating areas, while those in Fig. 10 and Fig. 11 were calculated across all airway segments/branches in each generation for bifurcating/nonbifurcating areas. The Wilcoxon rank-sum test was performed to compare the errors in the bifurcation/nonbifurcation and carina/noncarina areas (Table IV) and showed that the unsigned errors in the bifurcation/nonbifurcation and carina/noncarina areas were not significantly different ($P = \text{NS}$) except for the carina/noncarina comparison for B35 in generation 7 ($P < 0.05$).

IV. Airway Wall Thickness Assessment in Human *In Vivo* Data

A. Experimental Methods

Once the method's parameters have been optimized in phantoms and the method's performance demonstrated, our double-wall airway tree segmentation method was applied to human *in vivo* MDCT data to demonstrate the general applicability of our method to studies of the airway wall thickness *in vivo*. The analysis included 1992 airway branches from 25 normal nonsmoking human subjects (12 males, ages 20–70) imaged by X-ray MDCT (studied as part of the human lung atlas project NIH HL-064368, approved by the University of Iowa IRB and radiation safety committees). The image sizes varied from $512 \times 512 \times 425$ to $512 \times 512 \times 847$, and the voxel sizes ranged from $0.5 \times 0.5 \times 0.5 \text{ mm}^3$ to $0.73 \times 0.73 \times 0.73 \text{ mm}^3$. Since no independent standard was available—as discussed above—the segmentation correctness was first assessed qualitatively by an expert observer to establish validity of all derived quantitative measurements. It was determined that the algorithm identified both the inner and outer airway wall surfaces without any obvious errors.

The work on *in vivo* segmented airway trees had several goals, namely, to demonstrate the method's ability to obtain the following quantitative relationships in the initial proof-of-concept set of 25 normal human lungs.

1. Airway wall thickness as a function of the airway luminal dimension.
2. Airway wall thickness as a function of the airway tree generation, performed separately in bifurcation/nonbifurcation and in carina/noncarina regions.
3. Airway wall thickness differences in the same branch of the airway tree, calculating the differences for the bifurcation/ nonbifurcation and carina/noncarina regions and reporting by generation.

To calculate the airway wall thickness as a function of the airway dimension, the airway wall thickness was averaged for each location along the airway tree centerline and binned according to the luminal (inner) diameter, in 1 mm intervals. Standard deviation of wall thickness was calculated as a function of the luminal diameter.

In all analyzed airway trees, the bifurcation/nonbifurcation and carina/noncarina regions were first determined as described in Sections III-A1 and Sections III-A2. To obtain a relationship between the wall thickness and generation, all segments belonging to a specific tree generation were grouped and the averages and standard deviations of the generation-based wall thicknesses in all bifurcation/nonbifurcation and carina/noncarina regions were calculated.

To determine the airway wall thickness differences between the bifurcation/nonbifurcation and carina/noncarina regions of the same airway tree branches and thus distinguish between larger and smaller airway segments in the same generation (which is common for the third and higher generations), branch-specific measurements were introduced. Differences of the wall thickness for the same branches were averaged, standard deviations calculated, and reported as a function of the tree generation. Note that this and the previous evaluations differ in that only the same-branch differences contributed to the calculations while the

previous index was based on averaging wall thickness from all segments of the same generation without considering whether or not they belonged to the anatomically-corresponding tree branches. The correspondence between the bifurcating and nonbifurcating areas of the same branches were determined by a depth-first search process. Each straight (nonbifurcating) section was labeled with a unique number, and the bifurcating section following it in the depth-first search was labeled identically. The bifurcating and nonbifurcating areas labeled with the same number were considered as the corresponding areas. More specifically, to compare the wall thickness of the, say, bifurcation and nonbifurcation regions of the same airway branch, the wall thickness was independently averaged for each airway branch in these two surface subsets. The difference of the wall thickness was computed for each pair of the branch-specific bifurcation and nonbifurcation regions and grouped by airway generations. As such, the wall thickness differences are calculated as

$$\Delta WT_{\text{bifurc}} = WT_{\text{nonbifurc}} - WT_{\text{bifurc}}$$

where $WT_{\text{nonbifurc}}$ denotes the average wall thickness of the nonbifurcation regions, and WT_{bifurc} denotes the average wall thickness of the corresponding bifurcation region of the same branch. Carina-specific wall thickness differences are calculated in a similar fashion

$$\Delta WT_{\text{carina}} = WT_{\text{noncarina}} - WT_{\text{carina}}$$

Note that a positive value of ΔWT denotes a thinner wall at the bifurcation (carina) regions compared to that at the nonbifurcation (noncarina) regions. The standard deviations are then computed across all branches of each generation. From the first to eleventh generations, the numbers of analyzed airway segments contributing to each generation were: 25, 50, 94, 171, 326, 472, 367, 224, 138, 82, and 43. Note that the number of branches in each generation is determined by the presegmentation that captures the global topology of the object. If the presegmentation fails to detect certain airway branches, then there is no way for our approach to recover that branch. As long as the presegmentation is able to capture the branch, our approach will work to optimize the boundaries of both surfaces.

To determine, for which generation the bifurcation/nonbifurcation and carina/noncarina regions of the same airway segment differ, a Wilcoxon rank-sum test was used to compare wall thickness values $WT_{\text{nonbifurc}}$ versus WT_{bifurc} and $WT_{\text{noncarina}}$ versus WT_{carina} , respectively; $p = 0.05$ was considered significant.

B. Results—Human in Vivo Data

Fig. 12 shows a 3-D example of the inner and outer surfaces of a typical airway tree segmentation obtained using our approach. The captured wall thickness variations as a function of tree branch generation are clearly visible in the visualized normal human airway tree. Examples of contour positioning on individual image slices are given in Figs. 13 and 14. Note that in some places, the outer wall is barely visible in the original MDCT image data. In Fig. 14, the preliminary segmentation failed to capture the bifurcation of the airway lumen, which is clearly visible as two disconnected dark regions. However, when we search

for both inner and outer surfaces simultaneously in one single optimization process of the graph search, the bifurcation of airway lumen is identified as two disconnected boundaries in the image. It demonstrates that the accuracy of the single-surface presegmentation can be improved by searching for multiple interrelated surfaces simultaneously. In this case, the graph search approach not only delineates the outer surface based on the presegmentation of inner surface, but also improves the delineation of inner surface when searching for two surfaces together.

The measurements and relationships reported below are all based on analyses of the complete airway trees from all 25 available subjects. Fig. 15 gives the observed relationship between the wall thickness and airway inner diameter, mean $\pm$ standard deviation is shown. Fig. 16(a) gives the average and standard deviation values of generation-based wall thickness at the bifurcation and nonbifurcation areas. Similarly, Fig. 16(b) gives generation-based values of the wall thickness in the carina and noncarina regions. Both panels depict a similar trend of the wall thickness behavior, decreasing from the first to the sixth generations. This is of course consistent with the generational decrease of the local diameter. For the seventh to the eleventh generations, for which the airway wall is relatively thin, the wall thickness reaches a plateau. The possible reasons for this finding are discussed in the following section.

Fig. 17(a) shows that the average signed differences of wall thickness in the bifurcation and nonbifurcation regions of the same branches are small. As a result of Wilcoxon rank-sum test, wall thickness differences between the bifurcation/ nonbifurcation regions were statistically significant ($p < 0.05$) for generations 6, 7, 8, and 9. Fig. 17(b) shows the corresponding relationship between the carina and noncarina wall thickness. In carina/ noncarina regions, the wall thickness was statistically different ($p < 0.05$) for generations 1, 4, 5, 6, 7, and 8. The generations, for which the bifurcation/nonbifurcation and/or carina/ noncarina regional wall thickness values differ statistically significantly are marked by asterisks in Fig. 17(a) and (b).

V. Discussion

We have extended the optimal graph search based approaches of [23], [24] to segmenting double surfaces of 3-D airway trees. The method's performance and utility were assessed by accurately segmenting the inner and outer airway tree walls in MDCT-imaged physical phantoms and in *in vivo* MDCT lung images.

The discussion focuses on the following six main areas: 1) methodology extensions, 2) performance evaluation strategy, 3) limitations of the methodology, 4) limitation of the experimental methods, 5) interpretation of the results obtained *in vivo*, and 6) future work.

A. Methodology Extensions

The previous methods for optimal multi-surface segmentation were not well-suited for objects with complex bifurcating topologies, like those associated with intrathoracic airway trees, for which inner and outer wall surfaces should be determined in volumetric CT images for the purposes of wall thickness measurement across the entire tree. We have developed

and reported a nontrivial extension of our earlier approach facilitating wall thickness measurements in clinically important regions of airway bifurcations. The method's parameters were determined in physical phantoms by optimizing its performance in this controlled environment and then applied to a small dataset of 25 *in vivo* normal MDCT images of human lungs to demonstrate its utility for future studies.

Graph construction in bifurcations is one of the main problems that was solved by our new method. By using the medial axes of the presegmented objects, the input image is resampled according to the topology of the preliminary segmentation allowing a new way of graph construction. Even though the airways have complicated tree structures and multiple inter-related surfaces, our proposed resampling scheme is able to extract sufficient information from the image data and construct proper graphs, which were employed for dual-wall airway segmentation. By applying cost functions with directional information, our algorithm successfully obtained highly accurate segmentations of both the inner and outer surfaces of the airway walls. This novel graph construction approach allowed wall-surface pairs to be segmented across bifurcations—resulting in a complete tree segmentation of both wall surfaces.

B. Performance Evaluation Strategy

The designed performance assessment approach first demonstrated that the developed method—if proper parameters are set—is capable of segmenting airway walls and assessing airway wall thickness without measurement bias and with high consistency across generations, within and outside of bifurcations, and for differing reconstruction kernels. Once the parameters were set, the method was applied to human *in vivo* scans to assess airway wall thickness for the entire presegmented airway tree and provide the first available statistical evaluation of wall thickness in bifurcations per generation.

To evaluate our double-surface airway tree segmentation, the surface points were labeled with their associated airway tree generations. The bifurcation regions and relatively smaller carina regions were defined using two different methods [36], [39] for extracting the 3-D medial axes/skeletons of the airway trees. The experimental results on both the bifurcation/nonbifurcation and carina/noncarina areas achieved very good accuracy and zero measurement bias on physical double-wall phantoms. In this context, the employed approach must be understood as a two-step process of training on a phantom (with demonstration that the method works if parameters are properly set) and the trained method is then applied to *in vivo* human CT data.

C. Limitations of Methodology

Our approach requires intersection of the constructed graph with the desired surfaces. This may not always be achievable for two main reasons. 1) Very sharp bifurcation angles may not allow the graph columns to be sufficiently long to allow the correct border to be determined, especially if the a combination occurs of a sharp bifurcation and a presegmentation that too far away from the desired border. While we have not observed such behavior in our human airway tree datasets, this remains a limitation of the proposed approach. 2) Since the reported approach is designed to determine the most appropriate

locations of the wall surfaces and does not have any way to augment object topology, the presegmentation must be topologically correct. In our case, this requires the presegmentation to determine complete airway trees, which is not always the case for a number of reasons, including but not limited to the CT image resolution, partial volume effects, scanner point-spread function, cardiac or even breathing motion, etc. As such, the coverage of the higher-generation airway is typically incomplete and the numbers of higher generation airway segments (above approximately generation six) are decreasing in our reported results. Strictly speaking, this is of course rather a limitation of the available image data and the employed presegmentation approach, not of the graph-based technique reported here.

D. Limitations of Experimental Method

The parameters of our method were optimized on the physical phantom before being applied to human *in vivo* data. The phantom study served as a proof that the method is capable of determining wall surfaces accurately if correct parameters are set. It is important to state that there is no good way to determine proper sets of analysis parameters by training on human airway trees imaged *in vivo* due to a complete lack of a reliable independent standard. Humans are neither very good at identifying complete airway trees nor in accurate identification of the airway wall thicknesses. The manual tracing also suffers from inter- and intra-observer variability. Postmortem histology assessment suffers from its own limitations, most notably specimen shrinkage and typical lack of full three-dimensionality causing a total loss of generational relationships. Therefore, we have elected to construct a physical phantom based on *in vivo* human airway data and image the phantom in a sophisticated way as described above. This said, no phantom is ever going to fully mimic the human *in vivo* anatomy. In our case, other structures like lobar fissures, vascular trees, lymph nodes, and others were not modeled. Additionally, one can argue that it would be useful to perform an independent validation in a phantom or phantoms not used for training the parameters. Still, the main objective of this work *to develop a method applicable to analysis of tree-like double-wall structures* has been fulfilled by the presented study.

E. Interpretation of In-Vivo Results

In the presented proof-of-concept *in vivo* study, the method was applied to 25 normal human datasets, a sizable but still relatively small set of pulmonary MDCT images. The reported results represent the first wall thickness information obtained for airway bifurcations in a generational manner. As stated in the Result section, all segmentations were visually assessed by expert observers and the segmentations were found correct without any obvious errors. The wall thickness analysis on the human *in vivo* data suggested significant differences between wall thickness measures comparing the various airway wall regions. In light of the fact that no true validation *in vivo* was possible in these areas and considering that the employed phantoms did not model lymph nodes and close-proximity vessels, the presented results must be considered preliminary. Nevertheless, since no such differences were detected when analyzing the phantom images with bifurcation wall thicknesses constructed with a more-or-less uniform wall thickness, it is conceivable and likely that the observed wall thickness differences in bifurcations are real and not caused by the method itself. The importance this observation has when correlating endobronchial assessment of

airway remodeling (samples taken) at the airway branch region versus CT airway wall assessment requires further exploration.

Additionally, the wall thickness plateau observed for higher generation airways in Fig. 16 may or may not be real. The limited resolution of the CT scanner (0.5–0.7 mm voxel sizes in all x , y , z directions), the scanner point spread function, and partial volume effects may affect these measurements—we may simply be reaching the scanner ability to discern small differences in wall thickness. While the signed errors of wall thickness did not show any consistent bias for higher generations in the phantom study across all reconstruction kernels, thus increasing the likelihood that the observations may be real, additional larger-size studies will be needed to confirm or disprove these preliminary observations.

Our results provide an example baseline measurement against which others can compare their data. Additionally, when one uses this approach to compare two groups of subjects or the same group longitudinally at different time points, both data sets will have the same limitations and therefore likely the same biases, still allowing the comparisons to be valid as long as the same airway tree branches or similarly distributed branch (sub)trees are compared.

F. Future Work

Further work will need to concentrate on attempting to fully validate the measurements—a very difficult but important next step. It will be necessary to model effects of lymphatic tissues and close-proximity vessels on the airway wall thickness measurements, both along the airway segments and in bifurcations, especially considering that small lymph nodes characteristically are located just outside the airway wall at carina locations.

To demonstrate the method's robustness, future studies need to include larger sets of pulmonary CT data to increase the power of the observed trends of the relationships given in Figs. 15–17. Once applied to population-representative datasets, this approach can be used for building atlases of intrathoracic airway tree morphology across bifurcations, thus contributing information that has not been previously available. Such atlases of normal airway morphology are currently being formed for both genders and for different decades of life.

Future studies also need to include MDCT images from subjects with airway-related pathologies, including severe and non-severe asthma, COPD (including emphysema and chronic bronchitis), cystic fibrosis, bronchial associated cancer, alterations associated with lung transplantation, geometric differences in premature birth, alterations associated with environmental exposures, etc.

Importantly, the future studies can benefit from the existence of the novel approach reported in this work. This method and its demonstrated performance evaluation in bifurcations are a valuable contribution to performing such studies.

VI. Conclusion

To summarize, the proposed segmentation method now allows for the separate measurements of the airway wall thickness in the bifurcation and carina regions of the airway trees using a globally optimal approach. The quantification of wall properties in bifurcations offers an effective basis for novel disease-specific studies of the intrathoracic airway tree morphology and function. Our method is general and can be applied to segmenting other complex objects with multiple inter-related surfaces in 3-D and higher-D images.

Acknowledgments

This work was supported in part by the National Science Foundation (NSF) under Grant CCF-0515203, Grant CCF-0830402, Grant CCF-0844765, Grant CCF-0916606, and Grant CCF-1217906; in part by the National Institutes of Health (NIH) under Grant R01-EB004640, Grant R01-HL64368, and Grant K25-CA123112; and in part by the Faculty Research Program of the University of Notre Dame. The work of X. Liu was supported in part by a graduate fellowship from the Center for Applied Mathematics, University of Notre Dame.

References

1. Hoffman EA, Simon BA, McLennan G. State of the art. a structural and functional assessment of the lung via multidetector-row computed tomography: Phenotyping chronic obstructive pulmonary disease. *Proceedings of the American Thoracic Society*. 2006; 3:519–532. [PubMed: 16921136]
2. Coxson HO. Quantitative computed tomography assessment of airway wall dimensions: Current status and potential applications for phenotyping chronic obstructive pulmonary disease. *Proceedings of the American Thoracic Society*. 2008; 5:940–945. [PubMed: 19056721]
3. Coxson HO, Rogers RM. Quantitative computed tomography of chronic obstructive pulmonary disease. *Academic Radiology*. 2005; 12:1457–1463. [PubMed: 16253858]
4. Pua J, Gu S, Liu S, Zhu S, Wilson D, Siegfried JM, Gur D. CT based computerized identification and analysis of human airways: a review. *Medical Physics*. 2012; 39:2603–2616. [PubMed: 22559631]
5. Aysola RS, Hoffman EA, Gierada D, Wenzel S, Cook-Granroth J, Tarsi J, Zheng J, Schechtman KB, Ramkumar TP, Cochran R, Xueping E, Christie C, Newell j, Fain S, Altes TA, Castro M. Airway remodeling measured by multidetector ct is increased in severe asthma and correlates with pathology. *Chest*. 2008; 134:1183–1191. [PubMed: 18641116]
6. Nakano, y. Quantitative assessment of airway remodeling using high-resolution CT. *Chest*. 2002; 122:271s–275s. [PubMed: 12475796]
7. Warheit DB, Hartskey MA, Plopper CG. Regional alveolar deposition patterns of inhaled particles are dependent upon airway branching patterns. *Ann. Occup. Hyg.* 1994; 38:55–61.
8. Schlesinger RB, Lippmann M. Selective particle deposition and bronchogenic carcinoma. *Environmental Research*. 1978; 15:424–431. [PubMed: 679903]
9. Xia G, Tawhai MH, Hoffman EA, Lin CL. Airway wall stiffening increases peak wall shear stress: A fluid-structure interaction study in rigid and compliant airways. *Ann Biomed Eng.* 2010; 38:1836–1853. [PubMed: 20162357]
10. Wood SA, Zerhouni EA, Hoford JD, Hoffman EA, Mitzner W. Quantitative 3-D reconstruction of airway and pulmonary vascular trees using HRCT. *Biomedical Image Processing and Biomedical Visualization, Proceedings SPIE*. 1993; 1905:316–323. SPIE.
11. Sonka, M.; Sundaramoorthy, G.; Hoffman, EA. Physiology and Function from Multidimensional Images, *Proceedings SPIE*. Vol. 168. Bellingham, WA: SPIE; 1994. Knowledge-based segmentation of intrathoracic airways from multidimensional high resolution CT images; p. 73-85.
12. Sonka M, Park W, Hoffman EA. Rule-based detection of intrathoracic airway trees. *IEEE Transaction on Medical Imaging*. 1996; 15(3)

13. Park W, Hoffman EA, Sonka M. Segmentation of intrathoracic airway trees: A fuzzy logic approach. *IEEE Transactions on Medical Imaging*. 1998; 17:489–497. [PubMed: 9845305]
14. Aykac D, Hoffman EA, McLennan G, Reinhardt JM. Segmentation and analysis of the human airway tree from three-dimensional X-ray CT images. *IEEE Transaction on Medical Imaging*. 2003; 22(8):940–950.
15. Fetita CI, Preteux F, Beigelman-Aubry C, Grenier P. Pulmonary airways: 3-D reconstruction from multislice CT and clinical investigation. *IEEE Transaction on Medical Imaging*. 23(11):1353–1364. 2004.
16. Amirav I, Krammer SS, Grunstein MM, Hoffman EA. Assessment of methacholine-induced airway constriction by high-resolution cine computed tomography (hrcct). *Journal of Applied Physiology*. 75(5):2239–2250. [PubMed: 8307884]
17. Saba OI, Hoffman EA, Reinhardt JM. Maximizing quantitative accuracy of lung airway lumen and wall measures obtained from X-ray CT imaging. *Journal of Applied Physiology*. 95(3):1063–1075. [PubMed: 12754180]
18. Estepar RSJ, Washko GG, Silverman EK, Reilly JJ, Kikinis R, Westin C. Accurate airway wall estimation using phase congruency. *Medical Image Computing and Computer-Assisted Intervention*. 2006:125–134. [PubMed: 17354764]
19. Tschirren J, Hoffman EA, McLennan G, Sonka M. Intrathoracic airway trees: Segmentation and airway morphology analysis from lowdose CT scans. *IEEE Transaction on Medical Imaging*. 2005; 24(12)
20. Kiraly AP, Odry B, Naidich DP, Novak CL. Boundary-specific cost functions for quantitative airway analysis. *Medical Image Computing and Computer Assisted Intervention* 2007. 2007:784–791.
21. Odry B, Kiraly A, Slabaugh G, Novak CL, Naidich DP, Lerallut JF. Active contour approach for accurate quantitative airway analysis. *Proceedings of SPIE Medical Imaging 2008: Physiology, Function, and Structure From Medical Images*. 2008; 6916:691613.
22. Saragaglia, A.; Fetita, C.; Brillet, PY.; Preteux, F.; Grenier, PA. Airway wall thickness assessment: A new functionality in virtual bronchoscopy investigation. In: Manduca, A.; Hu, XP., editors. *Proc. of SPIE Medical Imaging 2007: Physiology, Function, and Structure From Medical Images*. Vol. 6511. 2007. p. 65110P
23. Wu X, Chen DZ. Optimal net surface problems with applications. *Proc. of the 29th International Colloquium on Automata, Languages and Programming*. 2002:1029–1042.
24. Li K, Wu X, Chen DZ, Sonka M. Optimal surface segmentation in volumetric images—A graph-theoretic approach. *IEEE Transactions on Pattern Analysis and Machine Intelligence*. 2006; 28(1): 119–134. [PubMed: 16402624]
25. Hochbaum D. A new-old algorithm for minimum cut in closure graphs. *Networks*. 2001; 37(4): 171–193.
26. Picard J. Maximal closure of a graph and applications to combinatorial problems. *Management Science*. 1976; 22:1268–1272.
27. Yin Y, Zhang X, Williams R, Wu X, Anderson DD, Sonka M. LOGISMOS—Layered optimal graph image segmentation of multiple objects and surfaces: Cartilage segmentation in the knee joint. *IEEE Trans. Med. Imaging*. 2010; 29(12):2023–2037. [PubMed: 20643602]
28. Petersen J, Nielsen M, Lo P, Saghir Z, Dirksen A, de Bruijne M. Optimal graph based segmentation using flow lines with application to airway wall segmentation. *Information Processing in Medical Imaging*. 2011:49–60. [PubMed: 21761645]
29. Balashazy I, Hofmann W, Heistracher T. Local particle deposition patterns may play a key role in the development of lung cancer. *Journal of Applied Physiology*. 2003; 94(5):1719–1725. [PubMed: 12533493]
30. Avila RS, Zulueta JJ, Shara NM, Jansen K, Veronesi G, Wang H, Mulshine JL. A quantitative method for estimating individual lung cancer risk. *Academic Radiology*. 2010; 17(7):830–840. [PubMed: 20540908]
31. Ellis, H. *Clinical Anatomy: A Revision and Applied Anatomy for Clinical Students*. 10th ed.. Blackwell: 2002.

32. Liu, X.; Chen, DZ.; Wu, X.; Sonka, M. Optimal graph search based image segmentation for objects with complex topologies. In: Pluim, JP.; Dawant, BM., editors. Proc. of SPIE Medical Imaging 2009: Image Processing. Vol. 7259. 2009. p. 725915paper
33. Liu X, Chen DZ, Tawhai M, Hoffman E, Sonka M. Measurement, evaluation, and analysis of wall thickness of 3D airway trees across bifurcations. Proc. of Second International Workshop on Pulmonary Image Processing. 2009:161–171.
34. Attali, D.; Boissonnat, JD.; Edelsbrunner, H. Stability and computation of medial axes: A state of the art report. In: Möller, BHT.; Russell, B., editors. Mathematical Foundations of Scientific Visualization, Computer Graphics, and Massive Data Exploration. Springer-Verlag, Mathematics and Visualization; 2007.
35. Lorensen WE, Cline HE. Marching cubes: A high resolution 3D surface construction algorithm. SIGGRAPH. 1987:163–169.
36. Dey TK, Sun J. Normal and feature approximations from noisy point clouds. Proc. of Foundations of Software Technology and Theoretical Computer Science. 2006:21–32.
37. Sonka, M.; Hlavac, V.; Boyle, R. Image Processing, Analysis, and Machine Vision. 3rd.. Toronto, Canada: Thomson Engineering; 2008. (1st edition Chapman and Hall, London, 1993; 2nd edition PWS Pacific Grove, CA, 1997)
38. Sonka M, Reddy GK, Winniford MD, Collins SM. Adaptive approach to accurate analysis of small-diameter vessels in cineangiograms. IEEE Trans. Med. Imag. 1997; 16(2):87–95.
39. Lee TC, Kashyap RL, Chu CN. Building skeleton models via 3-D medial surface/axis thinning algorithms. Computer Vision, Graphics, and Image Processing. 1994; 56(6):462–478.
40. Hoffman EA. Effect of body orientation on regional lung expansion: A computed-tomographic approach. Journal of Applied Physiology. 1985; 59:468–480. [PubMed: 4030599]

(a)

(b)

Fig. 1. Illustrating complex airway tree structure. (a) Original MDCT image. (b) Rendered airway tree presegmentation.

Fig. 2. Possible graph construction problems. (a) Column lengths are too short to capture the true surface. (b) Column lengths are too long and columns interfere with each other. The solid curves represent the presegmented surface, and the dashed curves represent the true surface.

Fig. 3. Image resampling and graph construction. (a) Interferences caused by inappropriate column lengths introduce disordered structures in the constructed graph. (b) 2-D example of image resampling based on medial axes to obtain columns with no interference.

Fig. 4.
Illustrating the poles v_{p1}, v_{p2} .

(a)

(b)

Fig. 5. Inner and outer medial axes of a bifurcating object in 3-D. (a) Inner medial axes. (b) Outer medial axes.

Fig. 6. Piecewise linear function depicting weights w of the cost function as a function of the presegmented luminal diameter. Parameters of this function were determined in phantoms and employed for the analysis of *in vivo* human CT data.

Fig. 7.
Cost function values are computed for each node of the graph.

(a)

(b)

Fig. 8.

Airway trees with identified bifurcation and carina regions. The bifurcation and carina areas are colored in red while the nonbifurcation and noncarina areas are colored differently according to their generations. (a) Airway tree with identified bifurcation regions. (b) Airway tree with identified carina regions.

Fig. 9.
2-D slice example from a CT scan of the double-wall phantom. The manufactured double-wall-surface phantom was placed in a chest phantom and surrounded by potato flakes to maximally resemble human lungs when imaged by X-ray CT.

Fig. 10.

Wall thickness signed errors for all scans of the double-wall phantoms reconstructed with kernels B30, B35, and B50. The standard deviation was computed for all airway segments in the same generations of the three scans. Signed errors and their standard deviations are shown for (a) bifurcation/nonbifurcation regions of the three scans with reconstruction kernel B30; (b) carina/noncarina regions, kernel B30; (c) bifurcation/nonbifurcation regions, kernel B35; (d) ca-rina/noncarina regions, kernel B35; (e) bifurcation/nonbifurcation regions, kernel B50; (f) carina/noncarina regions, kernel B50. Note that for the last generation (the ninth one), there is no associated bifurcation/carina areas.

(a)

(b)

(c)

(d)

(e)

(f)

Fig. 11.

Wall thickness unsigned errors for all scans of the double-wall phantoms reconstructed with kernels B30, B35, and B50. The standard deviation was computed for all airway segments in the same generations of the three scans. Unsigned errors and their standard deviations are shown for (a) bifurcation/nonbifurcation regions of the three scans with reconstruction kernel B30; (b) carina/noncarina regions, kernel B30; (c) bifurcation/nonbifurcation regions, kernel B35; (d) carina/noncarina regions, kernel B35; (e) bifurcation/nonbifurcation regions, kernel B50; (f) carina/noncarina regions, kernel B50. Note that for the last generation (the ninth one), there is no associated bifurcation/carina areas.

Fig. 12.

Airway segmentation. (a) Partial results of the reconstructed inner wall from lumen presegmentation (above) and double surface segmentation resulting from the graph search. (b) Double surface segmentation of the entire airway tree. Note that the inner as well as the outer surfaces appear smooth and three-dimensionally accurate across the airway branches.

Fig. 13.

2-D contour examples of 3-D segmented inner and outer wall surfaces. (a) Original image. (b) Preliminary segmentation. (c) Our graph search result shows an accurate segmentation of the outer wall as well as improved delineation of the inner wall. Note the ability to correctly detect the airway wall surfaces even if the preliminary segmentation was locally quite inaccurate—as long as the preliminary segmentation remains in the vicinity of the desired surfaces (pointed by arrow). Our method is able to move far away from the preliminary segmentation, and possibly correct the errors of presegmentation.

Fig. 14.

Double wall segmentation around bifurcations. (a) The original image; (b) the segmentation results using inappropriate (fixed) column lengths; (c) the segmentation results using column lengths determined by medial axes. The arrows in (c) point at the positions where our method correctly segments the outer wall, but the method using fixed column lengths produces two surfaces crossing each other in (b).

Fig. 15.

Wall thickness as a function of the inner wall diameter. The result shown is the average of all local measurements from 25 human *in vivo* MDCT scans. The airway diameters were binned in 1 mm intervals and the standard deviation of the wall thickness is shown corresponding to the respective bins.

(a)

(b)

Fig. 16.

Wall thickness as a function of airway tree branch generation. (a) Average wall thickness in the bifurcation/nonbifurcation regions. (b) Average wall thickness in the carina/noncarina regions. Error bars depict standard deviations. Note that for the eleventh generation, no associated bifurcation/carina regions exist.

Fig. 17.

Wall thickness differences ΔWT between the bifurcation/nonbifurcation and carina/noncarina regions of the anatomically corresponding airway tree branches (also grouped by generation). (a) Average wall thickness differences ΔWT_{bifurc} between the bifurcation and nonbifurcation regions. (b) Average wall thickness differences ΔWT_{carina} between the carina and noncarina regions. Error bars depict standard deviations across all airway branches of a specific generation. Statistically significant differences of airway wall thickness contributing to the depicted values are marked by asterisks (*).

TABLE I

Wall thickness statistics for the physical phantom

Gen.	Mean [mm]	SD [mm]	Min [mm]	Max [mm]
1	2.36	0.12	2.04	2.69
2	1.73	0.31	0.97	2.45
3	1.30	0.13	0.84	1.76
4	1.25	0.16	0.46	2.84
5	0.96	0.16	0.11	1.54
6	0.90	0.19	0.05	1.36
7	1.09	0.16	0.60	2.82
8	0.83	0.18	0.42	2.99
9	0.82	0.10	0.33	1.20

TABLE II Mean wall thickness signed errors for a double-surface bifurcating phantom

	Non-bifurcation [mm]	Bifurcation [mm]	Non-carina [mm]	Carina [mm]
B30	-0.01 ± 0.24	0.01 ± 0.19	-0.01 ± 0.24	0.02 ± 0.17
B35	-0.08 ± 0.24	-0.05 ± 0.19	-0.09 ± 0.24	-0.05 ± 0.16
B50	0.03 ± 0.23	0.06 ± 0.18	0.03 ± 0.23	0.07 ± 0.16

TABLE III Mean wall thickness unsigned errors for a double-surface bifurcating phantom

	Non-bifurcation [mm]	Bifurcation [mm]	Non-carina [mm]	Carina [mm]
B30	0.18 $\pm$ 0.16	0.16 $\pm$ 0.12	0.17 $\pm$ 0.16	0.19 $\pm$ 0.11
B35	0.19 $\pm$ 0.16	0.16 $\pm$ 0.12	0.18 $\pm$ 0.17	0.19 $\pm$ 0.11
B50	0.18 $\pm$ 0.15	0.17 $\pm$ 0.13	0.18 $\pm$ 0.15	0.20 $\pm$ 0.11

p-values of the wilcoxon rank-sum test of unsigned wall thickness errors in the bifurcation/nonbifurcation and carina/noncarina regions. (The ninth generation is excluded as there are no corresponding bifurcation/carina regions available for the highest generation branches). Note that the unsigned wall thickness errors were not significantly different across the paired regions, except for the carina/noncarina comparison for B35 in generation 7

TABLE IV

p-value at generation	1	2	3	4	5	6	7	8
Reconstruction kernel B30								
Non-bifurcation vs. bifurcation	0.10	0.82	0.48	0.13	0.24	0.31	0.39	0.39
Non-carina vs. carina	0.10	0.82	0.70	0.67	0.60	0.94	0.09	0.48
Reconstruction kernel B35								
Non-bifurcation vs. bifurcation	0.10	0.82	0.31	0.29	0.06	0.39	0.13	0.39
Non-carina vs. carina	0.10	0.82	0.24	0.44	0.58	0.82	0.004	1
Reconstruction kernel B50								
Non-bifurcation vs. bifurcation	0.10	0.82	0.70	0.31	0.28	1	0.82	0.69
Non-carina vs. carina	0.10	0.70	0.09	0.08	0.35	0.94	0.13	0.69