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.

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 as 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.

Research Strategy

3(a) Significance

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].
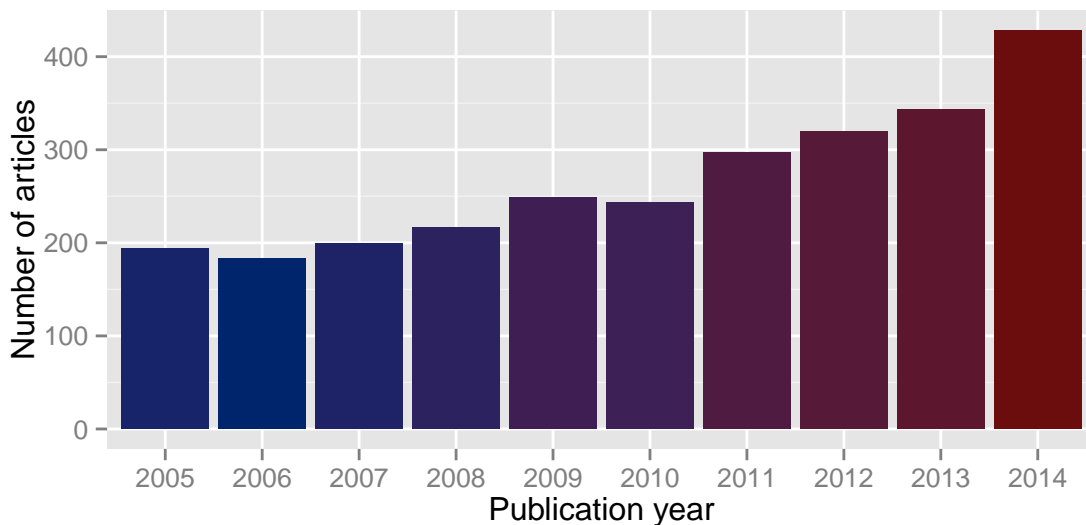

Figure 1: Number of articles per year which use common, publicly available neuroimaging analysis packages (i.e., FreeSurfer, AFNI, FSL, and SPM). Although the benefits seem clear for the neuroscience community, analogous efforts within the pulmonary community have yet to be undertaken.

Medical image analysis libraries (e.g., the Insight ToolKit) provide extensive algorithmic capabilities for a range of generic medical image analysis 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. Similar deficiency within the neuroscience community has been one of the primary motivations for the 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 examples and developer-tuned parameters) and have been used extensively by our group and others:

- brain normalization [6, 7],
- brain template generation [8],
- skull-stripping or brain extraction [9, 10],
- prior-based Bayesian brain tissue segmentation [6],
- cortical gray matter thickness estimation [10, 11],
- brain tumor segmentation [12], and
- cortical labeling [13, 14].

In addition to public availability, some of these algorithms have been showcased in international competitions and have performed extremely well [15, 16].

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 [17] 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. Following is a small sampling of more recently reported techniques for CT analysis:

- whole lung differentiation from the chest wall (e.g., [18–21])
- bronchial structure extraction (e.g.,[22, 23]; the many submissions to the recent Extraction of Airways from CT (ExACT) challenge of the 2nd International Workshop on Pulmonary Image Analysis [24]),
- vasculature segmentation (e.g., [25, 26]),
- lobe and/or fissure detection (e.g., [27, 28]), and
- feature extraction and classification (e.g., [29–31]).

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 [32] will also have significant impact in a comprehensive lung image analysis suite.

Important in any methodological discussion is the crucial importance of parameter selection which requires domain-specific experience. For example, although ANTs performance in brain registration has been independently evaluated and found to be of relatively high quality [Klein2009], applying 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 preferred normalizations [33], particularly for pulmonary data [34]. 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.

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 [35]. 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 [36].

3(b) Innovation

Given the lack of open-source solutions for pulmonary image analysis, the proposal goals would produce an innovative framework for corresponding research. Many algorithms have been proposed in various technical venues but that which we propose would provide well-vetted and easy-to-use implementations of these robust methodologies. Many of these have been developed by our group.

An additional innovation we are proposing is the inclusion of data and detailed instructions for generating a reproducible, multimodality pulmonary study using the proposed package. *Say more about the data specifics here.* Clinical findings will be published in a traditional journal (e.g., Chest) for the interested researcher. 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 [?,?]) Such a comprehensive clinical investigation using these tools will not only provide insight into the specifics of ?? but will also provide a tangible mechanism for using the tools created with this proposal.

3(c) Approach

Specific Aim 1. To develop a set of open-source software tools for CT, proton, and He-3 pulmonary computational analysis. Development will include several basic tools

Atlas-based lung segmentation. Identification of anatomical structure in MRI is often a crucial preprocessing step for quantification of morphological features or functional information. Quantitative regional analysis often requires the identification of lung and lobar anatomy. Although much algorithmic research for lung segmentation has been reported in the CT literature [37], 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 [34]. Multi-atlas approaches to segmentation have proven highly successful in neuroimaging [Reference 13;Wang:2013aa] which translates readily to a pulmonary context. 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.

B-spline-based Symmetric Normalization. A thorough comparative evaluation with the well-known ANTs SyN algorithm was performed with a B-spline variant. The evaluation utilized multiple publicly available, annotated brain data sets and demonstrated statistically significant improvement in label overlap measures [33]. We also used the EMPIRE10 challenge framework to provide an additional comparison in the context of pulmonary CT image registration [38]. Due to the performance of this new variant, it has become the preferred transformation model for small deformation image registration problems (e.g., lung and cardiac [39] applications).

Multi-feature CT and multi-modal MRI template generation. we generate subject-specific templates directly from the image data. Given the variability in lung shape across populations and the lack of publicly available lung atlases, generating population- or subject-specific templates enhances the accuracy of the longitudinal analysis described in this work. Applicable to pulmonary data is the template construction algorithm described in [8] which was applied to T1-weighted brain data. However, the simultaneous acquisition of the 3He and 1H images lends itself to multimodal processing [12] in which both modalities are used to simultaneously produce 3He and 1H templates. This process is represented in Fig. 1 for a single subject.

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, as mentioned previously, 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.

To generate the lobe segmentation in a target proton lung image, we first generate the binary lung mask for the proton lung image as described in the previous subsection. We then register the set of CT lung masks to the target binary lung mask using the same registration approach mentioned earlier [33]. Subsequently, we warp the set of CT lobe labels to the target image using the CT mask-to-proton mask transformation. Since we have no intensity information inside the target lung mask and CT atlas lung masks, we use a simply 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.

Ventilation-based image segmentation. Developments in MRI research utilizing noble gases, such as 3He and 129Xe, have demonstrated the capability of visualizing alveolar and bronchial air spaces. Currently, hyperpolarized 3He MRI is a low-risk investigatory technique that provides high spatial and temporal resolution images of the air spaces of the lungs and has been used to investigate a variety of lung diseases. Automated or semiautomated approaches for classifying areas of varying degrees of ventilation are of potential benefit for facilitating such investigation.

Quantitative CT indices. Imaging biomarkers for characterizing emphysema in CT have 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 and those that characterize the airways. 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. Such 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 historical overview of the type of discriminative measurements that have been used for CT lung assessment.

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

An important premise of this proposal is that many of these measurements can also be directly applied to discriminative analysis using 3HeMRI for a variety of lung diseases. 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., [40, 41]). 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.

[7;9;16;18;19;24;25;26;30;31;32;33;37;41;46;54;55;56;57;59;61;63;64;65;66;68;70;74;76;77;82;83;84;85;92;98;110;111;112;114;117;11

Airway and vessel segmentation. We should propose to implement something here. We should look at the Slicer/VMTK airway segmentation model.

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

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