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Computed Tomography Image Matching in Chronic Obstructive Pulmonary Disease

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Abstract

Chronic obstructive pulmonary disease (COPD), characterized by progressive airflow obstruction due to the combined effects of emphysema and small airways disease, is associated with high morbidity and mortality. The complex link between emphysema and airways disease is associated with significant heterogeneity in clinical presentation. Spirometry is the current gold standard for diagnosis and stratification of the severity of airflow obstruction in COPD. Although spirometry is simple to use, it does not enable the separation of emphysema from airways disease. Computed tomography (CT), on the other hand, provides the anatomic localization of disease and has been increasingly used to phenotype COPD. The majority of current CT measures are extracted from a single-volume CT scan and although useful to characterize emphysema and airways disease, they do not link structural and functional abnormalities. Alternatively, CT image matching combines information from both inspiratory and expiratory CT scans, thus enabling determination of functional changes such as regional ventilation and mechanical properties of the lung. In this review, we discuss recent applications of CT image matching that provide clinically meaningful information beyond spirometry and single-volume CT scan measures.

Keywords

COPD; CT; image matching; image registration; emphysema; COPD phenotypes; Jacobian; regional ventilation; parametric response mapping

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I. INTRODUCTION

Chronic obstructive pulmonary disease (COPD), now the third-leading cause of death in the United States, is associated with significant healthcare and economic burden.¹ Tobacco smoking and environmental exposures account for the majority of COPD. The main symptoms include chronic cough, sputum production, shortness of breath, wheezing, and reduced exercise capacity. A substantial number of subjects are asymptomatic, and it is estimated that ~12 million individuals in the United States with COPD remain undiagnosed.² Prolonged exposure to cigarette smoke induces inflammatory changes in the lungs, eventually resulting in persistent airflow obstruction.³

The term COPD is an umbrella term that includes emphysema and chronic bronchitis. Emphysema is the destruction of alveolar septae, leading to permanent enlargement of air spaces in the lung, thus resulting in decreased elastic recoil. Chronic bronchitis causes morphological changes to airways and is associated with airway inflammation and increased mucous production. The structural alterations include airway narrowing and loss of small airways. Spirometry is traditionally used to diagnose the presence and severity of airflow obstruction based on forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC) measurements. The Global Initiative for Obstructive Lung Disease (GOLD)—recommended guidelines state that diagnosis of COPD should be confirmed on spirometry by demonstrating a reduced FEV₁/FVC ratio of < 0.70, and disease severity is determined by percent of predicted FEV₁ derived from population normative values.¹ Airway obstruction is due to a combination of increased airway resistance due to narrowing and loss of small airways, primarily those < 2 mm in internal diameter, and loss of elastic recoil due to emphysema. Spirometry measurements provide a global assessment of disease severity but fail to distinguish emphysema from airway disease. Computed tomography (CT) is increasingly used in clinical practice and offers an opportunity to detect disease early.^{4,5} Multiple large cohort studies have used a combination of inspiratory and expiratory scans, enabling the application of advanced postimage processing to further the detection and characterization of disease.^{6,7} In this review, we provide an overview of traditional and novel CT measures of COPD and discuss several recent applications of CT image matching techniques.

II. CT MEASURES OF COPD

Pulmonary CT imaging enables the visualization of lung parenchyma and airway tree at high resolution. The structural alterations in the lungs associated with COPD are heterogeneous, and clinical presentation often varies from patient to patient. The appearance on CT does not always correlate with the degree of airflow limitation measured on spirometry, and CT diagnosis should be considered in combination with spirometry and other clinical measures of COPD.^{8,9}

A. Emphysema

1. Density-Based Quantification—Emphysema causes air spaces in the lung to permanently enlarge. The areas of emphysema appear as low-CT-density (in Hounsfield units [HUs]) regions closer to the HU value of air (−1024 HU). Hayhurst et al. first showed that

the frequency distribution of HU values on a CT image significantly differed between patients with and without emphysema.¹⁰ Later, the density-mask technique was introduced that highlighted CT voxels at less than a fixed HU threshold, thus providing anatomic localization of emphysema. The severity of emphysema was quantified as the percentage of low attenuation areas (LAAs), referred to as %LAA. Muller showed that the percentage of lung < -910 HU on 10-mm-thick CT slices yielded strong correlations with emphysema in resected lung tissue.¹¹ Gevenois et al. later reported best correlations with microscopic and macroscopic emphysema using a threshold of -950 HU on 1-mm high-resolution CT images.¹² Later, it was shown that all thresholds < -910 HU were significantly correlated with pathological emphysema, and a range of -960 to -980 HU was highly associated with severity of emphysema in modern multidetector CT images at varying slice thicknesses.¹³ Alternatively, emphysema was also quantified using an HU value at the n th percentile of the HU distribution curve.^{14,15} The 15th percentile HU value (perc15) on the distribution was shown to be a robust and highly reproducible measurement of emphysema in longitudinal studies involving subjects with α -1 antitrypsin deficiency.^{16–18} Both the density threshold (-950 HU) and perc15 methods quantify overall emphysema but lack information on the size of emphysema cluster and emphysema type. The fractal dimension (D) of the emphysematous regions on a CT scan has been proposed to evaluate the relationship between the size of the emphysematous cluster and number of such clusters in the lung.¹⁹ On the basis of the fractal dimension, Coxson and colleagues showed that patients with larger emphysematous clusters in the upper regions of the lung had better outcomes after lung volume reduction surgery than patients with a heterogeneous distribution of emphysema throughout the lung.²⁰ A similar relationship has been found between upper lung emphysema predominance, improved FEV₁, and exercise capacity in patients after lung volume reduction.^{21,22}

2. Texture Analysis—Emphysema is classified into three main subtypes: Centrilobular, panlobular, and paraseptal.²³ Centrilobular emphysema is the most common subtype, affecting the central part of the secondary pulmonary lobule and frequently seen in the upper lobes. Panlobular emphysema affects the entire secondary pulmonary lobule and predominantly occurs in the lower lobes. Paraseptal emphysema is characterized by enlargement of air spaces adjacent to the pleural surfaces in the lung. Each subtype can be identified by its own unique characteristics in terms of location and signature of tissue destruction. Image texture measures are statistical indices representing the spatial relationship between the intensity values of a given individual region of interest (ROI). Uppaluri et al. proposed an adaptive multiple feature method (AMFM) to estimate the mean, median, skewness, kurtosis, and standard deviation of the density (HU) distribution from individual ROIs on lung CT slices.²⁴ AMFM-based texture measures showed good sensitivity in separating lungs of smokers and nonsmokers.²⁴ Later, AMFM was extended from two-dimensional (2D) ROIs to 3D volumetric regions of interest and achieved 99% sensitivity in differentiating between normal-appearing lungs of healthy volunteers and those of smokers.²⁵ Sorensen and colleagues combined local binary pattern texture features and density information for individual ROIs in the lung and were able to achieve 95.2% classification accuracy in separating ROIs related to normal tissue, centrilobular emphysema, and paraseptal emphysema.^{26,27} The texture- and shape-based measures of

individual ROIs in the lung were also shown to better correlate with spirometry measures than those of density-based global quantification.²⁸ To the contrary, Mendoza et al. recently showed that density information alone is sufficient for emphysema discrimination, especially in a multicenter imaging data set.²⁹ The authors further showed that classification accuracy is even higher when modeling the local intensity distribution in each ROI with a kernel density estimation method. Gangeh and colleagues clustered individual ROIs in the lungs by representing an emphysema subtype. On the basis of texture similarities, these authors created a texton dictionary representing texture classes per subtype.³⁰ The texton-based classifier achieved an accuracy of 94.3% in distinguishing 168 annotated regions of normal tissue, centrilobular emphysema, and paraseptal emphysema. Recently, Castaldi et al. used local histograms to classify distinct patterns of tissue destruction in 9313 smokers in the COPDGene study. The local histogram-based quantification outperformed the density threshold-based quantification and was also significantly associated with respiratory morbidity indices.³¹ Several other studies successfully used texture analysis on several CT-based pulmonary applications, and proposed texture measures have been extensively discussed elsewhere.^{32–34}

B. Small Airways Disease

Small airways that are less than 2 mm in diameter are the predominant sites of airflow obstruction in COPD.^{35,36} However, it is not possible to visualize the airways of such small diameters using current CT scanning capabilities. Therefore, the presence of air trapping on an expiratory CT scan was used as an indirect measure of small airways disease. Similar to emphysema quantification on an inspiratory CT, low attenuation regions < -856 HU on an expiratory CT scan are termed regions of air trapping.^{14,37} The threshold of -856 HU was initially used in asthmatic studies and was chosen because it is the minimum HU value of normal lung tissue under inflation; the value is expected to be > -856 HU at expiration.^{38,39} To distinguish air trapping related to emphysema, Matsuoka and colleagues computed the expiratory to inspiratory difference in the relative volume of voxels between -860 and -950 HU ($RV_{-860 \text{ to } -950 \text{ HU}}$), where RV represents residual volume.⁴⁰ The proposed measure showed strong correlations with spirometry measures of airflow obstruction. Alternatively, expiratory to inspiratory mean lung density (E/I_{MLD}) ratio has also been used to measure airflow obstruction in COPD.⁴¹ Hersh et al. compared E/I_{MLD} , $RV_{-860 \text{ to } -950 \text{ HU}}$, and %LAA_{-856 HU} in a large clinical cohort of COPD patients and found that E/I_{MLD} had strong correlations with both spirometry and patient outcomes such as respiratory quality of life and 6-min walking distance.⁴²

C. Large Airways Disease

The morphological changes to the airway tree in COPD include airway narrowing or bronchial thickening—changes that have previously been associated with airflow obstruction.⁴³ Similar to density-based quantification of lung parenchyma, airway trees on pulmonary CT images were separated using a density threshold of -500 HU to quantify airway wall dimensions.^{44,45} The recent advancements in CT image postprocessing capabilities enable reconstruction of the 3D airway tree up to the sixth generation.^{46–48} The full-width-at-half-maximum (FWHM) technique is commonly used to quantify airway wall dimensions involving the projection of rays from the center point of an airway lumen

outward in all directions and then tracking the density value (in HU) changes on the rays.⁴⁹ The points at which the attenuation value is half of the maximum HU value on the luminal side and half of the maximum on the parenchymal side are considered to be airway wall boundaries. The distance between these two points is the airway wall thickness. However, the FWHM method was shown to overestimate the airway wall area, and point selection on the ray density curve was highly influenced by the CT reconstruction algorithm, orientation of the airway, and noise-related blurring at the airway wall edges.⁵⁰ Alternatively, a score-guided erosion algorithm was implemented, and airway wall edges were found using an edge-finding algorithm.⁵¹ Reinhardt et al. proposed a maximum-likelihood method, wherein boundary points were selected that were based on the ideal calculated ray. These authors also proposed an ellipse-fitting strategy to quantify wall thickness for obliquely cut airways.^{46,47} Weinheimer and colleagues proposed an integral-based method to reduce the blurring effect of small airway structures on CT images, and measurements were more accurate than those using the traditional FWHM method.⁵² In addition to airway wall thickness measurement on CT, other measures of airway wall dimensions have been used, such as wall area percent (WA%) and Pi10 measurements.^{53–55} Wall area percent is defined as the ratio of outer airway wall area to the total wall area including the lumen. pi10 measurements were proposed to account for errors in wall thickness measurements due to airway size differences among subjects. The regression of the square root of airway wall areas against the internal perimeter in each subject was used to measure the standardized airway wall thickness measurement.⁵³ Hoesen et al. showed greater associations between pi10 measurements and FEV₁.⁵⁶ In the same study, increased pi10 airway wall thickness was also shown to be associated with FEV₁ decline.⁵⁶ Airway wall measures from CT were also shown to independently predict bronchodilator responsiveness in COPD subjects.⁵⁷ Recently, Gietema and colleagues showed that the airway wall thickness measurement on CT was significantly associated with decreased quality of life in COPD subjects after adjusting for age, current smoking status, pack-years of smoking, body mass index, and FEV₁.⁵⁸

D. Limitations of Density-Based Measurements

Madani et al. showed that emphysema quantification on inspiratory CT using a single-density threshold of –950 HU is significantly affected by varying levels of inspiration, choice of slice thickness, and radiation dose.^{59,60} Density-based quantification is also influenced by a CT reconstruction algorithm and a gravity-based ventral–dorsal gradient on CT attenuation values.^{61,62} CT-based airway wall measurements based on the FWHM method are also affected by choice of reconstruction algorithm and radiation dose.^{63,64} Lung volume correction and standardized CT scanning protocol are highly recommended and implemented in current longitudinal and cross-sectional studies related to COPD.^{6,7,65–67} In addition, both density-based and airway wall measurements from single-volume CT scans are limited to quantification of structural alterations in the lungs associated with COPD. Recently, CT image matching techniques have been successfully implemented in several studies to derive clinically meaningful information from paired inspiratory and expiratory images.^{68–79} Image matching enables the comparison of corresponding locations between inspiration and expiration or between images acquired at different time points (baseline and follow-up), thus providing novel imaging markers of regional lung ventilation and disease progression.

III. CT IMAGE MATCHING

A. Objective

The goal of an image matching algorithm is to find spatial correspondence between two images, thus providing pixel-to-pixel (2D) or voxel-to-voxel (3D) comparisons. Image matching is often referred to as image registration and is generally performed between 3D pulmonary CT images acquired at different points of the breathing cycle or across time points in longitudinal studies. For instance, as part of the image matching process, the lungs at inspiration are spatially deformed to match the lungs at expiration. The change in density (HU) values between the newly deformed inspiration image and the original expiration image is then used to measure ventilation at each voxel and identify regions of air trapping. Additionally, image matching also attributes a 3D displacement vector to each voxel in the lung, representing its deformation from inspiration to expiration. The displacement vector information is further used to derive important mechanical properties of the lung tissue such as local volume change (Jacobian determinant of the deformation), strain, and the degree of anisotropic deformation. The comparison of density (HU) values among corresponding locations can also be used to track disease progression if matching has been performed between a baseline and a follow-up CT scan.

B. Image Matching Framework

Figure 1 shows the matching framework and workflow among different components of the matching process. The first step in the matching process is to define a fixed image (I_f) and a moving image (I_m). In the case of pulmonary CT image matching, the inspiratory CT is usually defined as the moving image, and the goal is to find anatomical correspondence with the fixed expiratory CT image. Image matching is an optimization problem in which a transformation function is used to deform the moving image, and the dissimilarity between the deformed image and the fixed image (cost function) is minimized at each iteration. The parameters of the transformation function are then updated through an optimizer, and the process is repeated until accurate point-to-point correspondence is achieved.

The most commonly used cost function to measure the degree of similarity is the sum of squared difference (SSD), which computes the voxel-to-voxel (HU) difference between the moving and fixed image. SSD is defined as

$$C(SSD) = \int_{\emptyset} \left\{ [I_f(x) - I_m(T(x))]^2 \right\} dx, \quad (1)$$

where $\emptyset$ represents the search space including all of the voxels in the lungs, and $T(x)$ is the transformation function. The goal of the matching process is to minimize SSD until perfect correspondence is achieved; this is usually best for matching images of the same modality. SSD is heavily reliant on the assumption that the intensity values do not change in images acquired at different time points. However, the assumption does not hold true for pulmonary CT images, where the density (HU) values do change due to changes in airflow. Lung tissue also undergoes significant mechanical alterations during respiration, and the deformation is

further influenced by body orientation, gravitational forces, and underlying pathology. A nonrigid matching algorithm comprising a nonlinear transformation function and cost function is needed to account for such variations.

Gorbunova and colleagues developed a modified SSD cost function that accounts for changes in CT density using lung mass-preserving criteria.⁷⁷ The proposed cost function is based on the assumption that the mass of lung parenchyma stays constant, and CT density is inversely related to change in air content (volume change). Thus, the density values on the moving image at each iteration of the matching process can be adjusted by estimating the Jacobian determinant of the transformation function. The simulated density (HU) value of the moving image is defined as

$$I_m(x) = \det(J_T(x)) \cdot I_M(T(x)), \quad (2)$$

and

$$C = \int_{\mathcal{O}} \left\{ [I_f(x) - \det(J_T(x)) \cdot I_m(T(x))]^2 \right\} dx. \quad (3)$$

The authors successfully showed that mass-preserving criteria could be used to account for changes in CT density during respiration. The matching improved, even for images with a considerable difference in volumes compared to the matching algorithm without the modified mass-preserving cost function.⁷⁷

Yin and colleagues recently developed another cost function in which mass-preserving criteria were incorporated by deriving tissue mass directly from the HU value instead of estimating the Jacobian determinant.⁸⁰ The proposed cost function is called the sum of squared tissue volume difference (SSTVD). The density (HU) value on the CT image is a function of tissue and air content, where the reference HU values for air and tissue are -1024 and 55 HU. On the basis of this information, the tissue volume (TV) and air volume (AV) in an individual voxel x can be estimated as

$$TV(x) = v(x) \frac{HU(x) - HU_{air}}{HU_{tissue} - HU_{air}} = v(x)\beta(I(x)), \quad (4)$$

and

$$AV(x) = v(x) \frac{HU_{tissue} - HU(x)}{HU_{tissue} - HU_{air}} = v(x)\alpha(I(x)), \quad (5)$$

where $HU(x)$ is the given density of the voxel. The tissue volume is then used in the cost function to measure the difference between two locations of the moving and fixed images at each iteration as follows:

$$C(SSTVD) = \int_{\mathcal{O}} \left\{ [TV_f(x) - TV_m(T(x))]^2 \right\} dx, \quad (6)$$

where TV_f represents the tissue volume in the fixed image, and TV_m represents the tissue volume in the transformed moving image. In addition to the choice of similarity in cost function, the accuracy of spatial matching is also reliant on the choice of transformation function and optimizer. A comprehensive list of pulmonary CT matching algorithms is evaluated and extensively discussed elsewhere.⁸¹

IV. APPLICATIONS IN COPD

A. Functional Small Airways Disease

Air trapping in COPD is currently defined to occur at regions that are < -856 HU on the expiratory CT image. However, air trapping results from both emphysema and small airways disease. Galbán et al. recently performed image matching of inspiratory and expiratory CT scans to distinguish between regions of air trapping caused by emphysema and regions of nonemphysematous air trapping.⁷⁴ The proposed method is called parametric response mapping (PRM) and is shown in Fig. 2. The density (HU) values on the deformed inspiratory CT image (moving image) are compared with the corresponding density values on the expiratory CT image (fixed image). PRM incorporates commonly used and well-validated density thresholds of emphysema (-950 HU on inspiratory CT) and air trapping (-856 HU on expiratory CT). After image matching, the corresponding voxels that are < -950 HU on the deformed inspiratory CT and < -856 HU on the expiratory CT show regions of emphysematous air trapping. But the corresponding voxels that are > -950 HU on the deformed inspiratory CT and < -856 HU on the expiratory CT show regions of nonemphysematous air trapping. Because it is not yet possible to visualize small airways on a CT image, the PRM measurement of nonemphysematous-related air trapping is deemed to be a functional measure of small airways disease (PRM-fSAD). The remaining voxels that are > -950 HU on inspiration and > -856 HU on expiration are labeled normal lung regions. Such separation of emphysematous regions from nonemphysematous regions of air trapping was not previously possible, because this requires anatomical correspondence during respiration. Hence, the introduction of the image matching-based PRM technique is a significant step forward in characterizing structural abnormalities in COPD.

Bhatt and colleagues showed that the percentage of PRM-fSAD in the lungs was significantly associated with FEV_1 decline in 1508 current and former smokers who completed a 5-yr follow-up as part of the COPDGene cohort study.⁷¹ The presence of PRM-fSAD was more closely correlated with FEV_1 measurements than emphysema at early stages, where the rate of FEV_1 decline is higher. PRM-fSAD was also significantly associated with increasing age, especially in subjects without evident airflow obstruction and past smoking history.⁸² Hoff and colleagues recently computed spatial relationship and local

distributions of PRM-fSAD regions in COPD subjects.⁷⁸ These authors showed that the surface area of PRM-fSAD is an independent predictor of clinical outcomes in COPD. The results were further validated on micro-CT lung specimens, where the structural alterations to lung parenchyma visualized on micro-CT were associated with unique spatial patterns of PRM-fSAD regions.

B. Regional Ventilation and Lung Mechanics

Another fundamental application of pulmonary CT image matching is the extraction of local ventilation and mechanical properties of lung parenchyma during respiration.⁸³ Instead of using density values on the deformed image, regional ventilation and lung mechanical measures are extracted using the lung deformation field obtained from the matching process. The deformation field is composed of 3D displacement vectors at each voxel in the lung that represent the direction of change (expansion or contraction) and the magnitude of the deformation. The Jacobian determinant of the deformation field estimates point-wise tissue expansion and contraction (volume change) during respiration.

Let $T(x) = [T_1(x) + T_2(x) + T_3(x)]^T$ be the 3D transformation function used for matching an inspiratory CT (moving) to an expiratory CT (fixed) image. Let $u(x) = [u_1(x) + u_2(x) + u_3(x)]^T$ be the displacement vectors at voxel x representing the deformation from inspiration to expiration. Then, the transformation function at voxel x can be written as

$$T(x) = x + u(x), \quad (7)$$

the Jacobian determinant $J(T(x))$ at location $x = (x_1, x_2, x_3)^T$ is defined as

$$J(T(x)) = \begin{vmatrix} \frac{\partial T_1(x)}{\partial x_1} & \frac{\partial T_2(x)}{\partial x_1} & \frac{\partial T_3(x)}{\partial x_1} \\ \frac{\partial T_1(x)}{\partial x_2} & \frac{\partial T_2(x)}{\partial x_2} & \frac{\partial T_3(x)}{\partial x_2} \\ \frac{\partial T_1(x)}{\partial x_3} & \frac{\partial T_2(x)}{\partial x_3} & \frac{\partial T_3(x)}{\partial x_3} \end{vmatrix}, \quad (8)$$

and

$$J(T(x)) = \begin{vmatrix} 1 + \frac{\partial u_1(x)}{\partial x_1} & \frac{\partial u_2(x)}{\partial x_1} & \frac{\partial u_3(x)}{\partial x_1} \\ \frac{\partial u_1(x)}{\partial x_2} & 1 + \frac{\partial u_2(x)}{\partial x_2} & \frac{\partial u_3(x)}{\partial x_2} \\ \frac{\partial u_1(x)}{\partial x_3} & \frac{\partial u_2(x)}{\partial x_3} & 1 + \frac{\partial u_3(x)}{\partial x_3} \end{vmatrix}. \quad (9)$$

The Jacobian determinant of the deformation field provides the magnitude of change, representing local volume change due to respiration at any given location in the lung. The

Jacobian determinant (J) ranges from 0 to infinity, where $J = 1$ represents neither contraction nor expansion, $J < 1$ represents contraction, and $J > 1$ represents tissue expansion.

In addition to Jacobian measurement of volume change, deformation field information can be used to estimate the degree of anisotropic deformation in the lung during respiration and how it is impacted in the presence of disease. The deformation tensor F derived from the matching process is same as the Jacobian matrix J , which can be further decomposed to rotation R and stretch U tensors:

$$F = RU, \quad (10)$$

and the right Cauchy-green deformation tensor is defined as

$$C = F^T F = U^T R^T R U = U^T U. \quad (11)$$

The principal stretches can be obtained from U by the Eigen decomposition of C and estimating the square root of three Eigen values as follows:

$$\lambda_i = \sqrt{\text{Eigen values of } C} (\lambda_1 > \lambda_2 > \lambda_3) \quad (12)$$

Thus, the ratio of maximal extension to minimal extension represents the anisotropy of lung deformation during respiration, and the measure is referred to as the anisotropic deformation index (ADI)⁸⁴:

$$ADI = \frac{\lambda_1}{\lambda_3}. \quad (13)$$

The value of ADI ranges from 1 to infinity, where the higher the ADI, the higher the anisotropy in the deformation.

Bodduluri and colleagues created a lung biomechanical feature set comprising Jacobian, strain, and ADI measurements obtained by matching inspiratory and expiratory CT scans in 194 COPD subjects.⁷³ Figure 3 shows the Jacobian measure of volume change in representative subjects with mild and severe COPD. The mechanical measures from the matching process outperformed single-volume CT density-based measurements in distinguishing COPD subjects across GOLD stages of disease severity (area under the curve = 0.82). J , a measure of volume change, was also shown to be strongly associated with spirometry measures of lung function and patient outcomes such as 6-min walk distance; the body mass, airflow obstruction, dyspnea, and exercise capacity index that predicts mortality; and the St. George's respiratory questionnaire score, which measures respiratory quality of life.⁷² The reported associations were adjusted for age, sex, body-mass index, pack-years of smoking, and CT scanning protocol. The significant association between the Jacobian

measure and patient outcomes indicates that poor elasticity of lung parenchyma is better reflected by mechanical measures such as the Jacobian determinant and the ADI, as compared to density-based measurements from single-volume CT scans. In a recent article, Bhatt et al. used voxel-level Jacobian measurement to investigate the influence of emphysematous tissue on surrounding normal lung tissue in COPD subjects.⁶⁹ The effect of emphysema in the lungs has previously been shown through computer simulations, wherein cyclic inflation and deflation during respiration appears to impose additional mechanical forces on lung regions near emphysema, thus leading to emphysema progression.^{85–88} In 680 subjects with COPD who completed a five-year follow-up, Bhatt and colleagues matched the inspiratory CT with expiratory CT to determine the Jacobian measurement of volume change at each lung voxel. Emphysema regions were then identified as voxels < -950 HU on the deformed inspiratory CT scan. To estimate the impact of emphysematous voxels on the surrounding normal voxels, the distance was computed between each normal voxel and the nearby emphysematous voxel. The average Jacobian of the regions within 1 to 5 mm of emphysematous regions was then calculated. The Jacobian determinant of regions up to 2 mm (but not beyond) of emphysema was an independent predictor of FEV₁ decline after adjustment for age, ethnic group, gender, pack-years of smoking, FEV₁ at baseline, CT emphysema on inspiratory CT, CT gas trapping on expiratory CT, CT airway wall area percent (WA%), and CT scanning protocol. These regions, referred to as mechanically affected lung (*MAL*_{2 mm}), could be quantified to predict lung function decline. The findings show that image matching-based measures of lung mechanics can identify lungs at risk in COPD at early stages and can be used as a potential biomarker for disease progression.

Instead of using the Jacobian determinant of deformation field, Simon proposed an alternative regional ventilation measurement called specific volume (SV) change, based on the HU values of the deformed and fixed image.⁸⁹ SV change provides a relationship between local change in air content and the corresponding density change (HU) during respiration. SV change is defined as

$$SV = \frac{1000(HU_{EXP} - HU_{INSP})}{(HU_{INSP}(HU_{EXP} + 1000))}, \quad (14)$$

where HU_{EXP} and HU_{INSP} represent the density values at corresponding locations on the expiratory CT and deformed inspiratory CT image. Yamamoto et al. further investigated the effectiveness of both SV and Jacobian determinant-based measurement of ventilation on 4D CT images of 12 subjects with emphysema.⁹⁰ SV change measurements were strongly correlated with severity of emphysema more so than the Jacobian measurements of ventilation.

Alternatively, Coxson et al. proposed another metric called specific gas volume (SV_g) to quantify air content in the lungs using single-volume CT images,^{91,92} defined as

$$SV_g = SV_{tissue\ and\ gas} - SV_{tissue}, \quad (15)$$

where

$$SV_{tissue\ and\ gas}(ml/g) = \frac{1024}{HU\ (mg/ml) + 1024}, \quad (16)$$

and the specific volume of the tissue (SV_{tissue}) was assumed to be 0.939 mL/g.⁹³ Salito and colleagues showed that SV_g is highly homogeneous in healthy subjects when compared to patients with severe COPD.⁹⁴ The authors also proposed a heterogeneity index representing SV_g variations in the entire lung and showed that the index is helpful in assessing the effect of different lung volume reduction treatments. Aliverti et al. compared both SV change and SV_g measurements of ventilation.⁶⁸ SV_g maps of ventilation have shown minimal gravity dependence, and heterogeneity in SV_g was directly related to underlying lung disease.⁶⁸

C. Disease Progression Measures

To quantify emphysema progression, Gorbunova and colleagues used image matching between a baseline CT and a follow-up CT scan from the same subject.⁷⁶ The authors subtracted the deformed inspiratory CT image (moving) from the expiratory CT image (fixed). Regions with negative values were attributed to disease progression, because emphysema results in low attenuation areas in the lung. Lung mass-preserving criteria have been used in the cost function to account for changes in lung density due to respiration. The density difference-based progression measurement correlated with FEV₁ decline over time. The authors proposed a new method to monitor disease progression at the local level, which was not available earlier. Later, the same investigators incorporated a new progression metric using image matching. This compared corresponding regions of interest between baseline and follow-up CT scans, instead of direct voxel-to-voxel density comparison.⁷⁵ Histogram-based features were obtained from random samples of corresponding regions in the lung and were compared using L1-norm and Kullback–Leibler divergence dissimilarity indices. The use of image matching for disease progression is heavily reliant on the comparison of CT densities between corresponding locations of baseline and follow-up scans. However, direct density comparison is not entirely representative of disease progression, because CT density values are also influenced by CT scanning parameters and the level of inspiration during image acquisition. Staring et al. evaluated three different density correction methods to minimize changes in CT density due to CT scanning parameters and level of inspiration.⁹⁵ The first method follows a sponge model of lungs that corrects CT density values based on the assumption that overall lung mass is preserved during respiration. However, the constant lung mass assumption does not hold true because mass changes as a result of changes in venous return. The second and third methods of density correction are based on the slope of log volume–log density (HU) relationship. The second method corrects the density based on the slope of patient-specific total lung volume and mean lung density (global slope), whereas the third method is based on the slope of log volume–log density for individual lung regions (local slope). The local slope-based density correction was shown to exert minimal influence due to external reasons. The density comparison after local slope-based corrections was more representative of emphysema progression.

D. Evaluation of Matching Accuracy

Although image matching provides much-needed anatomical correspondence among images acquired at different time points, it is also vital to evaluate spatial accuracy between the deformed image and fixed image. The current gold standard to evaluate the accuracy of image matching is to measure the distance between manually annotated anatomic landmarks in the two images. In the case of pulmonary CT image matching, the landmarks can be vessel and airway bifurcations, lobar fissures, and lung surfaces. However, the selection of landmarks is time intensive, requiring accurate domain knowledge; anatomical landmarks do not represent all lung regions. Several semiautomatic and automatic landmark selection software options have been developed.^{96–98} Alternatively, the quality of matching can also be evaluated using several similarity functions, such as the sum of squared difference, the sum of squared tissue volume difference, normalized cross-correlation, and mutual information.

V. CONCLUSION

CT imaging of pulmonary structures has revolutionized our understanding of underlying disease processes involved in COPD. Traditional measures using density-based emphysema, gas trapping, and airway wall morphology have been well validated and shown to have strong correlations with clinical measures of COPD. However, these measures are derived from single-volume images (either inspiratory or expiratory CT) and do not provide insights on regional ventilation and mechanics. Alternatively, CT image matching combines information from both inspiratory and expiratory scans and provides lung deformation patterns at the voxel level, thus offering novel ways to measure ventilation and mechanical properties of lung parenchyma during respiration. The combined use of single-volume CT measurements (emphysema, gas trapping, texture, and airway wall morphology indices) and dual-volume CT measurements (specific volume change, specific gas volume, Jacobian determinant, local tissue strain, and anisotropic deformation index) can lead to better understanding of COPD pathophysiology and disease progression.

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FIG. 1.
Image matching framework

FIG. 2.

PRM technique.⁷⁴ The inspiratory and expiratory CT images are spatially matched for voxel-to-voxel comparison in a representative subject. (Left columns) Original inspiratory and expiratory CT images before the matching process; (right columns) deformed inspiratory CT and expiratory CT images after the matching process. (Arrows) Voxel-to-voxel correspondence. Voxels that are > -950 HU on deformed inspiration and > -856 HU on expiration image are considered to be normal (green ovals); voxels that are < -950 HU on the deformed inspiratory CT and < 856 HU on the expiratory CT represent emphysema (red ovals); voxels that are > -950 HU on the deformed inspiratory CT but < -856 HU on the expiratory image show areas of functional small airways disease (fSAD).

FIG. 3.

Jacobian determinant map of volume change for representative subjects with mild and severe COPD. The inspiratory CT is spatially deformed to match the expiratory CT image. The Jacobian determinant of the deformation field (3D displacement vectors at each voxel) is then used to estimate local volume change. The value of the Jacobian ranges from 0 to infinity, where $J = 1$ represents no change in the region, $J > 1$ represents tissue expansion, and $J < 1$ represents tissue contraction.