

Specific Aims

Medical research significantly benefits from the development and proliferation of imaging-related analysis packages, particularly those softwares which have been tailored for specific application domains. Although several such established packages exist for *neuroimaging* research (e.g., FSL, FreeSurfer, AFNI, SPM), no such package exists for pulmonary imaging analysis. The primary goal of this proposal is to develop a robust, open-source image analysis toolkit and dissemination platform, along with annotated data, specifically targeted at the pulmonary research community.

Although methodological research is continually being presented at conferences and published in various venues, the unfortunate reality is that much of this work exists strictly in “advertisement” form. Oftentimes the underlying code is unavailable to other researchers or is implemented in a limited manner (i.e., strictly as proof-of-concept software). Frequently, crucial parameter choices are omitted in the corresponding publication(s) which makes external implementations difficult. In addition, the data used to showcase the proposed methodologies are often private and actual data visualization is limited to carefully selected snapshots for publication (i.e., advertisement) purposes which might not be representative of algorithmic performance. Finally, many of these analysis methods are patented and/or integrated into proprietary commercial software packages which severely limits accessibility to researchers.

As a corrective alternative, this proposal will provide an open-source software toolkit for core pulmonary image analysis tasks across multiple modalities, many of which we have proposed previously in past publications. These **basic tasks** include pulmonary image registration, template building for cross-sectional and longitudinal (i.e., respiratory cycle) analyses, and functional and structural lung image segmentation. In addition to the software, we will provide both the input and output data consistent with open-science principles not only so that other users can it to reproduce our results, but it will also allow researchers to use it in an unrestricted manner in their own studies. Formally, this proposal is defined by the following specific aims:

- **Specific Aim 1: Develop a set of open-source software tools for CT, proton, and He-3 pulmonary computational analysis.** These open-source software tools will specifically target pulmonary image analysis and comprise core application functions such as inspiratory/expiratory registration for inferring pulmonary kinematics, ventilation-based segmentation, lung and lobe estimation, airway segmentation, and calculation of clinical indices for characterization of lung development and pathology.
- **Specific Aim 2: Provide multiple sets of multi-modal annotated lung data (CT, proton, and He3) for unrestricted public use.** In addition to the public unavailability of the algorithms used to produce the results discussed in certain publications, the input and output data is also typically not available. Such availability would be invaluable to other researchers in the community for appropriation for their own purposes including algorithmic performance assessment and running the proposed prior-based methods requiring annotated input data.
- **Specific Aim 3: Evaluate and disseminate multiple complete studies with input data from multiple investigators to showcase the utility of the tools and data provided with this proposal.** In order to maximize the utility of the proposed pulmonary image analysis framework, our proposal also includes making available the input data from multiple researchers (with their permission) involved in a variety of pulmonary research questions and the output data produced by the framework. Among other purposes, this contribution will provide complete, concrete examples demonstrating usage of the proposed contribution.

As principal developers of the popular, open-source ANTs (Advanced Normalization Tools) package, we have extensive experience in the development of well-written software that has gained much traction in the neuroscience community. We have also participated in several image analysis competitions for a variety of applications (neuro, pulmonary, and cardiac) and data scaling and believe that this will also contribute to our success in accomplishing the goals of this application.

Research Strategy

3(a) Significance

3(a.1) The importance of publicly available software tools for domain-specific medical image analysis

Well-vetted and publicly available software is a significant benefit to targeted research communities. For example, the neuroscience community has greatly benefited from highly evolved software packages such as FreeSurfer [1], the FMRIB Software Library (FSL) [2], the Analysis of Functional NeuroImages (AFNI) package [3], and the Statistical Parametric Mapping (SPM) package [4]. Performing a pubmed query for any one of these softwares every year for the past decade (cf Figure 1) illustrates the growing use of such packages and the research studies that are produced as a result. However, despite the absolute number of articles produced using such software and the year-by-year usage increase, no such analogous set of tools exist for pulmonary-specific research. In fact, in a recent review of CT- and MRI-derived biomarkers for pulmonary clinical investigation, the authorial consensus is that “universally available image analysis software” is a major hinderance to more widespread usage of such imaging biomarkers [5].

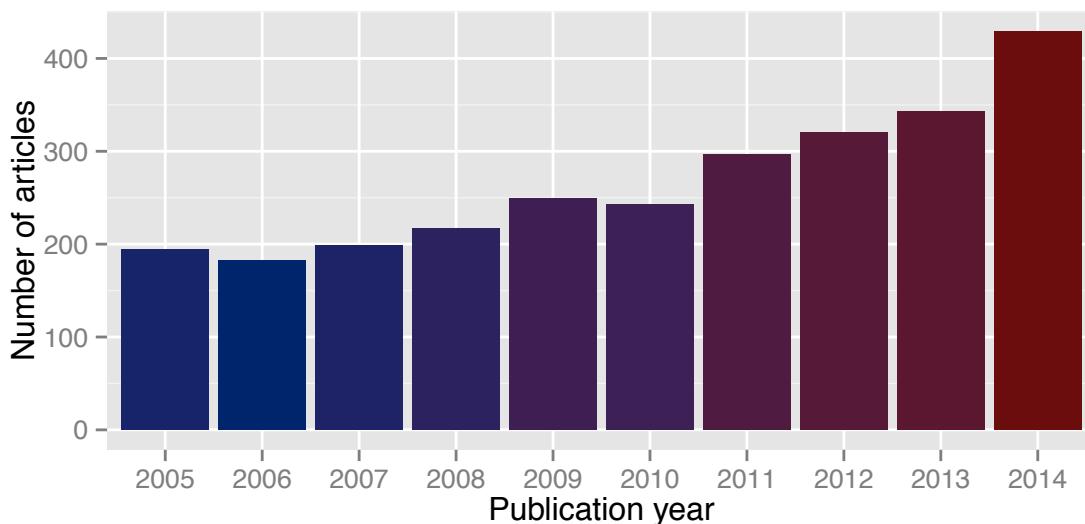


Figure 1: Number of articles per year which cite publicly available neuroimaging analysis packages (specifically, FreeSurfer, AFNI, FSL, and SPM). Although the benefits seem clear for the neuroscience community, analogous efforts within the pulmonary community have yet to be undertaken.

Medical image analysis libraries (e.g., the NIH-sponsored Insight ToolKit) provide extensive algorithmic capabilities for a range of generic image processing tasks. However, tailored software packages for certain application domains (e.g., lung image analysis) are not available despite the vast number of algorithms that have been proposed in the literature. Note that the goals of this proposal would significantly support the National Library of Medicine’s own open-source directives in that all software would be developed using the established Insight ToolKit’s coding and testing standards with the eventual idea that much (if not all) of the actual code would be contributed for inclusion in future versions of the Insight ToolKit as we have done in the past. It should also be noted that open-source software, in general, has documented benefits within the targeted communities for which it is developed and supported. In addition to the increase in research output illustrated earlier, open-source permits students and researchers to learn specific computational techniques in a social environment [6]. This, in turn, provides motivation for user-based support including potential contributions such as bug fixes and feature additions. Additional analyses have shown the tremendous cost savings that open-source software yields [7].

3(a.2) ANTs and the neuroimaging community

Deficiency of publicly available tools within the neuroscience community has been one of the primary motivations for the inception and continued development of our Advanced Normalization Tools (ANTs). ANTs takes advantage of the mature Insight

ToolKit in providing an optimal software framework for building scripts and programs specifically for neuroimaging. For example, the following core neuroimage processing algorithms have been made available through our ANTs toolkit (complete with online self-contained examples with developer-tuned parameters) and have been used extensively by our group and others:

- brain normalization [8, 9] (<https://github.com/stnava/BasicBrainMapping>),
- brain template generation [10] (<https://github.com/ntustison/TemplateBuildingExample>),
- skull-stripping or brain extraction [11, 12] (<https://github.com/ntustison/antsBrainExtractionExample>),
- prior-based brain tissue segmentation [8] (<https://github.com/ntustison/antsAtroposN4Example>),
- cortical thickness estimation [12, 13] (<https://github.com/ntustison/antsCorticalThicknessExample>),
- brain tumor segmentation [14] (<https://github.com/ntustison/ANTsAndArboles>), and
- cortical labeling [15, 16] (<https://github.com/ntustison/MalflLabelingExample>).

In addition to public availability, some of these algorithms have been showcased in international competitions and have performed extremely well [15, 17, 18].

3(a.3) The significance of ANTs for the pulmonary imaging community

Analogously, several algorithmic categories exist for lung image analysis which, as we have stated previously, do not exist in any comprehensive, publicly available package. An extensive survey concentrating on the years 1999–2004 is given in [19] which covers computer aided diagnosis of lung disease and lung cancer in CT (i.e., detection and tracking of pulmonary nodules) and provides an overview of the many relevant segmentation methods for pulmonary structures. Although many algorithms existed at the time, continued technical development has only increased the number of available algorithms. The following is a small sampling of more recently reported techniques for CT analysis:

- whole lung differentiation from the chest wall (e.g., [20–23])
- bronchial structure extraction (e.g., [24, 25]; the many submissions to the recent Extraction of Airways from CT (ExACT) challenge of the 2nd International Workshop on Pulmonary Image Analysis [26]),
- vasculature segmentation (e.g., [27, 28]),
- lobe and/or fissure detection (e.g., [29, 30]), and
- feature extraction and classification (e.g., [31–33]).

Since this list is restricted to CT image analysis, inclusion of additional techniques specific to other modalities will have additional benefit. For example, ventilation-based segmentation for analysis of ventilation lung imaging (e.g., [34] which was implemented within the ANTs framework) will also have significant impact in a comprehensive lung image analysis suite. Since most of the tools that have been developed within the ANTs framework have generic applicability, crucial to the development of our proposed toolset will be domain-specific experience. For example, although ANTs performance in brain registration has been independently evaluated and found to be of relatively high quality [Klein2009], tailoring our registration tool in the EMPIRE10 challenge (Evaluation of Methods for Pulmonary Image REGistration 2010) required significant empirically-based tuning. In addition, new innovations in diffeomorphic registration technology has led to a Symmetric Normalization B-spline variant which has demonstrated accurate normalizations [35], and transformations which are particularly well-suited for pulmonary data [36].

3(b) Innovation

3(b.1) Open source pulmonary algorithmic innovation

Given the lack of open-source solutions for pulmonary image analysis, the proposal goals would produce an innovative platform for performing such research. Similar to the brain-specific algorithms provided in our ANTs toolkit, our novel and useful proposal would include several essential algorithms for analyzing lung images from different modalities including CT, ^{3}He , and proton MRI. Many algorithms have been proposed in various technical venues but that which we propose would provide

well-vetted and easy-to-use implementations of specific robust methodologies for pulmonary medical image analysis, many of which have been developed by our group. To facilitate the usage of these algorithms, we will provide several self-contained online examples (complete with data).

3(b.2) Publicly available multi-site data as a reproducible and didactic component

An additional innovative component we are proposing is the inclusion of complete study data and detailed instructions for generating reproducible, multimodality pulmonary studies using the proposed package with input data from several of our external collaborators and colleagues. Specifically, we have asked several scientists and researchers who are familiar with our work to provide imaging data of various modalities which we will then process using the proposed toolkit. These processed data will then not only be returned to the corresponding providers with detailed instructions on reproducing these results in their own labs but will also be provided to the public for any interested researcher to reproduce the results. Given the different image acquisition sources, this strategy should also demonstrate the robustness of our tools.

Included in these analyses will be analyses of our own data. Any clinical findings of interest will be published in traditional venues (e.g., Chest). In addition, we will provide all image data and the quantitative analysis scripts as a companion release to accompany the paper (e.g., see previous similar offerings from our group [12, 35]). Such a comprehensive clinical investigation using these tools will not only provide insight into the specifics of certain pulmonary pathologies but will also provide a reproducible mechanism for using the tools created with this proposal.

3(c) Research design

3(c.1) Preliminary data

3(c.2) Specific Aim 1: To develop a set of open-source software tools for CT, proton, and ^{3}He pulmonary computational analysis.

Although the proposed software library would be extendable based on new methodological developments and continued analysis experience, the core development will include several fundamental tools:

B-spline-based Symmetric Normalization. A thorough comparison with the well-known ANTs SyN algorithm [37] was performed with a B-spline variant [35]. This evaluation utilized multiple publicly available, annotated brain data sets and demonstrated statistically significant improvement in label overlap measures. As part of that study, we produced the scripts `antsRegistrationSyN.sh` and `antsRegistrationSyNQuick.sh` which provide a simple interface to our normalization tools for brain-specific normalization based on our extensive experience.

Similarly, we used the EMPIRE10 challenge framework to provide an additional comparison in the context of pulmonary CT image registration [38]. Registration accuracy is based on a combination of factors including lung boundary and fissure overlap, landmark correspondence, and topology considerations in the displacement field. In this domain, the B-spline variant showed a separate performance gain and has since become the preferred transformation model for small deformation image registration problems (an additional domain is cardiac MRI where it recently won the best paper award [39]). As part of the development, we will provide simple script-based interfaces for lung-specific normalization tasks.

Multi-feature CT and multi-modal MRI template generation. Given the variability in lung shape across populations and the lack of publicly available lung atlases, generating population- or subject-specific templates significantly enhances study potential. Although the template construction algorithm described in [10] was applied to T1-weighted brain data (with the extension of multimodal data described in [14]), it is sufficiently generic such that it is easily applied to pulmonary data.

For example, in Fig. 4, we illustrate the major processing components of a recent study analyzing local changes based on a pulmonary treatment plan [40]. This study employed several of the tools we are proposing for inclusion in the specified aims. The first major component is the construction of a single-subject ^{3}He /proton MRI template for all five imaging time points. This step generates the statistical coordinate system for the voxelwise regression analysis of the normalized intensities to determine correlation with expected treatment effects.

Atlas-based lung segmentation. Identification of anatomical structure in MRI is often a crucial preprocessing step for quantification of morphological features or ventilation information from functional images. Quantitative regional analysis

Longitudinal voxelwise analysis of ventilation data

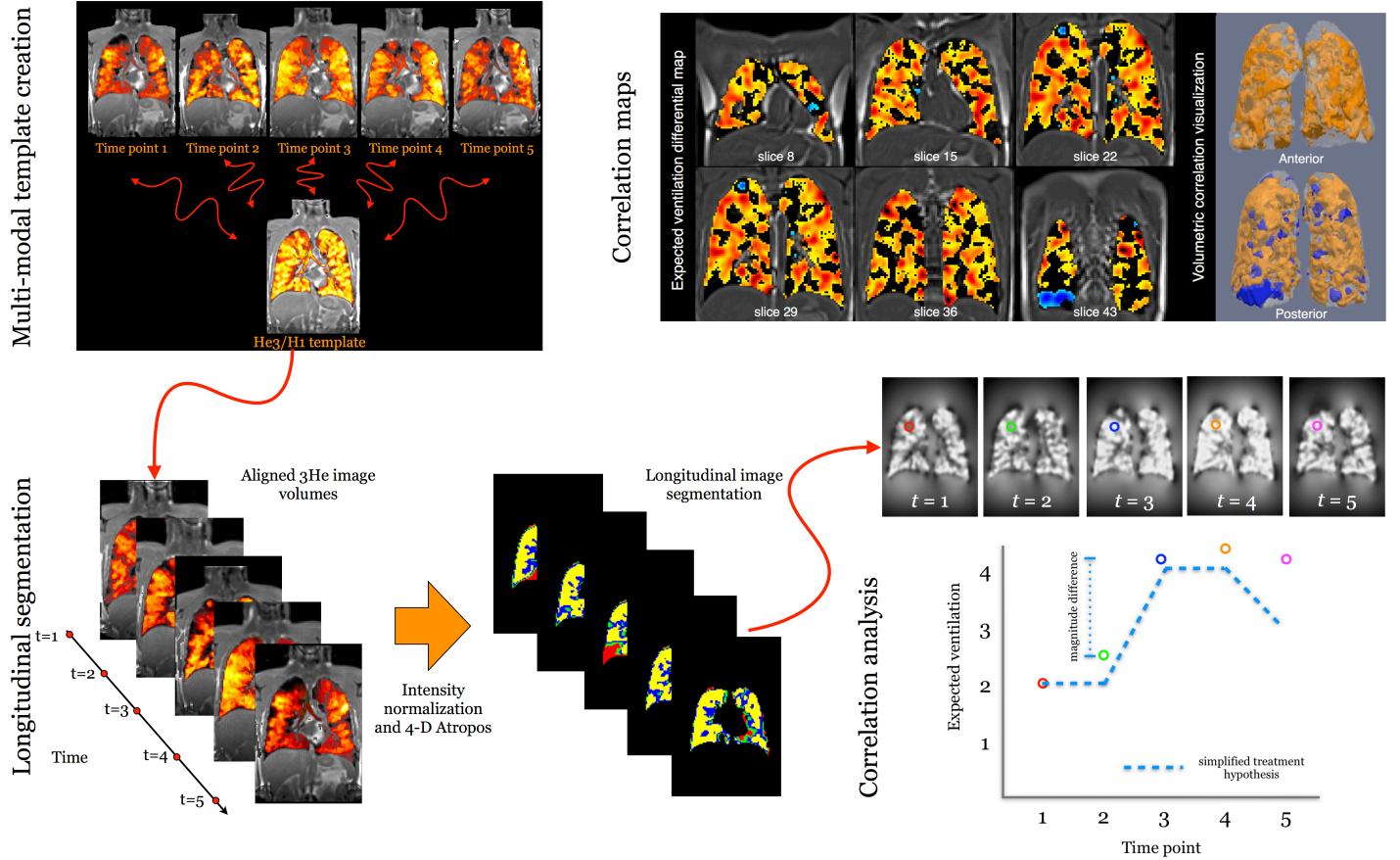


Figure 2: Voxelwise regression analysis to determine image-based response to treatment. First, a multi-modal, single-subject template is created to bring all time point images to the same coordinate system. 4-D segmentation is performed on the longitudinal time series of 3-D image volumes. Treatment effects are expected to follow the simplified treatment hypothesis illustrated with the dashed blue line in the plot on the right. To explore how the longitudinal change in expected ventilation follows this treatment hypothesis with image data, we smooth the aligned expected ventilation maps (to account for potential voxelwise misalignments) and then quantify how the voxelwise intensities regress with the simplified treatment hypothesis. This quantification is visualized using the correlation maps depicted in the template space (top right). Positive correlations with the expected treatment effect are rendered in orange whereas negative correlations are rendered in blue.

often requires the identification of lung and lobar anatomy. Although much algorithmic research for lung segmentation has been reported in the CT literature [41], co-opting such technologies is complicated by MRI-specific issues such as RF coil inhomogeneity, presence and resolution of structural detail, and the absence of a physically-based intensity scaling.

We recently proposed a multi-atlas approach for automatically segmenting the left and right lungs in proton MRI [36]. Multi-atlas approaches to segmentation have proven highly successful in neuroimaging [15, 16] and these methods translate readily to the pulmonary domain. Whereas many current strategies for lung image segmentation employ low-level processing techniques based on encodable heuristics, consensus-based strategies, in contrast, optimize the prior knowledge applied to a specific segmentation problem (cf Figure 3). The evaluation of our proposed method [36] demonstrated good performance with Jaccard overlap measures for the left and right lungs being 0.966 ± 0.018 and 0.970 ± 0.016 , respectively. One of the benefits of this approach is that it can also be applied effectively to pulmonary CT.

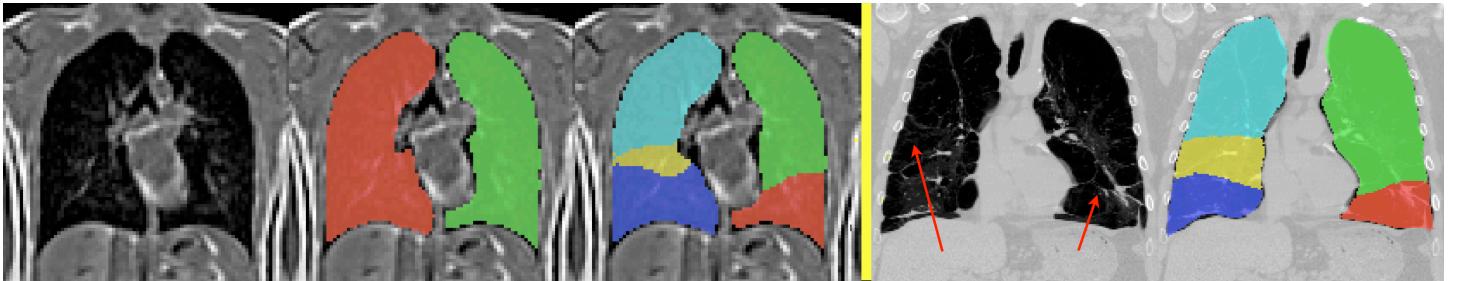


Figure 3: Sample lung and lobe estimation results in both proton MRI and CT using our atlas-based strategy. (Left) Lung segmentation and lobe estimation results for the given proton MRI. Although lobe estimation is dependent solely on the warped atlases, we are able to obtain accurate estimates of lobes which are useful for more regional analysis and provide a more intuitive and universal subdivision of the lungs than previous partitioning schemes. (Right) The utility of this method extends to CT where the integrity of lobar anatomical markers (such as the lack of fissures illustrated by the red arrows) have been compromised due to disease.

Atlas-based lobe estimation. For regional investigation of certain lung pathologies and conditions, it is often useful to quantify measurements of interest within more localized regions, such as the lobes. However there is little (if any) usable information in proton MRI for image-based lobar segmentation which has led to alternative geometric subdivisions which are ad hoc, non-anatomical, and do not adequately address intra- and inter-subject correspondences. However, we can take advantage of inter-subject similarities in lobar geometry to provide a prior-based estimation of lobar divisions using a consensus labeling approach (cf Figure 2).

To generate the lobe segmentation in a target proton or CT lung image, we first generate the binary whole lung mask using the whole lung atlas-based estimation. We then register the set of CT lung masks which have been expertly annotated to the target binary lung mask using the B-spline SyN registration approach described earlier [35]. Subsequently, we warp the set of CT lobe labels to the target image using the CT mask-to-target mask transformation. Since we have no intensity information inside the target lung mask and CT atlas lung masks, we use a simple majority voting strategy to generate the optimal labeling for the target image. Following the majority voting, we remove any labelings outside the lung mask and assign any unlabeled voxels with the label closest in distance to that voxel. This methodology is more thoroughly described in [36] where we showed that lobar overlap measures in proton MRI were on par with the state-of-the-art CT methods where fissure information is actually visible (left upper: 0.882 ± 0.059 , left lower: 0.868 ± 0.06 , right upper: 0.852 ± 0.067 , right middle: 0.657 ± 0.130 , right lower: 0.873 ± 0.063).

Ventilation quantification. Automated or semiautomated approaches for classifying areas of varying degrees of ventilation are of potential benefit for pulmonary functional analysis. In [34], we presented an automated algorithmic pipeline for ventilation-based partitioning of the lungs in hyperpolarized ^3He and ^{129}Xe MRI. Without ground truth data for evaluation, we used a consensus labeling approach [42] to simultaneously estimate the true segmentation from given “raters” which included the segmentation from our automated approach and the manual tracings of three trained individuals. In terms of combined specificity and sensitivity, our automated algorithm demonstrated superior performance with the added benefit of being reproducible and less time-consuming.

Since the initial development, we have continued to improve this segmentation pipeline by incorporating an iterative bias-correction/segmentation estimation scheme. An additional component that improves results is an ANTs-based implementation

of the patch-based denoising protocol described in [43]. Example longitudinal segmentation results are provided in Figure 4.

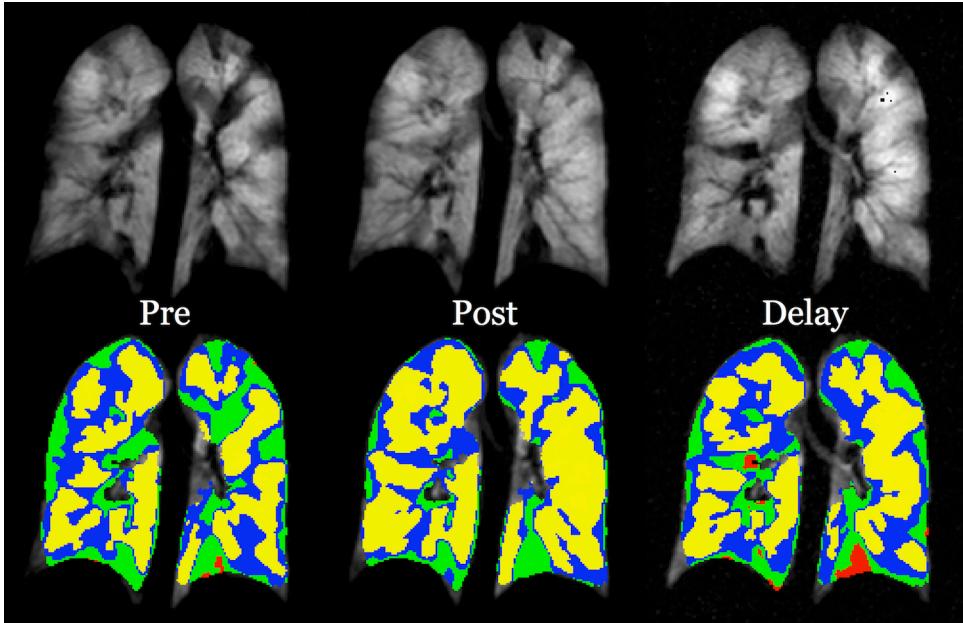


Figure 4: Pulmonary functional segmentation using the algorithmic framework first described in [34] for hyperpolarized ^3He MRI. These data were taken from a current study looking at the implications in ventilation pre- and post-albuterol intake including an additional acquisition at some delay period following the post-albuterol imaging. The ventilation-based segmentation is as follows: red = no ventilation, green = poorly ventilated, blue = normally ventilated, and yellow = well-ventilated. Note the improvement in both the qualitative assessment of the ventilation map (top) and the corresponding segmentation time course (bottom) followed by an approximate return to pre-albuterol conditions following the delay period.

Quantitative CT indices. Imaging biomarkers for characterizing emphysema in CT have been well researched, although there are ample opportunities to refine these methods as well as to introduce more advanced approaches. Examples of the latter include texture analysis for identifying the centrilobular and groundglass opacities and fractal and connectivity approaches to differentiate centrilobular from panlobular emphysema. The indices for CT image analysis can roughly be divided into those that characterize the pulmonary parenchyma: volumetric tissue (e.g., [44, 45]), distribution of low attenuation areas (LAA) (e.g., [46, 47]), cooccurrence and run-length matrix features (e.g., [31, 48]), attenuation statistics (e.g., [49, 50]), deformation measures (e.g., [51, 52]), and stochastic fractal dimension features (e.g., [31, 50]) and those that characterize the airways (e.g., [53–55]).

The former are important for subjects with an emphysematous component of disease, whereas the latter are important for subjects with a bronchitic component of disease. An important premise of this proposal is that many of these measurements can also be directly applied to discriminative analysis using ^3He MRI for a variety of lung diseases. These indices can also be studied not only at any particular single time point, but also for changes with time. The addition of quantitative morphologic measurements of the airways provides an assessment of the contribution of airway changes to chronic lung disease.

Table 1 provides an overview of these types of discriminative measurements that can be used for CT and ^3He lung assessment. We have already implemented many of these image features and have contributed the result of our work to the Insight Toolkit (ITK) of the National Institutes of Health (e.g., [56, 57]). As an open-source repository for medical image analysis algorithms, contribution of our work to the ITK allows researchers full access to the latest image analysis algorithms in addition to avoiding research redundancy. It is also beneficial in that the entire ITK community participates in the vetting of the software library.

Airway and vessel segmentation. In describing the quantitative CT lung indices, it was pointed out that lung airway morphology has been previously utilized as a biomarker for disease characterization. Additionally, there are other potential uses motivating the inclusion of airway segmentation in any pulmonary image analysis toolkit (cf Figure 5). In an evaluation of 15 airway segmentation algorithms [58] it was shown that no algorithm was capable of “extracting more than 77% of the reference.” Our plan is to initially provide an implementation of the algorithm developed by our group [59]. Instead of mixing airway segmentation and leakage detection at every iteration, this work divides this problem into a hypothesis generation of thin airway paths and a post processing procedure of removing leakage path candidates. For the purpose of generating as many

Volumetric Tissue Indices	Cooccurrence Matrix Texture Indices	Attenuation Histogram Statistics
lung volume lobar volume surface area surface area to volume ratio total lung weight tissue/airspace volumes of lung inspiration vs. expiration*	energy inertia contrast entropy correlation inverse difference moment cluster shade* cluster prominence* Haralick's correlation*	attenuation mean attenuation variance attenuation skewness attenuation kurtosis attenuation grey level entropy regional variants inspiration vs. expiration
Airway Indices		Deformation Indices
airway luminal diameter and area airway wall thickness percentage wall area thickness to diameter ratio airway branch angles airway segment length airway wall volumes (segmental and total)* inspiration vs. expiration		Jacobian of lung displacement lung deformation strain
Run-length Matrix Texture Indices		Stochastic Fractal Image Statistics
	short run emphasis long run emphasis grey level non-uniformity run-length non-uniformity run percentage low grey level run emphasis* high grey level run emphasis* short run low grey level emphasis* short high grey level run emphasis* long run low grey level emphasis* long high grey level run emphasis* inspiration vs. expiration*	mean variance skewness kurtosis grey level entropy inspiration vs. expiration*
Distribution of LAA Heterogeneity		Attenuation Mask Indices
10 partitions (std of 15 th %) slopes of density mask curves % size distribution of LAA areas volumetric cluster analysis inner core vs. outer rind inspiration vs. expiration*		HU density mask % HU density mask inspiration vs. expiration*

Table 1: Quantitative CT indices proposed for inclusion in the lung image analysis pipeline. Whole lung, regional, and voxelwise measurements are included, as well as population-based comparisons and longitudinal analysis of all indices. Indices marked with a '*' denote novel measures which have not been previously utilized in chronic lung disease assessment but have shown classification capability in other application domains.

hypotheses as possible, a novel speed function for thin airways is used. To exclude leakage regions, a novel cost function defined on the whole path candidate is used. Such a scheme is more flexible when evaluating the whole path and can be viewed as complementary to current region growing methods.

Specific Aim 2. To provide multiple sets of multi-modal annotated lung data (CT, proton, and He3) for public use.

Specific Aim 3. Evaluate and disseminate multiple complete studies with input data from multiple investigators to showcase the utility of the tools and data provided with this proposal.

Anticipated difficulties

Signal intensity in the lungs is poor in areas of low ventilation. COPD and asthma are obstructive lung diseases which exhibit focal areas of decreased signal intensity on 3HeMRI which are thought to correspond to areas of reduced ventilation. These ventilation defects severely inhibit our ability to detect the lung boundaries for proper segmentation. Also, most of the COPD and asthmatic patients will have ventilation defects with the moderate asthmatics having greater than 1 defect per slice also negatively affecting boundary delineation. Note that there are similar issues for CT images of severe pathologies. However, given the shape and intensity prior statistics contained by our 3HeMRI and CT lung templates, it is expected that the templates, in combination with our proposed segmentation algorithms, will be sufficient to provide a good initialization for subsequent manual segmentation if they do not yield an adequate segmentation result. The CT data, which provides excellent contrast between the lung and chest wall, can also be used to inform the 3HeMRI segmentation.

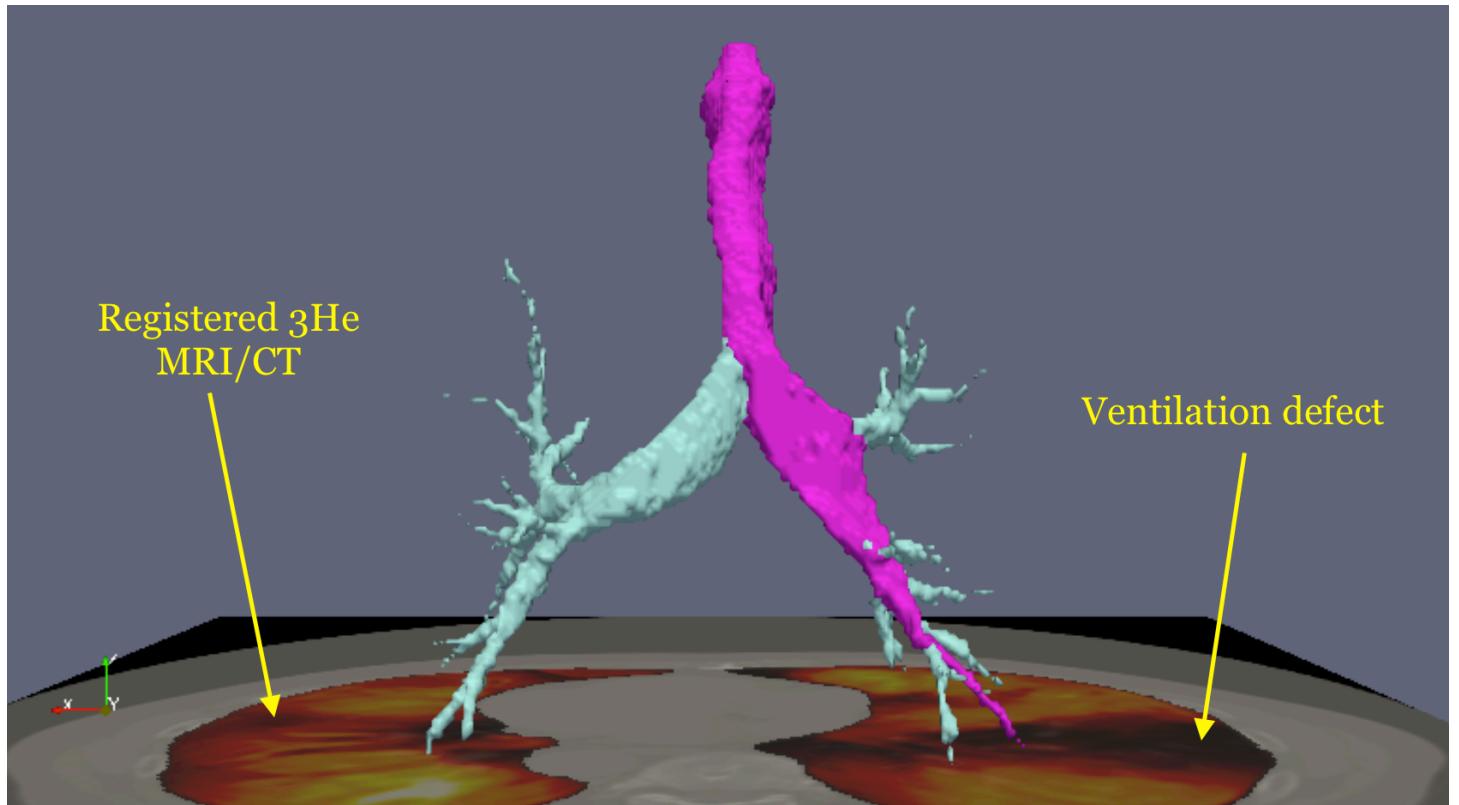


Figure 5: Potential clinical use case for identifying the feeding airway branch path to the ventilation defect. The functional ventilation image is normalized to the corresponding CT image. The airways are segmented in the individual subject space. After identification of the ventilation defect of interest, we can automatically determine the bronchiole pathway from the trachea to the defect.

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