Pulmonary Analysis Software Suite 9.0: Integrating Quantitative Measures of Function with Structural Analyses

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Abstract. With the recent advances in multidetector-row CT (MDCT) to dynamically assess the lung with a z axis coverage now including up to 70% of the whole lung, we have integrated quantitative measures of regional pulmonary perfusion and ventilation into the Pulmonary Analysis Software Suite (PASS), allowing for detailed assessments of structure-to-function relationships and are using this integrated system to identify early smokers at risk of chronic obstructive pulmonary disease (COPD). Previously we developed methods to segment lungs, lobes, airways, and blood vessels and extract histogram and texture-based measures of the lung parenchyma. These segmentation, analysis and display tasks were integrated into a comprehensive software package: PASS.

Keywords: MDCT, Medical Image Analysis, Texture Analysis, Functional Imaging, Ventilation, Perfusion

1 Introduction

Quantitative assessment of lung structure along with indices of parenchymal pathology are taking on increased roles in the detection and tracking of pulmonary disease. To date the focus has largely been on airway morphometry and indices of parenchymal destruction, and air trapping. The parenchymal analysis has, in large part, focused on the use of the density histogram within the lung field to identify voxels falling below a given density threshold to define volumes of emphysema-like lung or air trapping. Some work has shown that texture measures can provide more accurate detection and quantification of pathology not limited to enlargement of peripheral air spaces [1, 2]. To date, our quantitative tools for the assessment of the lung parenchyma have been integrated into a software package which we have dubbed the Pulmonary Analysis Software Suite or PASS, and PASS has been used in a number of large multi-center studies including the NIH sponsored National Emphysema Treatment Trial [3], the Lung Imaging Database Consortium [4], and as

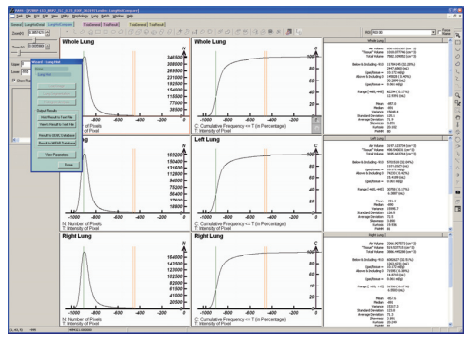
clinical applications for PASS have expanded, this software has been commercialized and integrated with airway analysis and guidance software (Pulmonary Workstation Plus, VIDA Diagnostics, Coralville, IA). In addition to structural information, dynamic CT imaging is capable of delivering regional measures of ventilation and perfusion by following the accumulation of Xenon gas over multiple breaths [5, 6, 7] or the first pass kinetics of a sharp bolus of iodinated contrast agent as it passes through the lungs [8, 9]. To date, the functional measures have been limited largely to research studies because of the limited z-axis coverage during axial scanning protocols. With the recent advances in multidetector-row CT (MDCT) to dynamically assess the lung with a z axis coverage now including up to 70% of the whole lung, we have been motivated to integrate our quantitative measures of regional pulmonary perfusion and ventilation into PASS, allowing for detailed assessments of structure-to-function relationships. In an early application of integrated system we are identifying smokers at risk of chronic obstructive pulmonary disease (COPD) but with normal pulmonary function tests to assess correlations between early structural (histogram-based analysis) and functional (perfusion measures) changes. In this paper, we present an overview of the newly expanded PASS that now provides the link between structure and function for the inclusion of regional distribution of ventilation and perfusion as part of a comprehensive phenotype determination [10].

2 Software Components

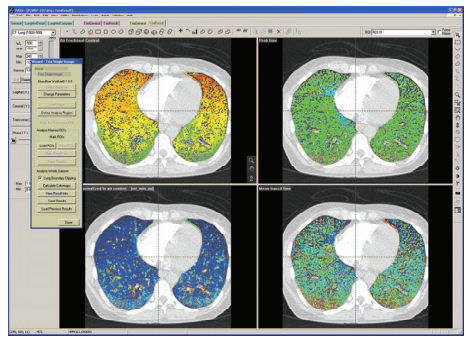
2.1 PASS Core Functionality

2.1.1 Task Concept

The PASS framework is organized with a task-document-frame-view hierarchical structure. Depending on the task, one or more documents can be opened simultaneously, each document can open one or more frames, and each frame can show multiple different kinds of views. This design schema can be separated into two layers, the underneath layer is the document-frame-view structure which is a traditional multi-document interface (MDI). The upper layer is the task manager that uses a sequence of wizard dialogs to guide the user through predefined steps to finish a particular analysis process. The goal of this schema is to make the PASS software as flexible as a traditional MDI while also being simple to use as similar wizard driven applications. **Figure 1** shows an example of the task concept in which three tasks are open simultaneously. Each task is distinguished by a unique background color for both the tab bar at the top of the window and the floating dialog box. The floating dialog box is the interface to task manager that controls the task. Users can switch tasks by pressing the colored tabs at the top of the window, and the task manager will be switched automatically to the correct task.



(a)



(b)

Fig. 1. Three tasks are opened in PASS. **(a)** The first task is the Histogram Analysis task (displayed in blue). This task opens one document which in turn opens three frames of result data. The third frame, which contains 9 views, is pictured above. **(b)** The third open task is the TSIA Single Image task (displayed in yellow). One document is opened which creates two frames. The second frame, which contains 4 views, is currently in display.

2.1.2 PASS Profile

In order to facilitate situational based behavior of the general class pieces of the PASS structure while under control of a wizard, a profile method has been designed. Each instance object of the above class will be assigned a corresponding type of profile that defines the behavior of that object. For example, depending on the task, document, frame, or location within a frame, an object of the transverse view class may display

different content. Similarly, parameters are saved for each algorithm, allowing them to be retrieved based on a user's previous usage. Each task has a user-configurable set of default profiles for the objects used in that task.

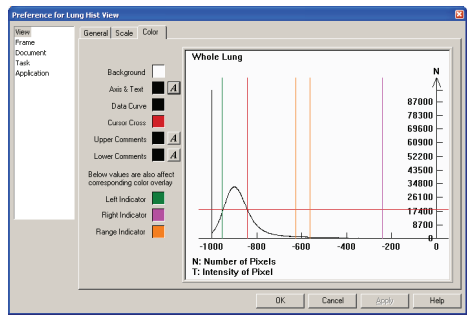


Fig. 2. PASS includes a Profile editing interface, pictured above are the settings for Lung Histogram View. Through this interface the user can adjust the profile settings for current view, frame, document, or task respectively. The options that can be adjusted vary depending on the type of the object selected in the profile editor.

2.1.3 Separation of Core Functionality and Time Series Algorithms

The PASS software package is extensive, containing hundreds of GUI components and algorithm modules. In order to manage the development in an efficient way, the GUI framework is separated from the algorithm modules. For example, the Time Series Image Analysis (TSIA) algorithm modules are independently developed outside of PASS framework and are dynamically loaded into PASS at runtime using a common memory module (CMM) interface.

2.1.4 DICOM Viewer

PASS enables the viewing of 2D, 3D, and 4D image data in a variety of ways. Typically, the input to the PASS is a multi-dimensional MDCT data set of thorax as a series of DICOM files. Inside a user specified directory, PASS finds all valid DICOM files, automatically detects the scan plan, and organizes them into a single multi-dimensional dataset. In some situations, a multi-dimensional scan is acquired in multiple steps; with each step making up only a smaller portion of the thorax or of the time series. The final dataset needs to be created by intelligently joining several of these partial datasets. In the case where extra slices or overlap occurs between datasets, a dialog prompts the user to interactively remove the extra slices. The newly created dataset can be saved in the extended DICOM format for future use enabling the user to skip the joining process in the future.

2.1.5 Extension to DICOM Standard

The standard DICOM file format is limited to 2D images. Additions have been made to the standard to enable it to handle higher-dimensional (3D & 4D) image data. A private section is inserted into the standard 2D DICOM tag structure that includes information regarding the higher-dimensionality of the dataset including number of phases, depth of volume, phase timing, etc. The pixel bitmap for the first slice is stored in the public area as usual; while the rest of the pixel bitmaps are stored under the private section. A special tag is generated by grouping the series-varying information from the original series into a single tag. This method enables the retrieval of 2D DICOM information from within the new higher-dimensional dataset and also retains the ability to recover the original DICOM files if necessary without data loss.

2.1.6 Segmentation

Lungs. One of the important first steps for quantitative analysis is segmentation of left and right lungs. The PASS lung segmentation processing consists of three main steps: an extraction step to identify the lungs; a separation step to separate the right and left lungs; and an optional smoothing step to smooth the lung boundaries. Complete details and validation information for the lung segmentation algorithm are given in [11].

Airways. Airway processing consists of three separate steps: (1) segmentation of the airway lumen, (2) analysis of the tree structure to define the branch centerlines and branching relationships, and (3) measurement of the airway lumen and airway walls. Complete algorithm details are given in [12, 13].

Vessels. The vessels are segmented using a variant of the method described by Shikata et al. [14]. Shikata et al. use a two-step approach: a line-filtering of the raw data based on an eigen-analysis of the Hessian matrix calculated at multiple scales, followed by an optional vessel tracking approach to extract the small vessel segments which are missed in the first step. For most purposes the second step is not necessary and is undesirable because of the increased computational cost. We threshold the line-filtered result to retain only voxels with line-filtered value less than -0.08, and then subsequently use size filtering to remove all segments less than 75 mm^3.

Currently vessel segmentation in used in PASS as a step within the lobe segmentation process (see below). Additionally, vessel segmentation allows for 3D visualizations of the vascular tree. There is ongoing work to separate the arteries and veins for further quantification of the vessel tree.

Lobes. Identification of the lobar fissures can help decompose the 3D lung into its major structural components. These components can be used as a basis for reporting measurements, and for inter-subject comparisons. The lobar segmentation is guided by the airway tree and vessel trees. After vessel segmentation, a distance map is computed based on the segmented vasculature. This distance map is analyzed using a

watershed transform. The watershed simulation proceeds and the basins are merged using markers automatically generated from the anatomically labeled airway tree. After the watershed analysis is completed, we obtain an initial, approximate segmentation of the fissures. The initial segmentation is refined using a 3D optimal surface segmentation. Full details on the lobar segmentation are given in [15].

Free Hand Drawing. For certain applications such as lung nodule analysis [4], there has been the desire to have a tool for manually identifying structure boarders so that automatically defined edge locations can be compared with radiologist defined gold standards. The free hand drawing tool includes a live wire feature that aids the user in drawing boarders. The free hand drawing can also be modified by shifting individual points along a trace, or multiple points around a boarder can be identified and a cubic spline fit will complete the boarder.

2.1.7 ROI Dictionary / Indexing

Lung segmentation assigns every pixel a region property or ROI label. Typically a mask image is used to record these labels. However, a major limitation of this approach is that the meanings of ROI labels are defined locally. Thus the mask bitmap will be unexplainable without first knowing the specific type of the mask image and having detailed documentation regarding its labeling schema. It is impossible to make global definitions for ROI labels since each pixel in the mask image has limited size (usually 8-bits), but the meaning it should be able to describe is infinite. In order to solve the problem between the limited label and infinite meaning, we proposed a ROI Dictionary/Indexing method. In this method, we build a global ROI dictionary to record all global ROI names and their relationships. For each mask image, a file called ROI Indexing is created which maps the local ROI labels to the global ROI names. With the help of Indexing file, a previous locally defined ROI image becomes a global resource, allowing the use of a mask image in a simple and uniform way.

2.2 Structural Analysis

2.2.1 Histogram Analysis

The gray level histogram has been widely used as a tool for detection of early parenchymal disease. PASS calculates the histogram and cumulative histogram for all pixels in the lung parenchyma. Further subdivisions of the histogram can be achieved using the regions defined from segmentation. Measurements can be reported for any of the defined ROIs, including separating the lung on a lobar basis. Several statistical parameters, such as gray level mean, median, standard deviation, average deviation, skewness, kurtosis, and histogram full width at half maximum (FWHM) are calculated. Total volume, air volume, and tissue volume are computed for each region. The slope and intercept value of the knee line and ankle line of the cumulative histogram curve have been identified as key parameters that may distinguish normal lungs from lung showing signs of early parenchymal disease.

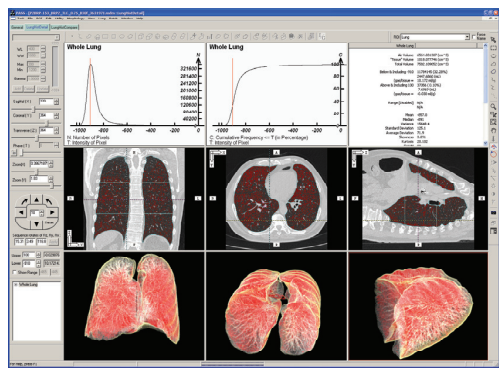


Fig. 3. Histogram analysis in PASS: Parenchymal histogram (upper row left), cumulative histogram (upper row middle), histogram results (upper row right), coronal – transverse – sagittal views (middle row), and 3D renderings (bottom row). Low attenuation areas in red.

2.2.2 Hole Analysis

The onset of emphysema is characterized by the development of poorly ventilated regions within the lungs ("holes"). We try to assess the distribution of holes within the lungs to estimate the severity of the disease process. The distribution of the holes in the normal lung is due only to cross sectional sampling of air within the airway tree. Therefore, we expect the probability distribution of hole cross-sectional area to change as new holes are created and as smaller holes join together to create larger ones during disease progression. Thus the hole distribution curve provides information that can be used to assess the disease severity.

2.2.3 AMFM Texture Analysis

The adaptive multiple feature method (AMFM) was introduced as a texture-based method which could take into account co-existing pathologies and provide a simultaneous classification of multiple simultaneous disease processes. Two kinds of tasks are made possible in the package 2D and 3D. The 2D AMFM uses only 2D features, and therefore works on any 2D images; 3D AMFM uses 3D features and can produce better results for 3D isotropic datasets [1].

2.3 Functional Analysis

2.3.1 Time-Series Image Analysis (TSIA) Task

Overall Concept. The system uses an axially acquired time-series volumetric MDCT data set of the thorax as the input. The acquisitions of these 4D functional scans

employ either ECG or respiratory image gating techniques. The TSIA single image task is selected from the wizard that then guides the user through the analysis process. First an algorithm is selected and the appropriate parameters are set based on previous analyses or current user input. Lungs are segmented and for perfusion analysis a reference ROI is selected within a pulmonary artery region. Results are output either as 3D floating point Analyze images or comma separated value files. On a typical medical image workstation, for a 5x5 grid, Ventilation analysis takes approximately 10 minutes and Perfusion 0.5 hour. These times can clearly be reduced with optimization efforts. For our current human ventilation studies, the total effective radiation exposures dose (HE) is 315/480 mrem for male/female; for perfusion studies, the total effective dose (HE) is 236.25/360 mrem for male/female.

Shared Algorithm Framework. Although the internal algorithm can be totally different from method to method, the basic programming interface for different time sequence image analysis algorithm can be made very similar by passing parameters, options, and results all in format of dynamic array. This makes it possible for us to define a shared algorithm framework and a shared GUI interface. The actual algorithms are designed as plug-in modules and will be dynamically loaded at run time.

Perfusion Algorithm. A central bolus injection of iodinated contrast agent is delivered by a power injector system during an ECG-gated axial dynamic MDCT scan. This software uses indicator dilution theory and first pass kinetics, assuming a bolus injection, residue detection model, to determine the regional Pulmonary Blood Flow (PBF) and perfusion parameters as previously described [8, 9]. Data is filtered to remove major airways and vessels. Mean Transit Time (MTT) and PBF normalized to the mean PBF of the imaged region are examined and heterogeneity can be estimated from its coefficient of variation (CV). MDCT-based perfusion measurements demonstrate significant differences in heterogeneity of perfusion parameters in subjects with imaging-only based evidence of lung pathology and show potential for detection of early inflammatory changes in the lung [10].

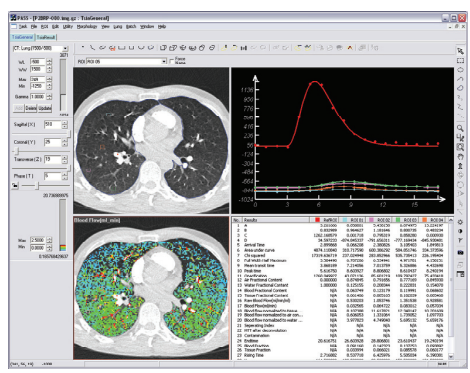


Fig. 4. This figure shows a screenshot of PASS using the TSIA Single Image Task using the perfusion algorithm on a human subject who is a smoker with early signs of emphysema on MDCT. Views: Gray scale CT image with user defined ROIs (upper left), Non-linear curve-fitted ROIs (upper right), Colormap of pulmonary blood flow (lower left) and per-ROI calculated perfusion parameters (lower right).

Ventilation Algorithm. Ventilation is evaluated from a Xenon wash-in series [5, 6, 7]. The density values for a ROI taken during the Xenon wash-in will yield a curve that can be fitted to a single exponential model with a time-constant τ. This time constant is equal to the inverse of the specific ventilation ($s\dot{V}$), the ventilation per unit volume. $\tau = 1 / s\dot{V}$.

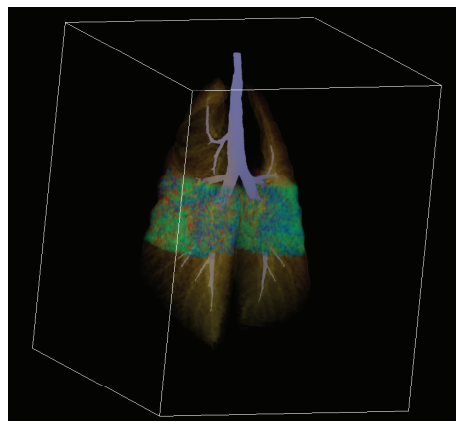


Fig. 5. Results from a ventilation study utilizing the 3D visualization component of PASS. Combination overlay of the lung parenchyma (yellow), airway tree (light blue), and 3D ventilation colormap.

3 Conclusion

Overlay functional data onto the structural image, in both 2D section slice and 3D volume rendering display, provides a unique way to include functional with structural data as efforts increase to use imaging as a means of determining disease phenotypes as part of a search for underlying genetic bases for disease susceptibility.

Acknowledgments. We wish to thank Drs Kenneth Beck, Deokiee Chon, and Brett Simon for their ongoing scientific efforts contributing to this software development. This work was supported in part by NIH HL-064368.

References

1. Xu Y., Sonka M., McLennan G., Guo J., and Hoffman E.A.: MDCT-based 3-D texture classification of emphysema and early smoking related lung pathololegies. IEEE Transactions on Medical Imaging. 25(4), 464--475 (2006)
2. Uppaluri R., Hoffman E.A., Sonka M., Hartley P.G., Hunninghake G.W., McLennan G.: Computer recognition of regional lung disease patterns. Am J. Respiratory and Critical Care Medicine. 160, 648--654 (1999)
3. National Emphysema Treatment Trial Research Group: A Randomized Trial Comparing Lung-Volume Reduction Surgery with Medical Therapy for Severe Emphysema. The New England Journal of Medicine. 348(21), 2059--2073 (2003)
4. Armato S.G. 3rd, McNitt-Gray M.F., Reeves A.P., Meyer C.R., McLennan G., Aberle D.R., Kazerooni E.A., MacMahon H., van Beek E.J., Yankelevitz D., Hoffman E.A., Henschke C.I., Roberts R.Y., Brown M.S., Engelmann R.M., Pais R.C., Piker C.W., Qing D., Kocherginsky M., Croft B.Y., Clarke L.P., The Lung Image Database Consortium (LIDC): an evaluation of radiologist variability in the identification of lung nodules on CT scans. Acad Radiol. 14(11), 1409--21 (2007)
5. Simon B.A., Marcucci C., Fung M., and Lele S.R.: Parameter estimation and confidence intervals for Xe-CT ventilation studies: a Monte Carlo approach. J Appl Physiol. 84, 709--716 (1998)
6. Chon D., Simon B.A., Beck K.C., Shikata H., Saba O.I., Won C., and Hoffman E.A.: Differences in regional wash-in and wash-out time constants for xenon-CT ventilation studies. Respiratory Physiology & Neurobiology. 148(1-2), 65--83 (2005)
7. Tajik J.K., Chon D., Won C., Tran B.Q., Hoffman E.A.: Subsecond multisection CT of regional pulmonary ventilation. Acad Radiol. 9(2), 130--46 (2002)
8. Won C., Chon D., et al.: CT-based assessment of regional pulmonary microvascular blood flow parameters. J Appl Physiol. 94(6), 2483--93 (2003)
9. Chon, D., Beck K.C., et al.: Regional pulmonary blood flow in dogs by 4D-X-ray CT. J Appl Physiol. 101(5), 1451--65 (2006)
10. Alford S.K., van Beek E.J., Hudson M., Baumhauer H., McLennan G., and Hoffman E.A.: Characterization of regional alterations in pulmonary perfusion via MDCT in nonsmokers and smokers. European Congress of Radiology, March 2008. Oral Presentation B-820.
11. Hu S., Hoffman E.A., Reinhardt J.M.: Automatic lung segmentation for accurate quantitation of volumetric X-ray CT images. IEEE Transactions on Medical Imaging. 20 (6), 490—498 (2001)
12. Tschirren J., Hoffman E.A., McLennan G., Sonka M.: Intrathoracic airway trees: segmentation and airway morphology analysis from low-dose CT scans., IEEE Transactions on Medical Imaging. 24(12), 1529--1539 (2005)
13. Tschirren, J., McLennan, G., Palagyi, K. Hoffman, E.A., Sonka, M.: Matching and anatomical labeling of human airway tree. IEEE Transactions on Medical Imaging. 24(12), 1540--1547 (2005)
14. Shikata H., Hoffman E.A., and Sonka M.: Automated segmentation of pulmonary vascular tree from 3D CT images. Proc. SPIE. 5369, 107-116 (2004)
15. Ukil S., Reinhardt J.M., etc: Lung lobe segmentation in X-ray CT image using anatomic guidance. IEEE Transactions on Medical Imaging. (2008, in press)