Computer Analysis of Computed Tomography Scans of the Lung: A Survey

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***Abstract*—Current computed tomography (CT) technology allows for near isotropic, submillimeter resolution acquisition of the complete chest in a single breath hold. These thin-slice chest scans have become indispensable in thoracic radiology, but have also substantially increased the data load for radiologists. Automating the analysis of such data is, therefore, a necessity and this has created a rapidly developing research area in medical imaging. This paper presents a review of the literature on computer analysis of the lungs in CT scans and addresses segmentation of various pulmonary structures, registration of chest scans, and applications aimed at detection, classification and quantification of chest abnormalities. In addition, research trends and challenges are identified and directions for future research are discussed.**

***Index Terms*—Airway disease, chest, computer-aided diagnosis, CT, emphysema quantification, interstitial lung disease, literature review, literature survey, lung cancer, nodule characterization, nodule detection, nodule size measurements, pulmonary embolism, registration, segmentation.**

I. Introduction

ANN	Artificial neural network.
A_z	Area under the ROC curve.
BI	Bullae index.
BO	Bronchiolitis obliterans.
CAD	Computer-aided detection/diagnosis.
CBIR	Content-based image retrieval.
CLE	Centrilobular emphysema.
COPD	Chronic obstructive pulmonary disease.
CT	Computed tomography.
CTA	CT angiography.
DPLD	Diffuse parenchymal lung disease.
EC	Explosion controlled region growing.
FN	False negative.
FDA	Food and Drug Administration.
FP	False positive.
GG	Ground glass.
HIST(x)	Lowest x-th percentile of the histogram.
HRCT	High-resolution computed tomography.
HU	Hounsfield unit.
ILD	Interstitial lung disease.
IPF	Idiopathic pulmonary fibrosis.
PF	Pulmonary function tests.
LAA	Low attenuation area(s).
LDC	Linear discriminant classifier.
LVRS	Lung volume reduction surgery.
MC	Metastatic calcification.
MLD	Mean lung density.
pCa	Probability of cancer.
PCP	Pneumocystis carinii pneumonia.
PE	Pulmonary embolism.
PET	Positron emission tomography.
PF	Pulmonary function.
PI	Pixel index.
PLE	Panlobular emphysema.
PSE	Paraseptal emphysema.
PVE	Partial volume effect.
SPECT	Single photon emission computed tomography.
ROC	Receiver operating characteristic.
ROI	Region of interest.
TN	True negative.
TP	True positive.
UIP	Usual interstitial pneumonia.
VOI	Volume of interest.

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II. Introduction

COMPUTED tomography (CT) for the body has been available since 1975. Originally, CT was not considered a technique particularly well suited for the thorax. Low resolution resulted in large partial volume effects (PVEs) and the large difference in attenuation values between tissue and air (currently a main reason for the effectiveness of CT in thoracic imaging) made it difficult to correctly interprete small lesions. In 1977, Kollins [1] concluded that CT had revolutionized neuroradiology and its impact in abdominal and pelvic imaging had been similarly great but "the ultimate role of computed tomography in the study of diseases of the chest is not as certain."

Technical strides forward have since completely transformed CT and thoracic imaging with it. Early on, the essential role of image processing was recognized, for example in the work on the Mayo Clinic's dynamic spatial reconstructor [2]. Two advances in particular have had the most repercussions for CT of the chest. About twenty years ago, improved axial resolution made HRCT scans possible. Slices of 1 mm thick could provide anatomical detail of the lungs similar to that available from gross pathological specimens [3]. However, scanner speed limitations at the time meant that a 1-cm gap between slices was necessary to cover the entire thorax while avoiding breathing artifacts. This limitation has been effectively removed in the last

decade with the advent of multi-detector-row scanners that can acquire up to 64 1-mm slices simultaneously per rotation and perform each rotation in less than a second. Present day scanners allow for isotropic acquisition of the complete chest with submillimeter resolution well within a single breath hold. Compared to other modalities, CT excels in the imaging of the lungs.

A major challenge accompanying these spectacular improvements is dealing with the enormous increase in images that are generated and have to be reported on. This challenge has been coined the *data explosion* by Rubin [4]. It is becoming clear that computer vision techniques are essential to facilitate CT interpretation. As a consequence, the rapid developments in chest CT acquisition techniques have been followed by a sharp increase in research on computer analysis of thoracic CT scans.

This paper aims to provide an overview of the literature on computer analysis of CT images of the human lungs. For our purposes here, we define this area as including segmentation of various pulmonary structures (Section II), registration of chest scans (Section III), and applications aimed at detection, classification and quantification of chest abnormalities (Section IV).

The work on segmentation can be further subdivided into segmentations of the complete lung fields (Section II-A), the bronchial tree (Section II-B), the vascular tree (Section II-C) and the lung lobes (Section II-D). Application areas involve emphysema (Section IV-A), lung cancer (Section IV-B1, IV-B2, IV-B3), Pulmonary embolisms (PEs) (Section IVC), (bronchial) signs of airway diseases (Section IV-D), and differential diagnosis of lung disease (Section IV-E).

The survey covers the period 1999–2004, but relevant work before 1999 has been included as well. Details of the literature collection procedure can be found in the Appendix. Studies on reconstruction algorithms, scans parameters and image quality improvement, and visualization techniques have been excluded, except for some studies that pertain particularly to chest CT. There is a large body of work on virtual bronchoscopy. Work on image analysis in this field, mainly about airway segmentation, has been included. Studies that focus on the application of such techniques and on effective visualization are considered outside the scope of this survey.

In terms of methodology, most reviewed works employ standard image processing techniques, such as filtering, region growing and connected component analysis, mathematical morphology, etc. which can be found in standard textbooks, e.g., [5] and [6]. A large number of studies investigates the detection and classification of abnormalities. This field is often referred to as computer-aided detection or diagnosis (CAD). The typical set-up of a CAD system is preprocessing, segmentation, candidate extraction, feature extraction, and classification. The first four steps are usually considered to be part of image processing. The final classification step deals with patterns that are represented as points in a feature space. Finding decision boundaries in these vector spaces is a central problem in pattern recognition theory. Popular techniques such as ANNs or LDCs can be found in many textbooks, e.g., [7] and [8].

III. Segmentation

Segmentation is often a necessary first step to computer analysis. In CT of the lungs, the various anatomical entities that can require segmentation are the lungs themselves, the airways, the vessels and the lung lobes. Each of these is discussed in more detail in the following subsections.

A. Lung Segmentation

Any computer system that analyzes the lungs and does not work on manually delineated regions of interest must incorporate an automatic lung segmentation. Armato and Sensakovic [9] illustrated the importance of accurate segmentation as a preprocessing step in a CAD scheme. In a nodule detection setting, they showed that 5% –17% of the lung nodules in their test data was missed due to the preprocessing segmentation, depending on whether or not the segmentation algorithm was adapted specifically to the nodule detection task.

As the lung is essentially a bag of air in the body, it shows up as a dark region in CT scans. This contrast between lung and surrounding tissues forms the basis for the majority of the segmentation schemes. Most of the methods are rule-based [9]–[14]. The main lung volume is found in one of two ways. Gray-level thresholding and component analysis can be used, after which the objects that are the lungs are identified by imposing restrictions on size and location. Alternatively, the volume is found by region growing from the trachea. The trachea itself is found by searching for two-dimensional (2-D) circular air-filled regions in the first slices of the scan, or by searching for a three-dimensional (3-D) tubular air-filled object located centrally in the top half of the scan. After identification of the combined lung and airway volume, separation of left and right lung and removal of the trachea and mainstem bronchi are performed. This is followed by morphological processing to obtain lung volumes without holes and with smooth borders. Li and Reinhardt [15] have taken a statistical rather than rule-based approach. A 3-D active shape model provided an approximate segmentation of a single lung and was combined with multiple 2-D refinements by snakes to capture fine details and shape variance not present in the statistics of the training data.

Often it remains unclear at what points the segmentations are supposed to cut through the major bronchi and vessels in the hilar area where they enter the lung. Manual delineations also show much variance around the hilum, depending on definitions (or a lack thereof) and personal preferences with respect to smoothness. Ukil and Reinhardt[16] used a segmentation of the bronchial tree to improve their lung segmentation in this region.

Other parts of the segmentation requiring special attention are the posterior and anterior junctions between left and right lung. These junctions can be very narrow and consequently of low contrast due to the PVE. The common solution to this problem is to heuristically define a search region in each affected axial slice and identify a separating junction line inside it. The line is either defined as a shortest distance in anterior-posterior direction [12]–[14], or the soft tissue interface is traced by searching for a minimum cost path through the gray values [9]–[11].

A challenge that has not yet been met is the segmentation of lungs affected by high density pathologies that are connected to the lung border. Due to a lack of contrast between lung and surrounding tissues, rule-based thresholding methods will fail to segment these pathological parts of the lung. The statistical method in [15] employed a shape model and should, therefore, be

more robust against pathology, but it was not tested on such scans. Sluimer *et al.* [17] proposed registration with a presegmented reference scan. Another approach could be to identify surrounding structures, such as the rib cage and the diaphragm, and combine those algorithms into a comprehensive segmentation scheme.

Apart from the segmentation of scans containing pathology, another direction of research that should be focused on are the incorporation of user-feedback in automatic systems or alternatively the development of user-interactive segmentation tools, as well as the implementation of automatic means of failure detection. In clinical practice, it is often most important to know when the automatic algorithm failed without having to review every segmentation result, and to be able to quickly improve the result without having to resort to complete manual delineation.

B. Segmentation of Airways

The airways exhibit a tree structure (the tracheobronchial tree) of roughly cylindrical branches of decreasing radius. The trachea bifurcates into the left and right main bronchus. These bronchi repeatedly bifurcate (or trifurcate) into smaller bronchi, up to the 23th generation [18]. The bronchial lumen is (normally) filled with air, surrounded by the bronchial wall which has a relatively high CT value.

On a normal dose CT scan, an expert might trace bronchi up to generation 7. After that, the PVE is too severe, smearing lumen and bronchus wall into an indistinguishable mass. In the last decade, a number of methods have been proposed to (semi) automatically segment the tracheobronchial tree [19]–[33]. Based upon such segmentations, computerized schemes have been developed to label the different bronchi such that branches with problems can be pinpointed anatomically [22], [34], [35]. There are also a number of schemes proposed to measure the geometrical properties of the bronchi at user given locations [36]–[38], which can be used to diagnose a number of respiratory diseases (see also the small overview of semi-automated measurements of airway dimensions given by Müller and Coxson [39]).

The proposed methods for airways segmentation can be split up into four main strategies: *(i)* knowledge-based segmentation [19], [20]; *(ii)* region growing/wave propagation [19], [20], [22], [25], [27]–[33], [40]; *(iii)* centreline extraction [23], [24], [26]; *(iv)* mathematical morphology [25], [41], [42]. Indeed, many of the proposed schemes combine two or more of these strategies.

An example of the region growing/wave propagation strategy is explosion controlled region growing (EC), first introduced by Mori *et al.* [43], and used in [22], [25], [28]. EC is an iterative region growing process with increasing threshold value until the total number of voxels grown increases too much in one iteration step.

Mathematical morphology methods focus more on identifying regions that might be part of the airways. For example Aykac *et al.* [42] used 2-D gray-scale reconstruction (gray-scale closings with increasing kernel size) to find gray-scale valleys.

In Table I, the different studies on tracheobronchial tree segmentation are listed. The items in the table include a description of the data (number of scans, slice thickness, and radiation dose), a short description of the algorithm, whether the method is automatic or needs manual seed points, if it is a fully 3-D model, and the reported performance.

From Table I it is apparent that proper validation of the models and a good description of the data used is not always covered in the articles. It appears that humans outperform the discussed segmentation algorithms. Furthermore, reported calculation times range from several minutes up to one hour per scan, depending on the comprehensiveness of the segmentation. Clearly, improved performance of automatic segmentation is still wanted.

More challenges lie ahead in the segmentation of pathological and low-dose scans. The problems to overcome are twofold: leakage and obstructions. The source of these problems might be artificial (noise, heart movement, high-density implants, PVE) or real (mucus, pathology). As Table I shows, only the work of Tschirren *et al.* [32] was validated for low-dose and severe pathology, for which they reported encouraging results.

C. Segmentation of Vessels

Each lung contains an arterial and a venous vessel tree. Where the pulmonary arteries and veins enter the lungs, their diameter can be up to 30 mm. As they branch, vessel diameters decrease. On a normal CT scan vessels can be seen up to 5–10 mm from the pleura. The arteries follow the course of the bronchial tree (when the bronchial wall is thickened, bronchus and artery have the appearance of a signet ring).

A segmentation of the vessel trees can be of interest for matching follow-up scans and to remove FPs of CAD schemes, for example in the case of nodule detection (see Section IV-B1). Conversely, vessel segmentation can provide a VOI for abnormalities that occur inside the vessels, e.g., PEs (see Section IV-C). For the latter task, contrast material is administered, which can make the vessel segmentation task easier.

The number of studies on pulmonary vessel segmentation is limited. Shikata *et al.* [45] enhanced the vessels with a filter based on the Hessian tensor [21] that responds to bright elongated structures. Different filter scales were used depending on the distance to the chest wall. The filtered data was thresholded to provide a first segmentation. Seed points on vessel centerlines were used to initialize a tracking algorithm also based on the local Hessian tensor that could detect bifurcations that may be missed by the vessel filter. In an experiment on five normal scans, the method showed high sensitivity compared to manual labelings, but specificity was not evaluated. Wu *et al.* [46] did not use elongatedness to obtain a first segmentation, but instead employed a locally adaptive threshold. Regulated morphological processing was applied to obtain a representation of the segmented structures in terms of fuzzy spheres which were connected by a tracking algorithm. Only the robustness to noise was evaluated. Kiraly *et al.* [47] presented a vessel tree segmentation algorithm with the aim of segmenting the arterial subtree distal to a site of PE. A fixed threshold and removal of small structures was used to obtain an initial segmentation. The plane perpendicular to the embolism was determined. In a VOI located distal from this plane, a tree was extracted by skeletonization. Rules for branch sizes and branching angles were used to remove false branches and separate connected subtrees. The output of the algorithm is the volume of the lung affected by PE. The same group of authors used a similar vessel segmentation to visualize the densities inside the vessel which can be useful for radiological evaluation of

TABLE I
STUDIES ON TRACHEOBRONCHIAL TREE SEGMENTATION. FOR EACH STUDY, THE NUMBER (#) OF SCANS USED AND THEIR SLICE THICKNESS (mm) IS GIVEN. THE METHOD IS BRIEFLY DESCRIBED AND IT IS STATED WHETHER IT IS 2-D OR 3-D, AND IF A MANUAL SEED IS NEEDED (AUTO). PERFORMANCE REPORTS THE EVALUATION METHOD AND THE RESULTS

Study	#	mm	Method	2/3D	Auto	Performance
Sonka et al. [19]	5	3	lung segmentation, region grow, rule-based candidate detection	2/3D	—	count branches; TP = 68.5%, FP=11.5%
Park et al. [20]	5	3	lung segmentation, region grow, fuzzy-logic candidate detection	2/3D	—	count branches; TP = 69.1%, FP=8.8%
Sato et al. [21]	1	1	cropping, threshold, slice interpolation, multi-scale line filtering, threshold, connected components	3D	—	count centreline points; ROC-curve higher than without line filtering
Mori et al. [22]	14	2/5	EC, thinning, rule-based FP removal	3D	Y	count branches; 67% detected, 85% of $\leq 4^{th}$
Deschamps and Cohen [23]	1	—	calculate minimal path between 2 points	3D	N	path found
Aylward and Bullitt [24]	1	—	dynamic ridge traversal	3D	N	looks good
Fetita and Prêteux [41]	15	1.25	window, morphological filtering, energy minimization controlled growth	3D	—	count branches; segmented $< 6^{th}$
Kiraly et al. [25]	33	1.3	median filter, lung segmentation, EC, 2D dilation	2/3D	N	count branches, compare to EC; more TP, more FP
Schlathölter et al. [40]	1	—	front propagation, monitor branching and leakage	3D	N	count branches; 3^{rd} 100%, 4^{th} 90%, 5^{th} 60%, 6^{th} 25%
Swift et al. [26]	13	3	fit sphere, detect branching, fit centreline, fit 2D outlines	2/3D	N	compare centreline to manual; mean coordinate difference 2.21 ± 0.38 voxels.
Tschirren et al. [27]	4	0.7	region grow similar intensities, thinning, find branchpoints	3D	Y	match branchpoints to manual; 85 and 89% matches
Aykac et al. [42]	8	3	average, closed space dilations, gray-scale closings	2/3D	Y	count branches; 73% detected (most of $\leq 2^{nd}$)
Kitasaka et al. [28]	3	2	EC, VOI extraction, edge enhancement	3D	—	count branches; 4^{th} 82%, 5^{th} 49%, 6^{th} 20%
Palagyi et al. [35]	33	—	binary tree, fill holes, root detection, thinning, FP removal, find branchpoints, label branches	3D	—	looks good
Yu et al. [29]	—	—	Wan et al. [44] (sigma filter, region growing, fill holes, graph representation, removal of FP), interactive correction	3D	N	looks good
Mayer et al. [30]	22	1.25	region grow (3 states), wave propagation with fuzzy logic, template matching	2/3D	—	count branches; Sensitivity: 3^{rd} 98%4^{th} 94%, 5^{th} 80%, 6^{th} 53%
Singh et al. [31]	—	—	region grow (3 states), information gain increase to accept uncertain voxels	3D	N	compare to manual; segmentations are closely correlated
Tschirren et al. [32]	33	—	place VOI, multi-seeded fuzzy connectivity, monitor leaks, find next VOIs	3D	—	compare to region grow; new: better 9, 21 equivalent, 3 worse
Zidowitz et al. [33]	—	0.7	auto threshold region grow, graph representation, extend tree by template matching and anatomical model	2/3D	Y	simulate ventilation; expected regional effects detected

scans that may contain PE [48]. In the design of CAD systems to detect PE, several vessel segmentation procedures are briefly described [49], [50] but these are not specifically evaluated.

One of the main future challenges is the automatic separation of arterial and venous trees. Furthermore, algorithms need to be validated on larger data sets and their robustness in the presence of pathology and noise is yet unclear.

D. Lobar Segmentation

Lungs consists of distinct anatomical compartments called lobes. The left lung contains two lobes, and the right lung three. The lobes are separated by fissures, which are thin sheets of tissue. The major and minor fissures separate the lobes and are visible on thin-slice CT. Lobar segmentation and fissure detection are, however, not equivalent: The major and minor fissures can be incomplete, while at the same time other, accessory fissures can be visible [51], [52]. Vascular and bronchial trees do not cross the lobar boundaries and, therefore, in the absence of fissures the positions of the lobes can be inferred from the course of vessels and bronchi.

It is often clinically important to determine whether a disease affects one or more lobes, for example when lobar resection is considered. In addition, the extraction of quantitative parameters per lobe can provide valuable information. Lobe segmentation may also prove useful in intrapatient registration.

There are several strategies that can be employed to segment the lobes. The most obvious is to detect the fissures directly, by locating sheet-like bright structures in 3-D or, as is also common, line-like structures in 2-D slices. Knowledge about the typical shape of lobes and their positions within the lungs can be exploited. Finally, the regions containing the lobe borders are almost devoid of larger blood vessels, so a vessel segmentation can be used to infer lobar boundaries. Similarly, a segmentation of the airway tree can be used.

Zhang *et al.* [53], [54] performed fissure detection. A rough estimation of fissure positions was obtained through atlas registration. Subsequently fissures were delineated with ridge detection in 2-D slices. The method allowed for interaction through manually provided anchor points. Performance was evaluated by comparing computer results with manual tracings in 22 scans of 12 subjects. Kuhnigk *et al.* [55] enhanced the fissures by extracting the vasculature with region growing, computing a distance transform on this segmentation and adding that to the original data. Next, the lobes were segmented by an interactive watershed computed from this fissure-enhanced data. The method was evaluated by measuring interobserver differences on a set of five scans. Saita and co-workers have described various related systems for fissure detection. In a recent version [56], a four step approach was presented. First the vessels were segmented using a line filter [21]. From this segmentation search volumes were determined. A set of filters was applied to enhance sheet-like structures in these volumes. Subsequently the fissures were found by morphological processing. A qualitative evaluation on 20 low-dose scans was given. Wang *et al.* [57] presented a 2-D algorithm that detected line-like structures through energy minimization. Once initialized in one slice, the algorithm propagated through the scan and used shape information from the previous slices. The method was tested on scans from four patients.

We conclude that previous work shows encouraging results but automatic lobe segmentation is still largely unsolved, especially in the presence of incomplete fissures and pathology, an issue not specifically addressed in any paper.

The lobes are further subdivided in segments: ten for the right lung and eight for the left. The segmental boundaries can only be estimated from the course of bronchi and veins. Automatic identification of segments is a completely open research area.

IV. Registration

Bringing images into spatial alignment, referred to as registration or matching, is one of the most common procedures and also one of the most active research areas in medical image analysis [58]–[60]. A plethora of algorithms has been proposed, many of these general in the sense that they could be applied as-is to chest CT. Publications on chest CT most often employ elastic registration and typically include some dedicated modifications to standard approaches.

There are four reasons for matching CT lung scans.

- Matching a CT scan to another scan of the same patient from a different modality, typically a PET scan.
- Matching to a follow-up CT scan of the same patient for effective visual or automatic comparison to detect or quantify interval change and/or monitor response to therapy.
- Intrapatient matching to scans acquired at a different inspiration level to study ventilation or to extract functional information.
- Interpatient matching, possibly to an atlas, to guide segmentations or detect deviations from normal appearance.

A recent example of intermodality matching is the work of Mattes *et al.* [61]. PET and CT chest scans were matched with a rigid deformation followed by an elastic deformation based on cubic B-splines. Mutual information was used as similarity criterion in a hierarchical multiresolution framework with a quasi- Newton optimization algorithm. This approach, similar to the system described in [62], is typical of contemporary volume-based elastic matching algorithms. Other works on PET-CT matching used thresholding to find the lung contours and chamfer-matching [63], preprocessing to make both images similar in appearance followed by multi-resolution elastic matching based on minimization of the squared difference image [64], and translations of several VOIs using mutual information [65].

Matching of follow-up scans serves many purposes, such as pairing and comparing nodules [66], [67] or, more generally, displaying similar slices to a radiologist [68] for which several commercial workstations already offer automatic solutions. Some studies use rigid deformations. Betke *et al.* [66] determined a rigid alignment based on a small number of automatically identified anatomical landmarks and the lung surfaces and succeeded in finding corresponding nodules in 56 out of 58 cases. Yamamoto *et al.* [68] detected similar slices in two studies based on anatomical landmarks and simple features computed over complete slices. Dougherty *et al.* [69] used an optical flow method. Stewart *et al.* [70] recently described a hybrid registration scheme that combined feature- and intensity-based approaches which was applied to chest CT scans. The latter three studies presented no quantitative results and showed experiments on small numbers of scans only. Blaffert and Wiemker [67] compared rigid, affine and elastic registration of follow-up scans with and without the use of segmentation masks and concluded that affine registration on the lung mask is a good compromise between speed, accuracy and robustness. The possibility of using the aligned scans to detect changes automatically in a CAD system is hinted at in some studies [70], [71] but actual application of CAD systems on follow-up scans is currently limited to commercial workstations for lung nodule work-up, e.g., [72].

Several studies focus specifically on the registration of scans acquired at different moments of the respiratory cycle. Matching inspiration and expiration scans is challenging because of the substantial, locally varying deformations that take place during breathing. Fan *et al.* [73] described a system to assess several functional parameters from registered scans, such as regional lung volume changes, local changes in air content and the distribution of ventilation. Their registration algorithm combined feature point matching with lung surface matching and constraints on the optical flow of mass and the smoothness of the deformation. Other studies focused on radiotherapy applications: Correcting for tumor motion is a major challenge in radiotherapy treatment planning. Boldea *et al.* [74] used the popular demons algorithm [75] to validate the use of active breath control during radiotherapy treatment. In [76], an elastic registration method was described that was tested on 2-D slices. Both methods require long computation times. Kaus *et al.* [77] compared volumetric B-spline registration with surface based registration using manual segmentations of heart and lungs and found that the surface based method is much faster with comparable accuracy.

Registration across individuals is another area. Similar methods can be employed, but many anatomical landmarks

that can be used for intrapatient registration are not always available in two scans of different patients. Li *et al.* [78] have constructed a human lung atlas as a general tool that can be used for many purposes. Examples are guiding of segmentations and establishing a normal range for local functional measurements that could be used to detect early indications of disease. An earlier work [79] showed that atlas registration could be used to pinpoint the approximate location of lobar fissures which was used later for fissure segmentation [54] (see also Section II-D). Sluimer *et al.* [17] used atlas registration to segment the lungs in scans with dense pathologies.

In any application, the proper registration method is a compromise between computation time and demands for accuracy and robustness. Providing fast and fully automatic registration with an accuracy comparable to manual indication of corresponding points is still a major challenge, especially in the presence of large (ventilation) deformations, pathology and noise. No studies which address these issues specifically have been published. On the other hand, several authors conclude that the performance of their method already suffices for their purposes.

V. Computerized Detection, Quantification, and Classification

Segmentation and registration are often precursors to a host of specific application-dependent image analysis systems. In this section, compound systems on automated detection, quantification and classification of pulmonary disorders are discussed. These are grouped by clinical application area: emphysema (Section IV-A), lung cancer (Section IV-B1, IV-B2, and IV-B3), PE (Section IVC), (bronchial) signs of airway diseases (Section IV-D), and differential diagnosis of lung disease (Section IV-E).

A. Emphysema

Emphysema is a pathology of the lung, characterized by the destruction of lung tissue. This deficiency can be measured by aberrations of PF tests, expressing the performance of the lungs (e.g., residual lung capacity and diffusion of gases) as compared to the expected performance. However, PF tests can only distinguish the progression of emphysema in rough stages: normal, mild, or severe. Studies have shown that a volume of tissue amounting to about a third of the total lung volume has to be destructed before PF tests indicate a significant deviation from healthy lungs [80]. There is a clear need for an *in vivo* diagnostic tool for emphysema which can diagnose emphysema at an earlier stage and is more sensitive to small changes in the progression of the disease. The best candidate for this tool is CT. Two earlier overviews of emphysema quantifications are by Madani *et al.* [81] and Müller and Coxson [39].

Because emphysema shows up on CT as areas with abnormally low attenuation coefficients (close to that of air), visual CT scoring of emphysema is feasible. A lot of studies on emphysema quantification with CT focus on a reliable automatic method as a replacement for the insensitive lung function tests [37], [82]–[88] and subjective visual scoring [83], [84], [87]–[94]. Indeed most of these show that computer scoring of CT is better suited for emphysema detection than PF tests, and more objective than visual scoring. In fact, for some studies on emphysema, CT has already become the accepted gold standard for quantification [83], [90], [95].

The emphysema detection studies mostly focus on extracting from CT a single value expressing the emphysematous fraction of the lungs. As emphysema is identified by air voxels in the lungs, thresholding seems the best way to obtain such a value. Usually this results in calculating one of the following.

- Fraction of lung voxels with intensity values below a given threshold T (density mask method [96], or pixel index (PI) $\mathrm{PI}(T)$ [97]).
- Lung area occupied by low attenuation areas larger than some minimum size, with intensities below threshold T: $\mathrm{LAA}\%(T)$.
- Mean lung density (MLD).
- Fraction of histogram covered by a given lowest percentile: $\mathrm{HIST}(5) \equiv \text{lowest fifth percentile}$.

Visually it is possible to distinguish a variety of emphysema patterns describing the sizes and the spatial distribution of the lesions (which can be termed bullae or LAAs in literature). However, few studies [84], [88], [89], [92], [98]–[101] tried to incorporate this additional knowledge in the emphysema quantification. Texture features to determine if a voxel represents emphysema or not were only used by [80] and [102].

In Table II, an overview is given of emphysema quantification studies. The table describes the data sets, the quantification methods, distinguishes 2-D and 3-D algorithms, and reports performance. The table covers researches concerning the (long-term) reproducibility and trends with time of automated CT scores [86], [95], [103]–[105], asthma scoring [88], and more informative descriptive emphysema staging [80], [84], [88]–[90], [98]–[102]. Studies that are primarily concerned with the validation of single value replacements for visual and PF test based grading of emphysema are not displayed in Table II.

A number of emphysema studies [82], [87], [90] focused on the selection of patients for lung volume reduction surgery (LVRS) instead of emphysema quantification. When emphysema is severe and concentrated in one lobe, a patient might be eligible for LVRS, in which the emphysematous lobe is resected.

The challenges for future research on emphysema quantification lie in quantification of emphysema patterns and prognosis of the disease. These topics are even more challenging for noisy, low-dose screening data. It is well known from older and relatively recent studies that the typically used emphysema scores are sensitive to noise, slice thickness, reconstruction filters and level of inspiration [97], [104], [106]–[108]. How to correct for this is an open area. Another issue is whether LAAs are in fact responsible for decreased PF; as there are many examples of asymptomatic patients with PI scores over 10%, it might be that the true disease is in fact not characterized by the dead space. Possibly there is a role for CAD in solving this medical issue.

The CAD techniques developed for emphysema quantification might also be used for quantification of airtrapping (airtrapping refers to the retention of air in the lungs during expiration). So far we haven't found any studies of automatic quantification of airtrapping, but the visual techniques used in medical literature (see e.g., [93]) are the same as those used for the assessment of emphysema, which suggest that CAD could be useful for quantification of airtrapping.

TABLE II
STUDIES ON EMPHYSEMA QUANTIFICATION. FOR EACH STUDY THE NUMBER OF NORMAL (#N) AND ABNORMAL (#A) SCANS USED IS GIVEN (WITH POSSIBLY A "NOTE" TO IT). THE METHOD IS BRIEFLY DESCRIBED AND IT IS STATED WHETHER IT IS 2-D OR FULLY 3-D. "PERFORMANCE" REPORTS THE EVALUATION METHOD AND THE RESULTS

Study	#N	#A	Note	Method	2D/3D	Performance
Uppaluri et al. [80]	9	10	4 slices	lung segmentation, edgementation, ROI selection, feature extraction (statistical and fractal), feature selection, Bayesian classification	2D	normal vs emphysema: Accuracy= Specificity= Sensitivity= 100%
Mishima et al. [98]	30	73	3 slices	cumulative frequency distribution of LAA(-960) sizes, fit to power law	2D	normal vs COPD: accurate fit; exponent distinguishes groups
Nakano et al. [84]	—	73	3 slices	PF; separate inner and outer lung, LAA%(-960)	2D	normal vs emphysema: more often LAA in inner segment; inner LAA stronger correlated to PF
Stoel et al. [103]	—	28	4 annual repeats	rescale intensities with mean blood density; MLD; HIST(12); PI(-950)	3D	follow changes over time: densitometry is spatially dependent; rescaling most important for MLD and HIST(12)
Soejima et al. [86]	36	47	3	PF; MLD; modus of CT intensities; LAA%(-912)	2D	follow annual changes: lower lung airway abnormalities increase with age; upper lung abnormalities increase with smoking history; inspiration images superior; no change in PF
Blechschmidt et al. [89]	20	60		visual; PI(-930); bullae index (BI) derived from size distribution over 4 classes	2D	correlate scores: BI well correlated with visual; BI distinguishes normal/emphysema better that PI
Gierada et al. [95]	—	25	1 repeat	PI(-900,-960) for upper lower long and total	3D	determine repeatability: correlation of 0.99; fraction scores within .01
Cederlund et al. [90]	—	66		visual Weder classification [109]; PI(-950) vs slice position	3D	reproduce Weder: 45 training 21 test separation reproduced
Guo et al. [99]	—	3		hole-size distribution left/right upper/lower	3D	mild vs moderate vs severe: mild: more small holes, severe more big holes; slope increases from mild to moderate to severe
Mitsunobu et al. [88]	23	105		PF; Mishima et al. [98]; visual	2D	distinguish asthma severity: exponent correlates with emphysema; LAA% both with emphysema and asthma
Nagao et al. [100]	1	4		segment lung tissue, adaptive region grow LAA(-945), measure distribution	3D	quantify 3D LAA distribution: LAA concentration useful measure for severity; few LAA close too bronchi and vessels
Silva et al. [101]	—	4		2D rule-based detection of bullae(-925); 3D rule-based based bullae(-925)	2/3D	detect bullae: both detect all bullae; 3D is faster
Tanaka et al. [93]	26	24		visual; MLD	2D	air trapping to distinguish smoking vs non-smoking: cannot be distinguished
Boedeker et al. [104]	—	42		PI(-910) for different scanner and reconstruction filters	3D	difference with standard reconstruction: differences up to 9.4% points
Parr et al. [105]	—	57	3 annual repeats	PI(-910); recalibrate PI(-870,...,-950)	2D	long term reproducibility of scores: recalibration critical; -950 best threshold
Prasad and Sowmya [102]	—	13	selected slices	combination of ANNs on gray-level features; PI(-910)	2D	detection and quantification: best sensitivity for PI; best positive predictive value for new method

B. Lung Cancer

Much of published CAD research is focused on detecting lung cancer, which is the main cause of cancer deaths. Especially since the start of a number of lung cancer CT screening programs, this CAD field has taken a prominent place in medical related literature. The main focus over the past years has been to aid the radiologists in the detection of lung nodules. Two related areas of research cover nodule size measurements and the characterization of nodule appearance. Both are used to attempt to estimate of the probability of malignancy. Published work for all three areas is described in more detail in the subsections IV-B-1 through IV-B-3 below.

In general, it can be concluded that for the development of systems that can be used in clinical practice it is necessary that the algorithms are trained and tested on larger numbers of cases. The collection of well-characterized cases requires a huge effort and cannot be done on a single site. The availability of common databases [110] could spur further development of the CAD systems substantially. It will also be increasingly important to measure system performance in a clinical setting and evaluate the usefulness of CAD as a second reader for both experienced and inexperienced radiologists.

1) Lung Cancer: Detection of Pulmonary Nodules: Over the years covered in this survey (1998–2004), the number of articles about automated nodule detection has roughly doubled each year. However, many of these articles deal with a small extension to a previously published method, or a different database is used for testing. If the results in the follow-up paper are not significantly different from the earlier results, only the latest version is discussed in this section.

As a rule, nodule detection systems consist of several steps: a) preprocessing; b) candidate detection; c) false positive reduction; d) classification. Most often the preprocessing stage is used to restrict the search space to the lungs and to reduce noise and image artifacts. As will be discussed below, there are many

TABLE III
THE REPORTED BEST PERFORMANCES OF VARIOUS NODULE DETECTION SYSTEMS AND THE FP REDUCTION TECHNIQUES EMPLOYED. IF THE PERFORMANCE IS OBTAINED BY MODIFYING A PREVIOUSLY REPORTED SYSTEM, THE ORIGINAL ALGORITHM IS GIVEN IN THE THIRD COLUMN. THE DATA PARAMETERS (NUMBER OF SCANS, NUMBER OF PATIENTS, SLICE THICKNESS, AND RADIATION DOSE) MENTIONED IN THE "DATA" COLUMN REFER TO THE DATA USED TO OBTAIN THE LISTED BEST PERFORMANCE

Study	FP reduction	Original system	Data	Best performance
Kanazawa et al. [120]	rule-based	—	450 screenings, 10 mm, low dose	90% of expert findings
Suzuki et al. [138]	massive training ANN	Armato et al. [111]	101 scans from 71 patients, 10 mm, low dose	80.3% of expert findings with 4.8 FPs/scan
Brown et al. [141]	—	—	31 scans, 5-10 mm, normal dose	86% of expert findings with 11 FPs/scan
Ko and Betke [112]	—	—	31 scans, 5-10 mm, normal dose	86% of expert findings with 11 FPs/scan
Lee et al. [140]	new 5 gray-scale features, tuned parameters	Lee et al. [118]	20 scans, 10 mm, low dose	72.4% of expert findings with 5.5 FPs/scan
Tanino et al. [116]	principal component analysis clustering	Ezoe et al. [114]	39 scans, 10 mm	100% with 33 FPs/scan
Saita et al. [125]	new features: relative positions to anatomical structures	Oda et al. [124]	12 scans, 2 mm, low dose	100% of expert findings with 2.6 FPs/scan
Ge et al. [139]	new feature: 3D gradient field	Gurcan et al. [121]	55 scans, 40 patients, 0.5-2.5 mm, normal dose	A_z=0.93
Kubo et al. [122]	rule based	—	155 nodules, 10 mm, low dose	91% with 15.9 FPs/scan
Takizawa et al. [133]	—	—	38 scans, 10 mm	95% with 3.74 FPs/scan
Wei et al. [126]	—	—	10 scans, 1.25 mm, low dose	67.6% with 6.2 FPs/scan
Wiemker et al. [129]	—	—	50 scans (271 nodules), 0.5-1 mm, normal dose	86% with 4.9 FPs/scan
Fetita et al. [115]	—	—	10 isotropic scans (300 nodules)	sensitivity=98%, specificity=97%
Fukano et al. [134]	ridge detection and model matching of vessels and nodules	—	37 scans, 10 mm, low dose	94.7% with 6 FPs/scan
Mekadaa et al. [127]	rule based	—	6 cases, .625-1.25 mm	71% with 7.4 FPs/scan
Yamada et al. [123]	rule based	—	54 nodules, 10 mm, low dose	94%
Awai et al. [117]	position dependent threshold on size	—	82 scans, 7.5 mm, normal dose	80% with 38.7 FPs/scan
Chang et al. [130]	sphericity test	—	8 scans (62 nodules)	100% with 0.88 FPs/scan
Enquobahrie et al. [128]	multi-stage surface-attachment filtering	—	50 scans, 2.5 mm, low dose	97.8% with 2 FPs/scan
Farag et al. [119]	Bayesian classification with 2 gray-level and 1 shape features	—	200 scans (130 nodules)	82.3% with 12 FPs in total
Li and Doi [131]	—	—	73 scans, 10 mm, low dose	93.4% with 130.1 FPs/scan
McCulloch et al. [143]	—	—	50 scans, 2.5 mm, low dose	70% with 8.3 FPs/case
Paik et al. [132]	—	—	8 scans, 2.5-3.75 mm	90% with 5.6 FPs/scan
Zhang et al. [142]	—	—	19 scans, .7-1.3 mm	83.9% with 3.5 FPs/case
Zhao et al. [113]	rule based	—	28 scans, 5 mm, low dose	60.6% with 8.7 FPs/case

ways to generate nodule candidates, but amongst those candidate there are always many (obvious) false positives. Therefore, one tries to cheaply and drastically reduce the number of these FPs [step c)] before going to the more computationally expensive classification step [step d)]. Still, after the classification stage, many false positives exist, and much of current research on nodule detection is in fact not focused on the detection part, but on FP reduction instead. Stages b)–d) of nodule detection systems will be covered in the following subsections.

Table III gives an overview of the different CAD models that are covered in this survey. The performances given are the best performances if previous models have been extended, or if new databases have been used in later articles. If there is explicit mention of a false positive reduction scheme in the study description, this is mentioned in the table.

a) Candidate detection schemes: For finding nodule candidates, the following techniques have been reported: multiple gray-level thresholding [111]–[113], mathematical morphology [114]–[117], genetic algorithm template matching of Gaussian spheres and discs [118], [119], clustering [120]–[123], connected component analysis of thresholded images [124], [125], thresholding [126]–[128], detection of (half) circles in thresholded images [129], gray-level distance transform [123], and filters enhancing (spherical) structures [130]–[132].

The multiple gray-level thresholding technique tried to find connected components of similar intensity, and to remove

attached vessels. For the schemes described, mathematical morphology covered a number of convolution filters: variable N-Quoit filter [114], [116], [133], [134], selective marking and depth constrained cost map [115], top-hat and sieve filter [117]. The used clustering methods differed in clustering technique and in the features used for clustering: Kanazawa *et al.* [120], Kubo *et al.* [122], Yamada *et al.* [123] applied fuzzy clustering to intensity values and Gurcan *et al.* [121] used k-means clustering on intensities in the original and median-filtered images.

b) Reduction of false positives: A good example of the shift in focus from nodule detection to false-positive reduction is the set of papers published by Armato and co-workers. In [111], their nodule detection scheme was described, containing the steps: preprocessing, candidate detection, and classification. In the first step, the lungs were segmented. Candidates were found by multiple gray-level thresholding. Using a number of geometric and gray-level features and linear discriminant analysis (LDA), the results of leave-one-out classification were the detection of 70% of the nodules marked by experts, with on average 3 FPs per image slice (i.e., about 80–90 FPs per scan). In later papers, Armato and co-workers concentrated on schemes to reduce the number of FPs: rule-based [135], [136], LDA [136], [137], and massive training ANN [136], [138]. The most successful of these techniques reported a nodule detection rate of 80.3% with on average 4.8 FPs/scan as opposed to 27.4 FPs/scan without FP reduction [138].

Saita *et al.* [125] added an FP reduction step to the nodule detection algorithm by Oda *et al.* [124]. For FP reduction prominent anatomical structures in or near the lungs were (roughly) extracted: bones, mediastinum, and vessels. Usage of the positions of nodule candidates relative to these structures resulted in a 100% detection rate with 2.6 FPs/scan. The original paper of Oda *et al.* [124] reported 59% detected at 19.2 FPs/scan.

The model by Gurcan *et al.* [121] was extended with FP reduction by Ge *et al.* [139]: They added a 3-D gradient field as an extra feature for the LDC. As a result the area under the ROC curve (A_z) increased from 0.91 to 0.93.

Lee and co-workers published their detection method in [118], and introduced an FP reduction step in [140]. In the latter work, they added five new gray-level features and tuned the threshold parameters of the original model. The sensitivity of the model remained 72.4%, but the FP rate dropped from 30.8 to 5.5 per scan.

c) Classification: There is a number of classification techniques used in the final stage of the nodule detection systems: rule-based or linear classifier [112], [118], [120], [126], [127], [130], [131]; LDA [111], [121]; template matching [141]; nearest cluster [114], [116]; Markov random field [133]; neural network [117], [142]; Bayesian classifier [119], [143]. The CAD schemes described in [115], [122]–[124], [129], [134] did not state explicitly how a label was determined. The most common features for classification were gray-level features, shape descriptions, and spatial and size information.

A growing area of interest related to nodule detection is that of nodule matching. This specific problem pertains to the localization of previously detected nodules in a follow-up scan.

Brown *et al.* [141] described the construction of an anatomical *a priori* fuzzy model which was used in combination with image primitives matching to find nodules. From the results obtained from a scan, a patient-specific model was tuned which could be applied to follow-up scans.

Ko and Betke [112] used multiple gray-level thresholding to find nodule candidates in both original and follow-up scans. Using position, shape, and volume information a rule-based classification found nodule matches between scans.

With the FDA approval[1] of several commercial CAD systems for nodule detection, it seems that CAD for this field has come to an acceptable performance. This performance is not perfect yet, but the increased chance of finding a nodule with the help of CAD and the achievable workload reduction for the radiologist demand for usage of these systems in CT screenings as well as daily hospital practice. For future work, research leading to improved detection of ground glass opacities should have top priority.

2) Lung Cancer: Characterization of Pulmonary Nodules: The pulmonary nodule is a dilemma for the radiologist. Most large nodules (diameter $>$ 1 cm) in subjects at high risk for cancer are malignant, but current CT scanners allow for the detection of small nodules with diameters well below a centimeter. Such nodules are extremely common and the vast majority of them is benign [144]. Follow-up procedures to determine malignancy are often invasive, and induce risks for the patient [145]. It is, however, of crucial importance for patient management to determine as soon as possible whether nodules are malignant, because symptoms of lung cancer often don't appear until the malignancy is advanced and unresectable. As a result, the 5 year survival for a patient diagnosed with lung cancer is only 10%–15%, but for patients in which early stage lung cancer has been completely resected, this increases to 65%–80% [146].

Several attempts have been made to design computer systems that can help to estimate the pCa. For the design of such systems it is obviously of crucial importance to know which characteristics point toward malignancy. This is also important for radiologists, and the subject of clinical research. It is becoming clear that rules of thumb that apply to larger nodules do not always hold for smaller nodules. For recent overview articles, see [144], [146]–[151].

Clinical information such as old age, male sex, a history of smoking, a history of cancer, and exposure to certain chemical compounds increases the pCa, while other factors decrease this probability. Bayesian analysis to include this information in the diagnostic process was proposed by [152], [153], but applied to nodule characterization in chest radiographs only.

The most important characteristics appear to be nodule size and growth rate. To accurately estimate this, precise segmentation of nodules is essential. This topic is further discussed in Section IV-B3. Another possibility is to perform a contrast-enhanced CT scan. A malignant tumor with a diameter over 2 mm must exhibit angiogenesis, which leads to contrast enhancement in the nodule [154]. To accurately determine enhancement in small nodules, again, precise segmentation is essential, as was shown by Wormanns *et al.* [154]. Another noninvasive follow-up procedure is PET with 18-fluorodeoxyglucose [155].

[1]The FDA is the government agency responsible for regulating medical devices in the USA.

TABLE IV
STUDIES ON NODULE CHARACTERIZATION. FOR EACH STUDY THE NUMBER OF BENIGN AND MALIGNANT NODULES IS GIVEN AND THE TYPE OF DATA IS LISTED (THIN-SLICE REFERS TO AROUND 1-mm THICKNESS, THICK SLICES ARE 3 mm OR MORE). THE FEATURES AND CLASSIFIER ARE BRIEFLY DESCRIBED, THE TYPE OF ANALYSIS (2-D/3-D) IS INDICATED, AND REPORTED RESULTS ARE SUMMARIZED

Study	Data	Features	2D/3D	Classifier	Purpose
Henschke et al. [156]	14 benign / 14 malignant, thick slices	pixel data used directly as features	2D	ANN	classification system, 89% accuracy, no comparison with radiologist
McNitt-Gray et al. [157, 158]	14 benign / 17 malignant, $\leq$3 mm slices	semi-automatic segmentation, size, shape, attenuation and a large number of texture features derived from cooccurrence matrices	2D	LDC with feature selection	classification system, 90.3% accuracy, no comparison with radiologist
Kawata et al. [159, 160]	100-200 nodules, thin-slice data	automatic segmentation, different types of histogram analysis and curvature shape measurements	3D	-	the separating power of various combinations of features is investigated; nodules are clustered in five classes
Kawata et al. [161, 162]	100-200 nodules, thin-slice data	automatic segmentation, different types of analysis	3D	-	a CBIR system is proposed
Matsuki et al. [163]	56 benign / 99 malignant, 5 to 10 mm slices	16 features scored by radiologists, and clinical information	2D	ANN	observer study on a subset of 50 cases, CAD system alone A_z= 0.95, radiologists A_z= 0.83, radiologists with CAD A_z= 0.96
Lo et al. [164]	24 benign / 24 malignant cases, thin-slices	direction of vasculature relative to nodule surface normal, together with over ten other features that characterize both the shape and the internal structures in the nodule	3D	ANN	classification system, A_z= 0.89, no comparison with radiologist
Li et al. [165]	413 benign / 76 malignant, 10 mm slices, low dose	7 features measuring shape and appearance	2D	various classifiers	compute similarity between nodules from similarity ratings provided by radiologists, used in CBIR
Armato and MacMahon [166]	401 benign / 69 malignant, 1 mm slices, low dose	automatic segmentation, shape and appearance features, feature selection	3D-2D	LDC	classification system, A_z= 0.79, no comparison with radiologist
Aoyama et al. [167]	see [165]	nodule outline segmented by dynamic programming, 2 clinical features, 41 from region in and outside the nodule	2D, multiple slices	LDC, feature selection	classification system, A_z= 0.85 vs. A_z= 0.70 for radiologists in observer studies on a subset of the data

The possibilities of computer analysis to estimate pCa from PET and CT scans simultaneously, or from both contrast and noncontrast CT have to our knowledge not yet been investigated. In this section, we restrict our attention to the estimation of pCa from noncontrast CT scans.

Table IV provides an overview of published studies on nodule characterization. All studies used a combination of features to characterize the size, shape and internal structure of the nodules. In that way, they indirectly encoded radiologists' knowledge about indicators of malignancy. For example, certain calcification patterns are reliable indicators of benignity, while other types can be present in malignancies [144], [149], [151]. The presence of fat in a nodule points toward benign hamartoma [146]. The border of nodules can be smooth, lobulated (consisting of multiple lobes) or spiculated. The former points toward benignity, and the latter to malignancy. According to Takashima *et al.* [168], [169] any nodule deviating significantly from a spherical shape is probably benign. It also appears that concave margins and a polygonal shape are typical for benign lesions [168], [169].

It is important to realize that thin sections are needed for good characterization; an ill-defined small lesion on thick slices may appear well-defined at high resolution. Moreover, 3-D computer analysis is hardly possible using thick slices. Nevertheless, several studies used thick slices only (Table IV). The use of low-dose may also negatively affect the possibility to make a reliable diagnosis, especially for segmentation (Section IV-B3). It has also been reported that the use of different reconstruction filters affected the likelihood that radiologists rate a nodule as calcified [170]. When human ratings of nodule characteristics are used to train computer systems, it is important to realize that such ratings are not always reliable and reproducible [171].

A clear trend is to switch from 2-D analysis on thick slices to 3-D analysis on thin-slice data. Recent studies tended to use more data, but the size of training and testing databases remains a limitation; all studies resorted to leave-one-out evaluation strategies. Often good results were reported but comparisons between systems cannot be made as no standard database is employed. Performance depends heavily on the data; when performance of radiologists was measured it ranged from $A_z = 0.56$ [165] to $A_z = 0.83$ [163]. It is interesting to note that in some studies [163], [167] stand-alone CAD systems outperformed radiologists.

Several systems for content-based image retrieval (CBIR) that retrieve similar cases from a database for a given nodule at hand have also been proposed. Display of similar cases with known classification may help radiologists to make a diagnosis. Modest improvements in observer performance when such similar cases are provided were reported in [165].

Signs that are not in the direct neighborhood of the nodule under consideration can influence the probability of malignancy. An example is the presence of metastases elsewhere [172]. It is a very difficult task—well beyond the capabilities of current computer analysis systems—to find such signs automatically in general. However, often findings in the direct vicinity of a nodule are important, such as the presence of peripheral subpleural lesions and pleural tags [168], [169] and could be integrated in more advanced CAD systems.

When malignancy is suspected, staging the tumor is required. CT scans are important for staging [173] but including computer analysis in tumor staging has not been attempted yet.

Further research on nodule characterization should be focused on the integration of multiple features, extracted from both patient history and several examinations—not just a single CT scan—in order to compute a reliable pCa.

3) Lung Cancer: Nodule Size Measurements: The size of a nodule highly correlates with the chance of malignancy. Growth rate is another important indicator. Benign nodules typically have either a very small ($<$1 month, e.g., for inflammation or pneumonia) or a very large doubling time ($>$16 months). The volume doubling time for cancers is typically between 40 and 360 days [146]. To measure nodule size and growth rate, accurate segmentation is needed. Segmentation is also required for shape characterization (Section IV-B2) and as part of nodule detection schemes (Section IV-B1). For these reasons, nodule segmentation has received considerable attention. Older studies use 2-D outlines, but recent algorithms segment in 3-D. The major industrial vendors currently all provide automatic nodule segmentation in their chest workstations, although they typically require a manually indicated seed point.

It is difficult or impossible to obtain a ground truth for nodule segmentations in real clinical data. Manual outlines, provided by experts, have been used often, but it has been shown that there can be interobserver and intraobserver differences in such outlines [174]. Size measurements can also be affected by slice thickness [175] and acquisition parameters [176]. Several studies have, therefore, used phantoms for algorithm validation and some of these phantoms even contain structures mimicking part-solid nodules [177]. However, it is very difficult to realistically model the wide variety of pulmonary structures encountered in patients using phantoms.

In absence of a ground truth, algorithms can also be evaluated in terms of their reproducibility. Most published algorithms require a manually indicated seed point, and a slightly different seed point should not lead to substantially different segmentation. This has been investigated in several studies [178]–[180]. More importantly, it has been investigated if consecutive scanning of the same patient leads to reproducible nodule size measurements [179]–[181]. Reasons for measurement deviations in repeated scans are image noise (especially evident in low dose scans), PVE and variations in inspiration level. Wormanns and Diederich [144] reported 95% limits of agreement for volume were around 20% using commercial software with manual interaction by a radiologist. Note also that algorithms that make errors in volume measurements for example when compared to manual segmentation, can still be reliable to determine growth rates, if the errors are systematic. This was observed by Mullally *et al.* [182].

The excellent contrast between tissue and air on CT makes segmentation of an isolated solid nodule of reasonable size a simple task. But difficulties arise when a) the nodule is small, so that PVE play an important role; b) the nodule is connected to vasculature or other structures such as the pleura, fissures or abnormalities; c) the nodule is part-solid or nonsolid, in which case it can be difficult to define the boundary; d) the data is noisy (typical for low-dose scans). The algorithms described in this section have been designed to cope with difficulties a) to c).

The PVE can be dealt with by supersampling the VOI around the nodule. A discussion of different ways to do this is given in [183]; a comparison between binary methods and methods that take the PVE into account is given in [177], [184]. Typically, the segmentation of solid nodules is performed by a dedicated algorithm that performs thresholding or region growing while constraining the shape of the grown nodule, or by template matching or—in the case of 2-D processing, dynamic programming (typically used in older studies, or e.g., [185]). In [182], fixed and variable thresholds and shape based segmentation methods were compared. Attached structures were removed by post-processing, usually with a sequence of mathematical morphological operators or basic image processing operations involving connected component labeling, distance transforms, etc. Vessel and pleura each had their own sequences.

Kostis *et al.* [183] described 3-D algorithms for four different types of nodules, depending on their attachments. The effect of varying parameters was described in detail and evaluation was on 16 scans for which a follow-up is available. The method appeared to improve upon a 2-D segmentation method from the same research group [186]. Fan *et al.* [178] described a method based on template matching. The union of the template and a thresholded VOI was taken and the segmentation was refined using certain rules. The method was extended and used in a recent study [72] which described a complete nodule detection, matching and size measurement system. Shen *et al.* [187] described an algorithm for nodules attached to the chest wall. Using 2-D projections, the chest wall was removed from the segmentation. Fetita *et al.* [188] used dedicated sequences of mathematical morphological operators to segment isolated, juxtavascular and peripheral nodules but evaluation was only performed qualitatively. Kuhnigk *et al.* [180] focused specifically on large, not necessarily spherical tumors with possibly complex attachments to vessels and pleura. Their algorithm had reasonably low (4.7%) interscan variability.

In the case of part-solid or nonsolid nodules, these approaches typically fail. Several alternative approaches have been proposed to deal particularly with such nodules. Okada *et al.* [189] used a two-step method based on scale-space analysis that first described the nodule by an ellipsoid which was subsequently deformed by attracting the boundary to the gradient. Zhang *et al.* [190] employed Markov random field modeling for ground glass nodule segmentation. In both cases, further evaluation is necessary to better assess the value of these techniques.

Finally, there are alternative approaches that do not directly segment the nodule but infer growth from the Jacobian matrix of an elastic registration of two consecutive nodules [191].

Given the large number of algorithms proposed, a comparative study on a common database with a reliable reference stan-

dard would be very worthwhile. The data collected by the Lung Image Database Consortium [110] could be used for such a study. An advanced system for nodule segmentation will likely consist of multiple algorithms each tailored for a particular type of nodule and attachments and a recipe for choosing the best algorithm for a nodule at hand. Systems that allow more user interaction to correct segmentation errors made by automatic algorithms with a simple and intuitive user interface could be very valuable in clinical practice and deserve more research. Other future challenges are automatic correction for inspiration level and suppression of inaccuracies caused by acquisition noise.

C. Pulmonary Embolism

Suspected acute PE is the main indication for pulmonary CT angiography (CTA, chest CT with arterial contrast). PE is a life-threatening complication which should be diagnosed promptly and treated with anti-coagulants. Thin-slice CT is the preferred modality when PE is suspected because it has high sensitivity, relatively high specificity and it can establish an alternative diagnosis in up to one third of patients [18].

The direct signs of PE are intraluminal filling defects and lack of enhancement of pulmonary arteries. Acute emboli can get trapped at bifurcations or in peripheral arteries. Complete occlusion of vessels by clots is possible but residual perfusion in the periphery is more common. This suggests two ways to detect PE: the direct detection of the clots from the HU values in the vessels or indirect detection by localization of perfusion defects. Herzog *et al.* [192] presented a visualization method for the latter. The lungs were segmented by a simple algorithm, vessel and bronchi were excluded by thresholding, and the average local attenuation in the remaining voxels was superimposed on the original data by color coding. Instead of presenting these results to a radiologist through visualization, these measurements could also prove valuable for a CAD system.

The few published CAD systems in this area have focused on direct detection. Masutani *et al.* [49] developed a scheme tested on 19 scans with 3.0 mm slices. A sensitivity of 85% was obtained at 2.6 false positives per case but scans with poor image quality in which vessel segmentation failed were excluded. Vessels were segmented with standard techniques such as hysteresis thresholding, region growing and mathematical morphology. For each voxel in the vessel segmentation, the HU value and a local contrast measure were determined and shape features based on second order derivatives were computed. Rules were used to select suspicious voxels. These were grouped into PE candidates and size measurements were added to the feature set. Rules with variable thresholds provided the final classification. Zhou *et al.* [50] developed a segmentation scheme for pulmonary vessels based on histogram analysis and an expectation-maximization algorithm followed by a tracking algorithm. The vessel tree was subdivided in distinct regions and intensity, shape and edge features were computed and entered in a rule-based classifier to detect PE. When tested on 6 cases of thin-slice CT data, 58% of manually indicated emboli were detected at the expense of 10.5 false positives per case. Pichon *et al.* [48] presented a method to segment the vessel tree and the intraluminal values were used to colorcode a rendering of the arterial tree to make locations of clot more evident. The main purpose of this work was to generate these renderings for use in clinical practice, but with a simple threshold on the result of their algorithm, component labeling and constraints on size they were also able to construct a CAD system with 86% PE detection sensitivity at the expense of 2 false positives per TP.

PE appears to be an area in which CAD has high potential, because of the encouraging results reported so far and the enormous clinical importance of prompt diagnosis. PE is, after cardiac disease, the second cause of sudden, unexpected death with over 50 000 deaths in the USA alone every year. Several major industrial vendors are, therefore, active in this area and have recently demonstrated prototypes of PE CAD systems. Considering the relatively small number of studies published so far, the small number of cases on which they have been tested, the modest performance obtained, and the simple sets of features and classifiers employed, there should be ample room for further improvement.

Apart from detection, quantification of PE is also important. Qanadli *et al.* [193] proposed a quantitative index, but automatic quantification of PE has not been reported yet.

D. Airways Diseases (Bronchial Signs)

Signs of airways diseases that the bronchi may exhibit on thin-slice CT examinations are wall thickening and dilation or narrowing [194], [195]. These three clear signs lend themselves well to automated analysis. Thus far, the work on this has centered on measurements of bronchial cross sections on 2-D transverse slices, in analogy to current methods of visual assessment by a radiologist.

The bronchi are usually of equal size as their accompanying artery. Normal bronchovascular cross-sectional pairs, therefore, appear on CT as a figure eight with one hole open (the bronchus) and one hole closed (the artery). It is the size relation between vessel and bronchus that indicates bronchial narrowing or dilatation. A few studies focus on the detection of normal [196] as well as abnormal [197] bronchovascular pairs. In other studies these pairs were indicated manually and automated size measurements were performed [36], [37], [198], [199]. Such size measurements always incorporated a correction for nonperpendicular cross sections and were always validated on phantoms. Nakano *et al.* [37] correlated bronchial size measurements to clinical parameters of COPD in smokers.

Two-dimensional analysis reflects the way in which a radiologist currently assesses the airways. This restricts the measurements to specific favorable cross sections in a transverse slice. Three-dimensional analysis will soon become the standard in this area, however. The combination of measurement and 3-D bronchial segmentation techniques (Section II-B) will provide more data for the analysis which can be of added clinical value. Techniques developed for comprehensive virtual bronchoscopy systems, e.g., [47] provide the basis for 3-D airway analysis.

E. Diffuse Lung Disease

There is a large group of disorders that primarily affect the lung parenchyma. This group is referred to by the generic term diffuse parenchymal lung disease (DPLD), but terms such as Interstitial lung disease (ILD) or infiltrative lung disease are also

encountered. The DPLDs account for about 15% of respiratory practice [200].

Thin slice CT plays an important role in the detection, diagnosis and follow-up of these disorders. They are characterized by specific abnormal findings mostly texture-like in appearance and it is the cooccurrence of several such findings that can point toward a specific diagnosis [194].

It is for this reason that computer analysis of DPLD is commonly viewed as a texture analysis problem. Systems designed to quantify certain lung diseases and/or differentiate between them, are without fail based on the vector space paradigm [7]. This means that ROIs are represented by features that are input to a classifier which is trained to (re)produce category labels. Most often the application of these systems revolves around the detection of abnormal tissue and its simultaneous classification into several textural categories [201]–[207]. One study focusses exclusively on the detection of abnormalities without further classification [208]. A different field of application (employing the same pattern recognition tools) is that of content-based image retrieval, in which one group has been active [209]–[212].

With respect to implementation, various choices are made about *(i)* what ROIs to use, *(ii)* what features, and *(iii)* what classifier. ROI sizes typically lie in the range of 31×31 to 96×96 pixels. The smallest ROIs are 9×9 pixels [204], the largest encompass an entire lung field [202]. For the features representing the ROIs, a discriminatory set can be automatically chosen by supervised feature selection from families of textural features known from pattern recognition theory, such as histogram statistics, features from filterbanks or cooccurrence matrices, run-length parameters or fractal features [201]–[203], [208], [213]. Alternatively, features may be designed for the task at hand [205], or a combination of both can be used [209]. Kauczor *et al.*[204] use a combination of two artificial neural networks into which the raw pixel values in the ROIs are input as features. The ANN (also employed by Uchiyama *et al.* [205]) is only one example of classifier. We find also LDCs [201], Bayesian classifiers [202], [203], [213] and k-nearest-neighbor classifiers [208], [209].

Table V provides a summary of the described studies with respect to their objective, the data that was used and the evaluation. Descriptions of purpose and the lists of used classification categories show considerable variation, illustrating that in this field there is no consensus yet on a common goal and exact definitions. Although follow-up measurements for the quantification of disease progression are mentioned as a possible area of interest, in none of the studies this task is performed explicitly.

A noticeable common problem to all studies is the establishment of a reliable reference standard. This is due to the fact that texture classification in thin-slice CT scans is a complex task even for experts: Low intraobserver and interobserver agreements of about 50% [203] reflect this. We see that in most studies the opinion of a single expert is used as a reference standard. In some cases, multiple radiologists are involved and a consensus is taken. For samples on which there is no agreement between the radiologists, the computer may be regarded as another observer. It can then be ascertained whether its behavior is statistically equivalent to that of the radiologists, avoiding the use of an explicit reference standard.

For completely automated differential diagnosis of DPLD, much more information will need to be incorporated into the computer systems than is the case at present. The scans need to be analyzed on a global rather than a local scale. This means that the full 3-D character of modern scan data should be exploited and information from the entire scan (e.g., from all regions of interest) should be combined to come to a single diagnosis. In this process, also, the use of anatomical knowledge is indispensable. Shyu *et al.* [209] are the only group incorporating forms of global and anatomical knowledge, combining features from several pathological regions and anatomical indicators per slice. The regions are, however, manually delineated rather than automatically detected. Recently also the first work appeared analyzing 3-D objects in complete scans [207], although these 3-D objects were combined from multiple candidates detected beforehand on 2-D slices. Another source of information that is of paramount diagnostic value but is not being taken into account so far is clinical data. Fukushima *et al.* [214] showed that an expert system can come to reasonable diagnoses of DPLD when image analysis results (in their case rated by radiologists, not automatically) are augmented by clinical parameters.

We conclude that with the systems described in this section the first steps toward more advanced processing schemes have been taken, but that in computer analysis of DPLD, the question on what exactly to aim for and how to achieve it is still open.

VI. Discussion

This final section consists of four parts. First we summarize what has been achieved so far and what is the state of the art. Then we identify a number of challenges for academic research. Several remarks to this end have already been raised specifically in each of the topics in Sections II–V; here we unify those issues. Third, we specifically focus on the discrepancy between theoretical availability of an algorithm and its availability in clinical routine, and try to explain its causes. Finally we provide an outlook to new developments that can be expected in the coming years.

A. State of the Art

Initially, the clinical use of computer analysis of CT of the lungs did not reach much further than the quantification of emphysema, a direct consequence of its relatively simple detection on CT. Simple tools for emphysema quantification are now available on commercial workstations.

Ongoing improvements in scanner speed and quality have broadened the field of applications. Currently, the emphasis lies on detection and analysis of pulmonary nodules. We see CAD for lung cancer follow in the footsteps of CAD for breast cancer: Several commercial systems for automated nodule detection have acquired FDA approval and research effort is shifting from detection to characterization and follow-up. In this field, industrial R&D efforts probably outweigh those of academic research. Commercial workstations are now capable of automatic nodule volumetry and nodule detection. These workstations perform segmentation, but beyond complete lung segmentation, these segmentation techniques are not directly available yet for clinical use.

TABLE V
STUDIES ON THE (TEXTURE) ANALYSIS OF DPLD. FOR EACH STUDY A DESCRIPTION OF THE PURPOSE IS GIVEN AND OF THE CATEGORIES INVOLVED (DISEASE OR TEXTURAL). THE DATA USED IS DESCRIBED ON THE LEVEL OF SUBJECTS/SCANS, AS WELL AS THE LEVEL OF SLICES/ROIS. IT IS STATED HOW A REFERENCE STANDARD WAS SET, AND A CHARACTERISTIC RESULT IS GIVEN

Study	Purpose	Categories	Subjects/scans	Slices/ROIs	Reference standard	Result
Delorme et al. [201]	classification into 6 textural classes	normal, emphysema, GG, intralobular fibrosis, vessel, bronchus	10 subjects: 5 normal, 5 proven UIP	3 slices per scan. Grid over slice gives ROIs. Train set consists of chosen ROIs. Test set has all ROIs.	opinion of single radiologist	70% accuracy
Uppaluri et al. [202]	classification into 4 disease classes	normal, emphysema, IPF, sarcoid	72 subjects: 20 normal, 13 emphysema, 19 IPF and 20 sarcoidosis	4 slices per scan. Complete lung field is ROI.	proven cases	81% accuracy
Uppaluri et al. [203]	classification into 6 textural classes	normal, emphysema, GG, honeycombing, nodular, bronchovascular	(see [202])	Marked pathologies from the 72 scans are used for training. 6 subjects / 1 slice per subject is used for evaluation. Grid over slice gives ROIs.	only for selection of samples where 3 out of 4 radiologists agreed	70% accuracy (kappa 0.62)
Shyu et al. [209]	CBIR / classification into 8 disease classes	CLE, PSE, BO, hemorrhage, MC, panacinar, sarcoid, PCP	78 subjects	302 slices in total. ROIs are delineated manually.	opinion of single radiologist / proven cases	On average, of the 4 retrieved most similar images, 72% has correct label
Kauczor et al. [204]	detection and quantification of ground glass	normal, GG	99 consecutive scans from clinic (84 subjects)	3 slices per scan. Grid over slice gives ROIs.	opinion of single radiologist	89% accuracy (sens. 99%, spec. 83%)
Chabat et al. [213]	detection of obstructive lung diseases	normal, CLE, PLE, BO	77 subjects: 20 normal, 20 CLE, 15 PLE, 22 BO	5 slices per scan at predefined anatomic levels. 4 ROIs per slice	opinion of a single radiologist	On average, 74% sensitivity and 92% specificity per class
Uchiyama et al. [205]	classification into 7 textural classes	normal, emphysema, GG, honeycombing, nodular, reticular, consolidation	105 subjects	3 slices per scan. Grid over slice gives ROIs.	only for selection of samples where all 3 radiologists agreed	2-class normal / abnormal : 85% accuracy
Sluimer et al. [208]	detection of abnormalities	normal, abnormal	116 consecutive scans from clinic (116 subjects)	1 to 6 selected ROIs per scan	opinion of single radiologist	area under ROC of CAD = 0.86 vs radiologists = 0.93 and 0.89

Apart from the pulmonary nodule, the lungs may contain much more pathology. Segmentation, registration and further image analysis of each anatomical structure has been researched, as is evident from this survey, but has not reached the status of routine clinical use.

B. Research Challenges

For all methods of analysis the present trend is to move from (axial) 2-D to 3-D processing, born out of possibility as much as necessity.

This inevitably leads to a need to create suitable reference standards in 3-D. This represents a major hurdle for evaluation of tasks such as segmentation, for which the reference standard is classically set using manually traced outlines. It is a prohibitively large amount of work to create manual delineations of structures of interest in thorax exams that typically consist of over 300 slices. More effort should be spent on the development of interactive tools (e.g., [215], [216]). Apart from their use in research for easy establishment of a ground truth, these tools can be used in clinical practice to manually correct the (as of yet) unsatisfactory automated segmentation outcomes. Moreover, these tools can be developed in such a way as to enforce consistency of manual segmentations in 3-D, as manual delineations performed on 2-D slices often lack such consistency over larger volumes.

Maybe the largest challenge is to design algorithms that are robust against pathological and anatomical variety, image noise and differences in acquisition parameters. Many of the algorithms reviewed here have only been tested on very select patient populations that do not necessarily represent clinical practice. It is well possible that fundamentally different methodological approaches are necessary to achieve this increased robustness.

Proper validation is indispensable in order to assess the quality and application range of an algorithm. Algorithms should be tested in context of their intended practical clinical use, with due consequences for the choice of test data and measures of performance. Test data should reflect the variety of pathology, noise levels and acquisition variety encountered in clinical practice. However, a lack of robustness does not have to hinder clinical use of a system as long as it is compensated by adequate means of failure detection. Failure detection is an important part of an automated system, but this fact is typically ignored in academic research. A clinical user should not be required to examine closely either the input data, or the (intermediate) results to estimate the validity of the final outcome of an automated analysis. Construction of adequate failure detection mechanisms is far from trivial and in our opinion this topic deserves more research.

Ideally, common, carefully annotated and representative databases should be available for algorithm benchmarking. This does, however, require consensus on the definition and relevance of the clinical questions to be answered, which has not been reached for all discussed areas of application. Detection of lung nodules is a task with a clear definition of purpose and a vast range of algorithms in need of competitive testing, presenting a prime example for which a common database can and should be assembled. This necessity has been recognized and steps in this direction are being undertaken [110].

In many of the studies describing application oriented work (Section IV), research efforts are necessarily focused on the final stages of the comprehensive image analysis system, and preprocessing modules (such as lung segmentation) are implemented in a suboptimal way. Many of these systems would benefit from incorporation of existing methods from other research groups. This is a common problem to science as well as industry and can not be solved easily (making research software publicly available might be a solution). It is important to be aware of the limitations this might set on system performance. Situations should be avoided where effort goes into refinement of the final stages of a compound system when the true bottleneck lies elsewhere.

C. Clinical Application

The advent of multislice CT has made isotropic imaging of the lung a standard technique. Since nonisotropic data was one of the main problems in computer vision of CT data, it should now be easy to use various computer assisted techniques in clinical routine practice. Unfortunately, of the many potential applications for the lungs described in this survey, only very few are available on the market and even fewer are provided by the large CT manufacturers.

What are the reasons for this discrepancy? For an algorithm to succeed in clinical practice, there needs to be a market for it (a real clinical need by a sufficient amount of radiologists), it needs to be fast and easy to use (patient throughput is ever increasing with multislice CT), it needs to be reliable (correct results in the vast amount of cases) and it should be correctable (easy adjustments in case the algorithm fails). Because radiologists are used to working without such algorithms, it is not easy to market new tools. Only when radiologists fail miserably, such as in the case of nodule volumetry and detection of small nodules, and when there is a growing need to perform such tasks (lung cancer screening depends on nodule detection and volumetry) do such algorithms find their way into clinical practice. In addition, regulatory bodies such as the FDA require positive proof of the benefit of such techniques and their use may be hampered by medico-legal considerations.

Many if not all techniques described in this survey have the potential to be important in clinical practice. How much so, however, will mainly depend on their ease of use and their reliability. As mentioned in the previous section, improving reliability and robustness is a major research challenge. In addition, most algorithms have not been optimized for speed, and even if they had, they probably would take longer than most radiologists would accept. New concepts are, therefore, needed to implement such algorithms in clinical practice. One potential solution could be automated preprocessing of the data as soon as it is sent from the scanner to the CT workstation: such preprocessing should include the time-consuming steps of any algorithm that is made available. The radiologist then should have the results at the fingertips and can easily use—and ideally also modify—the results in any patient in whom he deems a particular computer-assisted analysis valuable. By making results of CAD easily accessible in every patient, radiologists will be much more prone to using these results. Speed and ease of use, therefore, will be the determining factors as soon as performance of algorithms has risen beyond a certain basic level.

The fact that many good algorithms are not available in clinical practice demonstrates a general dilemma in the image processing community: Research money is mainly available for basic work and algorithm development but not for implementation and optimization of technique. Workflow issues will ultimately determine whether a new technique is practicable or not. Close collaboration between academic image analysis researchers, radiologists and industry is mandatory for success.

D. Outlook

The past few years have seen the introduction of nodule volumetry and detection into clinical workstations. Techniques for classification of nodules are ready to follow relatively soon but probably will be hampered by medico-legal considerations. The available techniques will have to be upgraded to suit the increased exposure to clinical cases, which will invariably lead to new problems that have previously not been considered. However, within a rather short period of time, nodule detection, measurement and classification can be expected to be standard in clinical practice.

A new "hot" application is the automated detection of PE, a task that has been previously considered trivial but now becomes more cumbersome because many more vessels are visible and have to be evaluated on multislice CT data sets. Techniques that indicate potential emboli, and later may even help in differentiating emboli from artifacts would be very welcome in clinical practice.

Registration of various types of scans is already available for PET/CT and SPECT/CT data. Registration of lung nodules is already implemented in commercial workstations but should become even more reliable in the future. The registration of

follow-up scans should have a bright future, mainly because it is a daily problem for radiologists. This problem is becoming increasingly important with the growing workload with new multislice CT systems but it is not trivial to solve because of varying inspirational levels.

Emphysema quantification has been around for many years but is still limited to research settings because the clinical benefit of a precise quantification is not yet evident for the vast majority of patients. Problems such as the correction for varying inspirational levels or the correction for image noise have not yet been fully solved. While simple threshold-based techniques have been made available on clinical workstations, there remains a substantial amount of work to be done before such techniques will be fully established in everyday practice.

Evaluation of airway morphology, especially airway thickness, may become an important topic in the future because airways are much more readily responsive to treatment, and computer analysis could be used as a faster way to study the effect of a new drug than analysis of lung function or patient outcome.

Classification and quantification of interstitial lung disease is difficult, and even experienced chest radiologists frequently struggle with differential diagnoses. Automated schemes that indicate a percentage of affected lung or the probability of a certain disease would certainly be welcome, but require much more research.

The combination of these issues—airway evaluation, regional texture analysis of parenchymal structure, quantification of ventilation, perfusion and airtrapping, etc.—turns MSCT into a modality that is suited for *functional* analysis of the lung, in addition to assessment of anatomy. An outlook on the possibilities for functional chest imaging with CT is given in [217]. But only robust automated image analysis and availability of reference data on both normal and abnormal variability will make such a comprehensive analysis valuable in clinical practice. This defines a challenging research agenda for the next decade.

A quick analysis of the roughly 300 publications considered for this survey reveals that the amount of publications in this field has grown on average by a factor 1.5 per year over the past five years: a practical indicator to the increase in research effort accompanying the modern (r)evolution of CT. Given the clinical importance of chest CT and the existing challenges that we have identified, it is to be expected that the computer analysis of chest CT scans will remain a very active research field in the years to come.

APPENDIX
LITERATURE COLLECTION

Of the following journals, all publications on chest CT analysis in the years 1999 through 2004 were included: *Medical Physics, Radiology*, IEEE TRANSACTIONS ON MEDICAL IMAGING (TMI), *Med. Image Anal.* (MedIA), *Acad. Radiol., American Journal of Roentgenology* (AJR), *American Journal of Respiratory and Critical Care Medicine* and the *European Journal of Radiology*. For some journals differing time spans were covered for reasons of availability. These were TMI (1988–2004), MedIA (1997–2004), *Acad. Radiol.* (2001–2004) and AJR (2000–2002). The following conference proceedings of the years 1999 through 2004 were searched: SPIE Medical Imaging, Medical Image Computing and Computer Assisted Intervention (MICCAI), Information Processing in Medical Imaging (IPMI), and the IEEE Symposium on Biomedical Imaging (ISBI). Contributions in alternate sources were identified from citations in the aforementioned publications and from searches using the online database search engines PubMed, IEEEXplore, and the Science Citation Index. The key that was sought on was ("computed tomography" OR CT) AND (chest OR thorax OR lung OR lungs OR pulmonary) AND (computer OR computerized OR automatic OR computerised OR automated) and this resulted in 1659, 197, and 883 hits, respectively. When similar contributions have appeared only the most recent or comprehensive paper has been included.

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