

ITK-Lung: A Software Framework for Lung Image Processing and Analysis

2 Specific Aims

The development and proliferation of quantitative image analysis methods have accelerated research efforts and are having an increasingly significant impact in modern clinical practice. Although the research utility of these techniques has been amply demonstrated in determining longitudinal and groupwise trends, they are also becoming increasingly relevant in the clinical setting in providing biomarkers for aiding patient diagnoses, monitoring disease progression, and determining treatment outcomes. Increases in the capabilities and accessibility of computational facilities and a corresponding sophistication in computational algorithms have only made such practices more commonplace.

One of the most significant hurdles in adopting more quantitative clinical practices and exploring additional novel research pathways is the availability of accurate, robust, and easy-to-use image analysis tools. Historically, the research and clinical communities (and their overlap) have significantly benefited 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 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 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 targeted for pulmonary research. As principal developers of the popular, open-source ANTS, ITK-SNAP and ITK packages, we have extensive experience in the development of well-written software that has gained much traction in the neuroscience community and propose to make a similar impact in the pulmonary community with this proposal. Specifically, we plan to provide methods for core pulmonary image analysis tasks across multiple modalities, many of which we have proposed in past publications. These basic tasks include pulmonary image registration, template building for cross-sectional and longitudinal (i.e., respiratory cycle) analyses, functional and structural lung image segmentation, and computation of quantitative image indices as potential imaging biomarkers. In addition to the software, we will provide scripts, documentation, and tutorial materials consistent with open-science principles. 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. To maximize usability code will be developed and distributed within the Insight Toolkit of the National Library of Medicine.
- **Specific Aim 2: Validate and disseminate the developed ITK-Lung resources by leveraging use cases from a broad network of partner investigators representing the state-of-the-science in lung imaging research.** This aim will evaluate and refine the developed methodology within the real-world context of pulmonary research being carried out at various partner sites. We will disseminate the results of the evaluation through open-source distribution of the software and write-ups, online user support, and conduct of hands-on training workshops.

3 Research Strategy

3(a) Significance

3(a.1) The importance of pulmonary image analysis tools for research and clinical investigation. The increased utilization of imaging for both research and clinical purposes has furthered the demand for quantitative image analysis techniques. The use of these computational techniques is motivated by the need for less subjectivity and more standardization in medical image interpretation, increased speed and automation in diagnosis, and greater robustness and accuracy for determining biological correlates with imaging findings. For example, in the area of pharmaceutical development and testing, imaging biomarkers are crucial. In order to determine fundamental study parameters such as drug safety and effectiveness, quantitative assessments derived from imaging measures must be objective and reproducible [1] which is often difficult without computational aid given the intra- and inter-reader variability in radiological practice [2, 3]. Additionally, the exciting possibilities associated with “big data” and the potential for improvement in individualized, evidence-based medicine has also increased the need for sophisticated data transformation and machine learning techniques.

3(a.2) Open-source as an essential attribute of high-impact image analysis toolkits. 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 [4], the FMRIB Software Library (FSL) [5], the Analysis of Functional NeuroImages (AFNI) package [6], the Statistical Parametric Mapping (SPM) package [7], and several others. 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 [8].

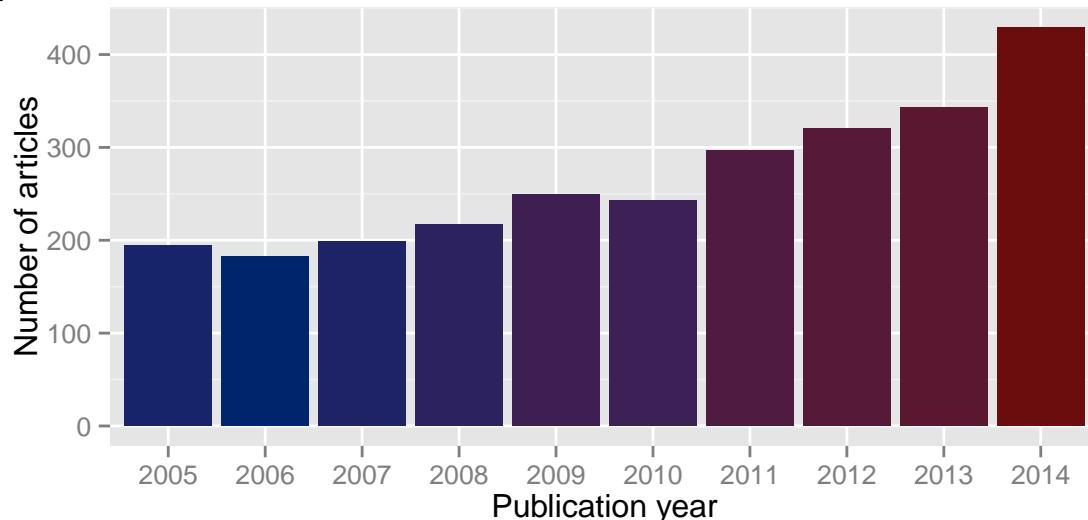


Figure 1: Number of articles per year which cite publicly available neuroimaging analysis packages (specifically, FreeSurfer, AFNI, FSL, and SPM). Although the benefits seem clear for the neuroscience community, analogous efforts within the pulmonary community have yet to be undertaken despite consensus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

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. It is important to 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 specific objective that all project 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 [9]. 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 [10]. Furthermore, open-source development and distribution within a large, and well-invested community (such as ITK) takes advantage of Linus’s law, i.e., “given enough eyeballs, all bugs are shallow,” for producing robust software.

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 proposal would include the most essential algorithms for analyzing lung images from different modalities including CT, ^{3}He , and ^{1}H 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 documentation including self-contained online examples, tutorials, and hands-on training workshops.

3(b.2) Use case studies with leading pulmonary research scientists. An additional innovative component we are proposing is the inclusion of extensive use cases from leading pulmonary research scientists in various locations with different image acquisition protocols, equipment, etc. to ensure quality and robustness of the processed data. Additionally, such use cases involving other groups would highlight existing deficiencies in algorithmic functionality in our proposal which would then be remedied by additional development efforts. These real-world use cases were solicited representing as broadly as possible the requirements of the community as well as the multiple modality and algorithmic variations which commonly occur.

We have asked several leading pulmonary research groups who are familiar with our work to provide study-specific imaging data of various modalities which we will then process using the proposed toolkit. These processed data will then be returned to the corresponding providers with detailed instructions on reproducing these results in their own labs. Software and tutorial materials drawn from these experiences will be provided to the public for any interested researcher to apply to their own data. 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 the quantitative analysis scripts as a companion release for the paper (e.g., see previous similar offerings from our group [11, 12]). 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.1.1) Generic ANTs core tools for image analysis and processing. Several core programs comprising portions of the proposed pulmonary software framework have been created and made available within ANTs (and either simultaneously or subsequently made available in ITK). However, as mentioned earlier, these programs have more general application and require pulmonary-specific tuning for the tasks targeted by this proposal. The following list comprises several core software tools for tuning, subsequent extensions, documentation, tutorial generation, and the creation of easy-to-use bash scripts for large-scale processing of pulmonary imaging data.

ANTs image registration. One of the most important methodological developments in medical image analysis is the advent of image registration techniques capable of accommodating the highly complex inter-individual variations seen in human anatomy. Our team is well-recognized for seminal contributions to the field that date back to the original elastic matching method of Bajcsy and co-investigators [13–15]. Our most recent work, embodied in the ANTs open-source, cross-platform toolkit for multiple modality image processing, continues to set the standard in the field. ANTs not only encodes the most advanced results in registration research, notably the Symmetric Normalization (SyN) algorithm for diffeomorphisms [16], but also packages these within a full featured platform that includes an extensive library of similarity measures, transformation types, and regularizers. Recently, a thorough comparison with the original SyN algorithm was performed using a B-spline variant [11]. 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 and are two of the most widely used scripts in the ANTs toolkit. *Similar to the developments that we are proposing, these scripts were extensively modified to serve as a follow-up entry into the EMPIRE10 lung registration challenge where B-spline SyN performed better than its original counterpart on pulmonary data [17].*

Multi-modal template generation. Given the variability in anatomical shape across populations and the lack of publicly available atlases for specific organs, generating population- or subject-specific optimal shape/intensity templates significantly enhances study potential [18, 19]. First, an average template is estimated via a voxel-wise mean of all the individual subject images. This estimate is iteratively updated by registering each image to the current template, performing a voxelwise average to create a new estimate, and then “reshaping” this template based on the average inverse transformation which “moves” the template estimate closer to the group mean. See Figure 2 for a cohort-specific multi-modal brain template for females in the age range 50–60. This functionality has proven to be a vital component of the ANTs toolkit for performing neuroimaging research (e.g., [12, 20–24]). *Similarly, this functionality has also demonstrated significant importance in pulmonary studies [25].*

Bayesian segmentation with spatial and MRF priors. Early statistically-based segmentation work appropriated NASA satellite image processing software for classification of head tissues in 2-D MR images [26]. Following this work, many researchers adopted statistical methods for n -tissue anatomical brain segmentation. The Expectation-Maximization (EM) framework is natural [27] given the “missing data” aspect of this problem. Core components of this type of work include the explicit modeling of the tissue intensity values as statistical distributions [28, 29] and the use of MRF modeling [30] for regularizing

the classification results [31]. Spatial prior probability maps of anatomical structures of interest are also employed within this framework [32, 33]. Although this particular segmentation framework has significant application in the neuroimaging domain, it has also applicable to other domains such as breast MRI [34, 35] and functional ventilation of the lung [36]. *However, despite the numerous developments which have been proposed over the years within this area, there are an extremely limited number of actual software implementations. This deficit inspired us to create our own Bayesian segmentation framework [37] (denoted as Atropos) which we have made publicly available within ANTs and has proven extremely useful in quantification of functional lung imaging [36, 38–40].*

N4 bias correction. Critical to quantitative processing of MRI is the minimization of field inhomogeneity effects which produce artificial low frequency intensity variation across the image. Large-scale studies, such as ADNI, employ perhaps the most widely used bias correction algorithm, N3 [41], as part of their standard protocol [42]. In [43] we introduced an improvement of N3, denoted as “N4”, which demonstrates a significant increase in performance and convergence behavior on a variety of data. This improvement is a result of an enhanced fitting routine (which includes multi-resolution capabilities) and a modified optimization formulation.

Joint label fusion for prior-based segmentation. Joint label fusion (JLF) is the current state-of-the-art for propagating expert labelings from a reference atlas library onto new instances of unlabeled data. Image registration is used to align the atlas library (images + segmentations) to a common space. A statistical model is then used to combine the “guesses” from all the normalized atlas labels to provide a “best guess” estimate of the target labeling. Several such algorithms have been developed and much effort has been devoted to determining relative performance levels—see, for example, the recent MICCAI 2012 Grand Challenge and Workshop on Multi-Atlas Labeling). The joint fusion (JLF) algorithm of [44, 45] from our group is one of the top performing JLF algorithms. JLF is capable of predicting anatomical labels with accuracy that rivals expert anatomists [46]. It has proven its effectiveness not only in cardiac data [47], the human brain [12], and in multiple modality canine MRI [47] *but has also proven incredibly important in applying prior-based information to lung and lobe segmentation [48].*

Spatially adaptive denoising. Patch-based denoising is critical for data “cleaning” prior to subsequent processing such as segmentation or spatial normalization. ANTs implements a state-of-the-art spatially adaptive version to denoising recently proposed in [49].

The previously described core tools, as well as several others, have been part of ANTs and ITK development efforts for more than a decade. The deficiency of publicly available tools within the neuroscience community was the original motivation for the inception and continued development of ANTs. As a result, our team is well-recognized for our many open-source contributions including important contributions to the field of image registration outlined earlier. Indeed, ANTs-based image registration serves as the basis for the registration component of the latest version of the National Library of Medicine Insight Toolkit (ITK) programming library (<http://www.itk.org>). *The combination of state-of-the-art algorithms and feature-rich flexibility has translated to top-placed rankings in major independent evaluations for core elements of the ANTs toolkit:*

- SyN was a top performer in a fairly recent large-scale brain normalization evaluation [50].
- SyN also competed in the Evaluation of Methods for Pulmonary Image REgistration 2010 (EMPIRE10) challenge [51] where it was the top performer for the benchmarks used to assess lung registration accuracy and biological plausibility of the inferred transform (i.e., boundary alignment, fissure alignment, landmark correspondence, and displacement field topology). The competition has continued to the present and SyN has remained the top-ranked algorithm.
- The joint label fusion algorithm of [44, 52] (coupled with SyN) was top-ranked in the MICCAI 2012 challenge for labeled brain data [53] and in 2013 for labeled canine hind leg data [54].
- The multivariate template capabilities in ANTs were combined with random forests to win the Brain Tumor segmentation (BRATS) competition at MICCAI 2013 [19].
- A B-spline variant of the SyN algorithm [11] won the best paper award at the STACOM 2014 workshop for cardiac motion estimation [55].

3(c.1.2) Neuroimaging with ANTs as a model for the pulmonary community. 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 [56, 57] (<https://github.com/stnava/BasicBrainMapping>),
- brain template generation [18] (<https://github.com/ntustison/TemplateBuildingExample>),
- skull-stripping or brain extraction [12, 58] (<https://github.com/ntustison/antsBrainExtractionExample>),
- prior-based brain tissue segmentation [56] (<https://github.com/ntustison/antsAtroposN4Example>),
- cortical thickness estimation [12, 59] (<https://github.com/ntustison/antsCorticalThicknessExample>),
- brain tumor segmentation [19] (<https://github.com/ntustison/ANTsAndArboles>), and
- cortical labeling [44, 52] (<https://github.com/ntustison/MalfLabelingExample>).

All of these tools have been wrapped in easy-to-use, well-documented shell scripts. For example, the ANTs cortical thickness

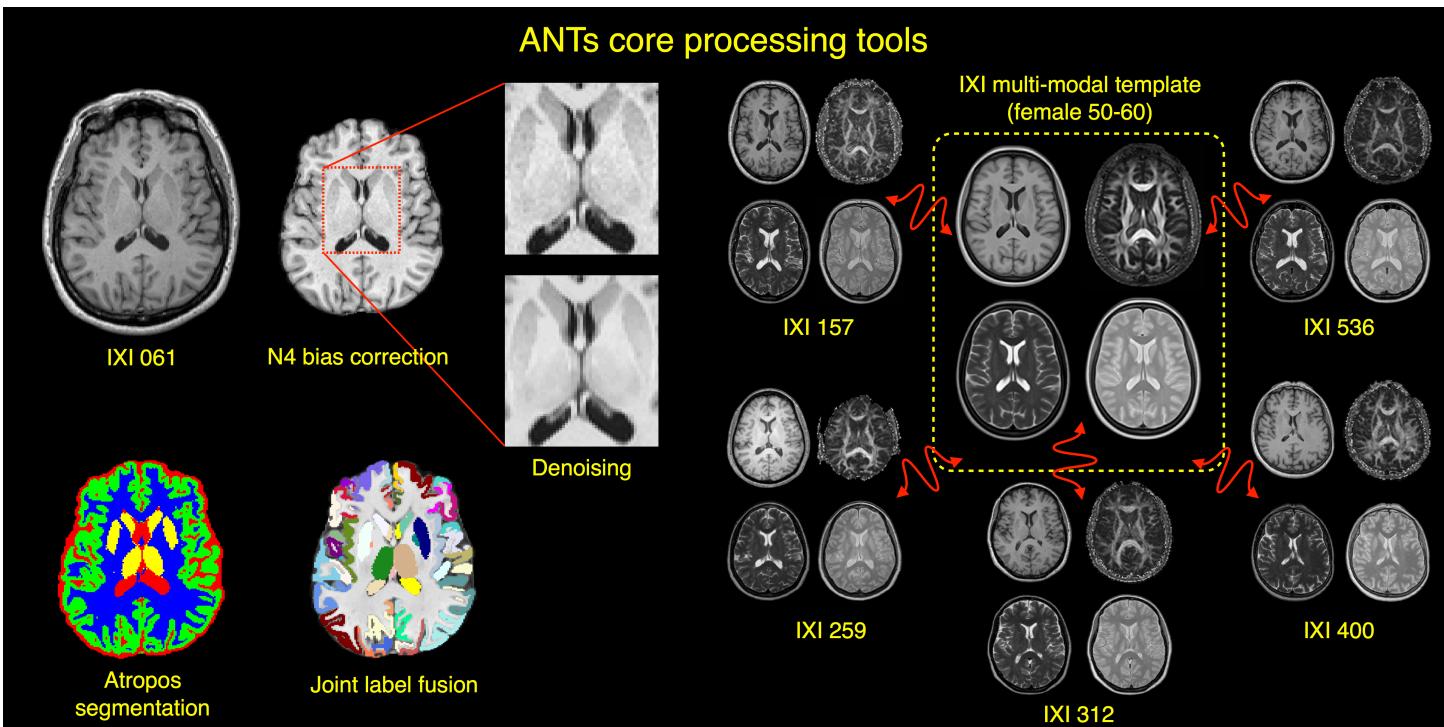


Figure 2: Core processing tools that have made the ANTs package one of the most popular neuroimaging toolkits. Fundamental processing tasks such as image registration, template generation, bias correction, denoising, intensity-based segmentation, and joint label fusion are extremely well-performing software components which have been utilized for neuroimaging tasks such as brain extraction and cortical thickness estimation. The target applications of these core tools have an immediate analog for lung-specific tasks such as lung and lobe segmentation.

pipeline, as outlined in [12], comprises four major steps: (1) bias correction, (2) brain extraction, (3) *n*-tissue segmentation, and (4) cortical thickness estimation. Each step requires its own set of ANTs tools with appropriately tuned parameters. To maximize the utility of the pipeline for the interested user, in [12] we provide all the necessary programs (properly tuned) with a minimal set of input data required to obtain good results for common data. The result is an easy-to-use script that can be invoked by the programmer and non-programmer alike to obtain the desired processed data which outperforms the current state-of-the-art [12]. An example command call for the ANTs cortical thickness pipeline is:

```
# ANTs processing call for a single subject

$ sh antsCorticalThickness.sh -d 3 \
-a IXI/T1/IXI002-Guys-0828-T1.nii.gz \
-e IXI/template/T_Template0.nii.gz \
-m IXI/template/T_template0ProbabilityMask.nii.gz \
-f IXI/template/T_template0ExtractionMask.nii.gz \
-p IXI/template/Priors/priors%d.nii.gz \
-o IXI/ANTsResults/IXI002-Guys-02828-
```

This approach to reducing the steep learning curve associated with many processing pipelines has several benefits. Bash is an extremely common command language that permits large-scale processing. Thus, running several jobs on a cluster infrastructure is straightforward with this approach (as opposed to a GUI-driven processing paradigm). Such scripts are readable by the interested user who can glean parameters as well as manually make changes.

3(c.1.3) ITK-SNAP. Project investigator Paul Yushkevich leads the development of ITK-SNAP [60], a multi-platform open-source tool for interactive user-guided medical image segmentation and data visualization. ITK-SNAP provides an effective combination of semi-automatic segmentation functionality based on active contours [61, 62] and manual delineation functionality, put together into a compact and easy-to-learn graphical user interface. ITK-SNAP supports segmentation of multiple volumetric imaging modalities, species, and anatomical regions, without bias to any particular problem domain. Compared to other, larger open-source image analysis tools, ITK-SNAP design focuses specifically on the problem of image segmentation, and extraneous or unrelated features are kept to a minimum. The design also emphasizes interaction and ease of use, with the bulk of the development effort dedicated to the user interface. ITK-SNAP has thousands of users (there have been over 2000 downloads per month in the last year), and our 2006 paper on ITK-SNAP [60] has been cited over 1400 times (Google Scholar) in the context of various biomedical domains. In recent years, ITK-SNAP development and maintenance were funded by grant

5R01 EB014346, and under this grant, powerful new functionality for registration was developed. ITK-SNAP will be used in this project for manual labeling of the proposed brain atlases; it is already used for this purpose by many investigators. Most crucially, we believe that our track record with ITK-SNAP as well as ANTs demonstrates our team's commitment to producing high-quality research software and making it accessible to the wider research community through open-source practices, intuitive user interfaces, and outreach efforts. These strengths of the team will be applied to the software and data developed in the course of this project.

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

Analogous to the neuroimaging tasks described earlier, several algorithmic categories exist for lung image analysis which, as we have stated previously, do not exist in any comprehensive, publicly available package. This is in spite of the fact that new algorithms for lung image analysis are frequently reported in the literature. An extensive survey concentrating on the years 1999–2004 is given in [63] 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. However, despite the continued reporting of pulmonary image analysis algorithms, there is no corresponding increase in algorithmic availability. Additionally, a major problem in the pulmonary image analysis community is that the lack of publicly available tools translates directly into a lack of baseline performance standards with which researchers can compare their own algorithms [64]. This proposal constitutes an important response to this deficiency.

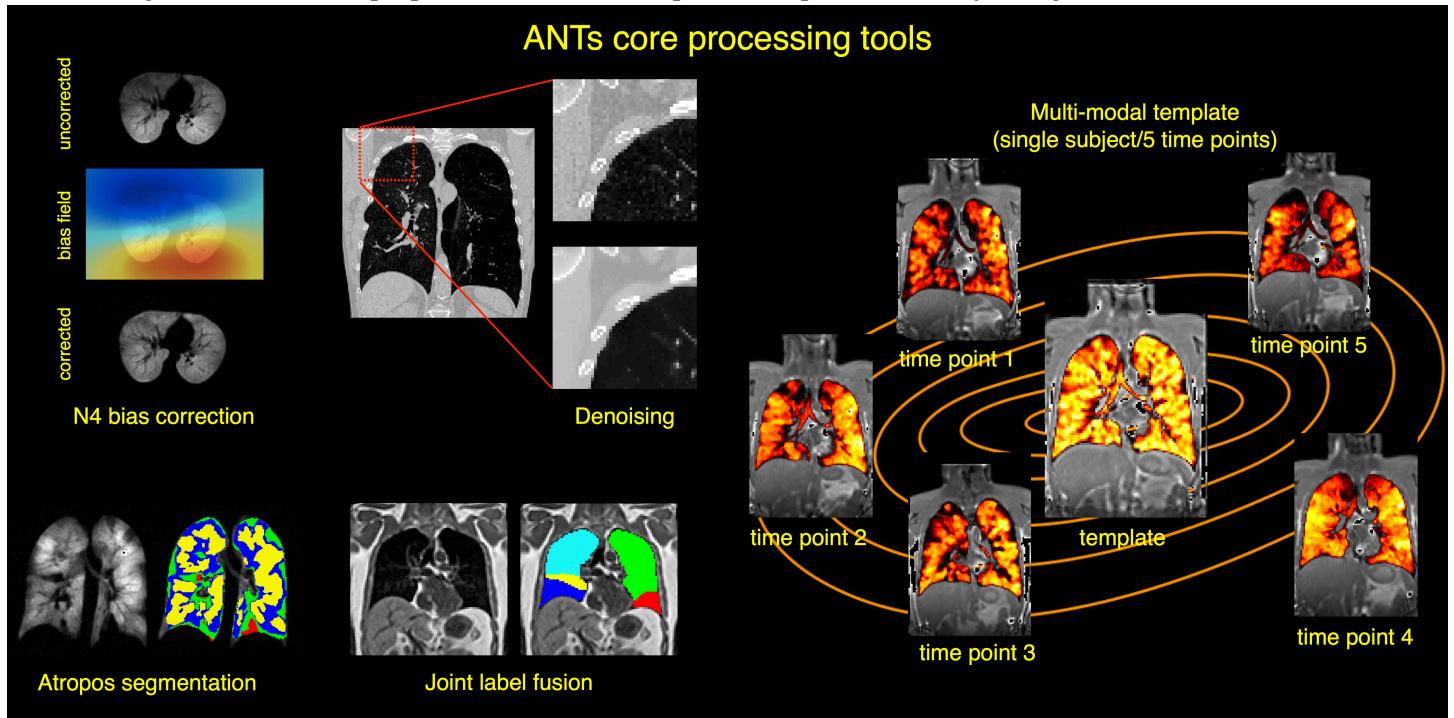


Figure 3: Using ANTs core processing tools, our team has developed several lung-specific extensions such as ventilation-based segmentation, lung and lobe estimation, and multi-modal pulmonary template building. Although each of these extensions requires significant additional development and tuning, a robust and generic software foundation ensures that these extensions are of high quality and are readily adapted to the pulmonary image domain.

A primary assumption for this proposal is that, through extension and continued development of ANTs and ITK functionality, we can make a significant impact for the pulmonary imaging research community in both basic science and clinical workflows by developing lung-specific algorithms which are easy to use as we have done for the neuroimaging community. The following is a sampling of more recently reported techniques for CT analysis that would be incorporated into ITK-Lung:

- whole lung differentiation from the chest wall (e.g., [65–68]),
- bronchial structure extraction (e.g., [69, 70] and the many submissions to the recent Extraction of Airways from CT (ExACT) challenge of the 2nd International Workshop on Pulmonary Image Analysis [71]),
- vasculature segmentation (e.g., [72, 73]),
- lobe and/or fissure detection (e.g., [74, 75]),
- feature extraction and classification (e.g., [76–78]), and
- nodule detection (e.g., [79] and the many submissions to the Automatic Nodule Detection (ANODE09) challenge of the 2009 CAD Conference of SPIE Medical Imaging [80]).

Although this list is restricted to CT image analysis, inclusion of additional techniques specific to other modalities has additional

Functionality	CT	1H MRI	^{3}He MRI
spatial normalization	•	•	•
template generation	•	•	•
lung segmentation	•	•	•
lobe segmentation	•	•	•
airway segmentation	•	•	•
vessel segmentation	•	•	•
functional segmentation	•	•	•
nodule detection	•	•	•
feature indices	•	•	•

Table 1: Specific outline of basic functionality offered with this proposal categorized by modality. One of the motivations for the collaborative use cases as a specific aim is the inevitability that other lung-specific algorithmic needs will be identified and will be added to the functionality developed and offered as part of this proposal. It should also be noted that some modality-specific modifications will be required. For example, although our lobe estimation approach works well for 1H MRI where no internal anatomical features are available for refinement, the same is not true for CT. However, this lobe estimation strategy can be applied to CT in providing spatial prior maps for subsequent subject-specific refinement.

benefit and are included in this proposal (cf Table 1). Using ANTs core tools, we have produced several lung-specific algorithms for core tasks such as:

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 often requires the identification of lung and lobar anatomy. Although much algorithmic research for lung segmentation has been reported in the CT literature [81], 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 1H MRI [48]. Multi-atlas approaches to segmentation have proven highly successful in neuroimaging [44, 52] 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 [48] demonstrated good performance with Jaccard overlap measures for the left and right lungs being 0.966 ± 0.018 and 0.970 ± 0.016 , respectively.

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 1H 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 3).

To generate the lobe segmentation in a target 1H 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 [11]. 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 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. This methodology is more thoroughly described in [48] where we showed that lobar overlap measures in 1H 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). It is important to note that this particular framework is immediately applicable to pulmonary CT in providing spatial prior probability maps augmented by image-specific CT data features as fissures, airways, and blood vessels for data-driven, subject-specific lobe segmentation [75].

Ventilation quantification. Automated or semiautomated approaches for classifying areas of varying degrees of ventilation are of potential benefit for pulmonary functional analysis. In [36], we presented an automated algorithmic pipeline for ventilation-based partitioning of the lungs in hyperpolarized ^{3}He and ^{129}Xe MRI. Without ground truth data for evaluation, we used a consensus labeling approach [82] 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 [49].

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
Distribution of LAA Heterogeneity	Run-length Matrix Texture Indices	Stochastic Fractal Image Statistics
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*	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*
		Attenuation Mask Indices
		HU density mask % HU density mask inspiration vs. expiration*

Table 2: Feature 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.

Multi-modal lung template construction. Additionally, although the template construction algorithm described in [18] is, as pointed out earlier, frequently applied to T1-weighted brain data, it is sufficiently generic such that it can also be applied to pulmonary data. Also, new innovations in diffeomorphic registration technology has led to a Symmetric Normalization B-spline variant which has demonstrated accurate normalizations [11] and transformations which are particularly well-suited for pulmonary data [17].

Feature 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., [83, 84]), distribution of low attenuation areas (LAA) (e.g., [85, 86]), cooccurrence and run-length matrix features (e.g., [76, 87]), attenuation statistics (e.g., [88, 89]), deformation measures (e.g., [90, 91]), and stochastic fractal dimension features (e.g., [76, 89]) and those that characterize the airways (e.g., [92–94]). 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 component 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 2 provides an overview of these types of discriminative measurements, many of which 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., [95, 96]). 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. In an evaluation of 15 airway segmentation algorithms [97] 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 [98]. 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 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.

Nodule detection. CT is used for screening of lung cancers (i.e., pulmonary nodules) which currently requires human intervention for the laborious and tedious task of manual scanning. Automated detection methods could potentially save much time and effort which has inspired much research literature on the topic including several commercial systems and specialized visualization hardware for facilitating detection. In 2009, a nodule detection competition was held for comparing performance of individual algorithms as well as their combinations [80]. This competition included entries from both academic institutions as well as a system from Philips (although, to our knowledge, none are available for public use).

3(c.3.1) Software engineering. Both ANTs and ITK-SNAP development, based on a solid foundation provided by the Insight Toolkit, utilizes open-source software engineering best practices, such as the use of Git version management software for collaborative development and easy branching and merging; use of a centralized repository (SourceForge) for code, executable and data sharing; use of the CMake/CTest/CDash suite for cross-platform development, testing and automatic builds. Virtual machines with different versions of Windows, MacOS and Linux operating systems generate nightly builds and execute test code, uploading a binary to the central SourceForge repository. ANTs and ITK-SNAP are documented through video and text tutorials, housed online on dedicated websites [99, 100]. A similar infrastructure will be developed for the software resources proposed in Aim 1.

3(c.4) Specific Aim 2. Validate and disseminate the developed resources by leveraging use cases from a broad network of partner investigators representing the state-of-the-science in lung imaging research

This aim builds on the project team's long and successful track record of collaboration with the general user community. In particular, the investigator-driven studies presented below are carefully selected both for their capacity to fully exercise the developed tools and to provide a comprehensive representation of the various processing and analysis tasks of interest to the community.

Novel imaging biomarkers for COPD. Co-investigator **Mike Shim** and his group have been actively developing 3D hyperpolarized xenon-129 dissolved-phase MRI (HXe MRI) as a sensitive biomarker for accurately characterizing phenotypes and severity of COPD. This protocol permits regional mapping of ventilation and gas uptake by tissue and blood in human lungs with single breath hold [101–103]. This project plans to establish connectivity between these advanced HXe MRI imaging signatures and important clinical outcomes of COPD to establish HXe MRI as a novel clinical diagnostic tool. They anticipate that this new biomarker tool will naturally lead to deeper mechanistic understanding of COPD at the molecular-physiologic and clinical levels and support identification of potential pathophysiologic derangement associated with COPD and a new method to accurately predict therapeutic response to current standard COPD therapies. Refinement of HXe MRI as a pulmonary diagnostic tool is anticipated to encourage development of new clinical interventions. HXe MRI is the first non-invasive imaging technique that can provide regional information about three unique characteristics of lung function: lung ventilation, size and connectedness of distal alveolar airspaces, and HXe gas transfer from airspaces to red blood cells. HXe MRI, therefore, is anticipated to overcome the limitation of pulmonary function testing (PFT) which only provides physiologic parameters of the lung as a whole unit, and High Resolution CT (HRCT) which only provides anatomic characterization without physiologic information. They anticipate that the HXe MRI will detect pathologic changes present in COPD patients with high sensitivity and specificity previously unattainable by current clinical standard (PFT and HRCT). Moreover, HXe MRI can determine whether gas transfer abnormalities are due to impaired ventilation or reduced gas-exchange, and provide new insights into pathogenesis of COPD in individual patients.

Crucial to the success of establishing the utility of HXe MRI as a sensitive biomarker for accurately characterizing COPD phenotypes is quantification of imaging signatures in an automated and robust fashion. Identification of ventilation dead space (V_D) for correlation with GOLD classification will utilize the previously described ventilation-based segmentation approach [36]. In order to determine lobar values of HXe MRI, they will utilize the recently proposed lobar estimation algorithm [48] in both proton MRI and CT.

Hyperpolarized gas imaging in children with asthma. Advances in rapid image sequencing methods have facilitated the acquisition of high-quality hyperpolarized gas MR images in pre-school children [104]. Furthermore improvements in image processing and signal intensity analysis can accurately measure lung volume compartments [36]. Co-investigators **Gerry Teague** and **Talissa Altes** are applying these innovations in children with asthma to study whether the lung defect volume % as measured by hyperpolarized lung MRI correlates with a range of clinical features. They hypothesize the ventilation defect volume % would be higher in children with severe asthma, and correlate not only with the degree of airflow limitation, but indicators of asthma control, treatment, and inflammation.

Precise measurement of ventilation volumes by hyperpolarized noble gas MRI not only has the potential to resolve the spatial and temporal characteristics of gas distribution in children with asthma, but could also expand clinically relevant information

in regards to asthma severity and its features. In the past simple computer-assisted systems [105] or hand counts of visual defects were used to estimate the ventilation defect volume [106]. Development of more advanced techniques (in terms of acquisition and analysis) will facilitate rapid conversion of complex hyperpolarized gas signal data into volume compartments for clinical applications.

Absolutely crucial to the advanced techniques being developed by Dr. Teague and his group are sophisticated image analysis tools like the ones being proposed. For example, the ventilation-based segmentation described in [36] is being used to determine volumetric compartments based on lung function. Additional “cleaning” necessary for these data include denoising techniques [49] implemented and made available in ANTs. Lobe estimation will be possible by refining the techniques originally described in [48].

Characterization of COPDGene cohort by hyperpolarized gas (HP) MRI. Co-investigator **Rahim Rizi** is leading a study of lung function and structure in Chronic Obstructive Pulmonary Disease (COPD) using HP MRI. Once inhaled, this gas can tell the researcher how well specific lung regions replace the air during the normal breathing cycle (Fractional Ventilation, FV), how much oxygen is in the airspaces (Oxygen Tension, PAO₂), and if the normal spongy tissue structure has been compromised in lung disease (Apparent Diffusion Coefficient). Subjects will include those at risk for lung disease, and those displaying mild and moderate COPD. Subjects will be mostly drawn from the well-characterized population currently enrolled in the COPDGene trial (10,000 subjects overall) such that standard clinical images (End Inspiration and End Expiration CT) and Pulmonary Function Tests (PFTs), as well as genetic sequencing, will already have been done. Each subject will be imaged twice during the course of the five-year study, and the regional features will be compared between the CT and MRI images to the genetic markers, changes in clinical measurements, and patient quality of life.

The proposed study will generate non-invasive biomarkers of COPD progression derived from minute, short-term alterations in lung function and microstructure. Due to the excellent safety profile of MRI, these metrics will be appropriate for use in novel, flexible study designs. Perhaps most importantly, this research will enhance understanding of the natural history of COPD. In doing so, it will provide a vital supplement to ongoing efforts to identify COPD subtypes by adding substantial physiologic detail to descriptions of this disease. The overall goals of the study experiments are:

- to develop imaging markers that better identify early COPD
- to develop tests that predict health deterioration due to COPD
- to determine if specific patterns of disease progression are associated with genetic markers identified in the larger COPDGene study, and
- to determine if disease progression is in part caused by excessive stretch in regions of the lung next to blocked-off areas unable to inflate normally.

More than 200 million people suffer from COPD worldwide. Yet effectively assessing the progression of this increasingly prevalent disease and monitoring its response to treatment remain problematic. Hyperpolarized gas MRI can help rectify these issues by providing sensitive measurements of lung physiology and microstructure, but its adoption by clinicians and investigators has been slow. In contrast, CT-based methods for measuring emphysema, airway wall thickening, and expiratory air trapping have become common in COPD clinical studies. There are several reasons for this: CT is more accessible, its images possess excellent spatial resolution, and quantification of these images is currently superior. However, most CT-based parameters have only an indirect relation to physiology, and the modality exposes patients to ionizing radiation. Both of these shortcomings can be addressed by HP gas MRI. Consequently, the study seeks to more fully exploit the clinical potential of HP gas MRI by optimizing and testing parameters for the regional assessment of COPD patients and symptomatic smokers.

A novel multi-breath HP MRI technique allows for the simultaneous measurement of fractional ventilation (FV), regional partial pressure of oxygen (PAO₂), and apparent diffusion coefficient (ADC). Obtaining all three parameters in a single scan reduces the necessary amount of imaging gas while increasing accuracy by correcting artifacts associated with collateral ventilation and the slow filling of parenchyma in diseased lungs. Each of these metrics allows for the investigation of a vital aspect of lung disease progression and their comparison with the current CT-scans and standard of care will help to more clearly understand different features and phenotypes of COPD.

The proposed image analysis software will be central to the successful conduct of the following tasks necessary to establish the goals of this study:

- Registration of the multibreath/multislice Gas MRI images of the whole-lung consisting of a minimum of seven time points
- Registration and analysis of inspiratory and expiratory CT for airway changes to assess airway collapsibility and remodeling and other CT markers
- Registration and analysis of inspiratory and expiratory CT with MRI to study the similarities and differences of the two modalities in phenotyping the COPD population
- Registration of the follow-up MRI and CT images (two years) to determine if disease progression is in part caused by excessive stretch in regions of the lung next to blocked-off areas unable to inflate normally (based on the baseline MRI and CT)

Advanced image analysis of CT for early diagnosis and prognosis of bronchiolitis obliterans syndrome (BOS) in lung transplant patients. Co-investigators **Eduardo Barbosa** and **Warren Gefter** are conducting a retrospective study of more than 300 lung transplant patients to advance the early diagnosis of BOS. Lung transplantation is an established treatment for end-stage, irreversible pulmonary disease, particularly due to COPD and interstitial lung disease (ILD). While continued improvements in surgical techniques and immunosuppressive medications have reduced the complication rates and increased short-term survival after the procedure, chronic allograft rejection due to bronchiolitis obliterans (a fibrous obliterative disease of bronchioles representing the histological hallmark of chronic rejection and resulting in obstructive pulmonary physiology) remains the major cause of morbidity and mortality after six months following transplantation. Bronchiolitis obliterans currently represents the greatest limitation to long-term survival after lung transplantation. While the diagnosis of bronchiolitis obliterans is a pathologic one and therefore requires invasive biopsy, the distribution of disease is patchy, with focal areas of abnormality surrounded by normal lung, and consequently even biopsies may fail to demonstrate the diagnosis. For these reasons, the International Society for Heart and Lung Transplantation has recommended using declining spirometry, termed bronchiolitis obliterans syndrome (BOS), as a surrogate marker of chronic allograft rejection. In clinical practice, the diagnosis of BOS is suspected based on an unexplained decline in lung function (measured by PFT, of greater than 20% of baseline FEV1) and worsening cough and dyspnea, in the absence of other explanations such as pulmonary infection or congestive heart failure. MDCT plays an important role by demonstrating low attenuation areas representing air trapping, particularly on expiratory images, which correlate with the presence of bronchiolitis obliterans. Prior studies reported limited sensitivity for the early diagnosis of bronchiolitis obliterans; however these utilized semi-quantitative or qualitative assessment of air trapping in non-volumetric data sets. This study aims to assess whether automated imaging analysis can detect early BOS prior to development of clinically apparent disease.

PFT is the current reference standard for diagnosis of BOS, however, by the time PFT abnormalities beyond the threshold of BOS diagnosis ensue, the disease is already manifest and is not reversible with existing therapies. It is conceivable that sophisticated analysis of CT, including quantitative attenuation masks in inspiratory and expiratory datasets, image registration and texture based feature extraction may allow earlier detection of BOS in the preclinical phase, potentially generating surrogate biomarkers for drug trials and earlier prognostication.

Application of the proposed advanced software tools and algorithms in this project for quantitative analysis of CT images in lung transplantation patients will be crucial to enable computation of an array of first and second order statistics which would capture not only attenuation maps but also regional deformation and texture based features. In combination, this may allow multiparametric statistical modeling that may predict which patients will develop BOS before PFT abnormalities beyond the diagnostic threshold ensue. Such tools will be extended to other diffuse lung diseases, potentially generating new biomarkers for diagnosis, prognostication and therapeutic trials.

Comparison of automated multi-modality registration methodologies to manual registration for lung CT bronchial morphologic changes and hyperpolarized helium MR ventilation defects in asthma patients: Can automation speed the work flow for combining structure and function using airways measures from CT and ventilation measures from HP gas MRI. Our collaborators **Sean Fain** and **Mark Schiebler**, **University of Wisconsin**, are part of the SARP (Severe Asthma Research Program) team developing imaging biomarkers of asthma severity for predicting asthma exacerbation. The approach of finding airway abnormalities that correlate with ventilation defects is viable only with the availability of robust image registration across the two modalities. Furthermore, translation to the clinic will require standardized implementations across sites, and the project's open-source platform is ideal for this purpose.

Deep functional phenotyping of COPD. Our collaborator **Hans-Ulrich Kauczor, University Medical Center Heidelberg**, is leading the COSYCONET (German COPD and Systemic Consequences–Comorbidities Network) study, the world's first prospective multicenter trial comparing proton MRI and CT imaging for characterizing COPD, with the latter modality serving as the reference standard. Automated image registration and segmentation will play a vital role in defining the quantitative CT (air trapping, airway collapsibility and remodeling, and pulmonary blood volume and vascular pruning) and MR (air trapping, perfusion volume defects, and hypoxic vasoconstriction) imaging biomarkers that form the basis for the study.

Longitudinal imaging follow-up in COPD and lung cancer Our collaborator Joon-Beom Seo, Asan Medical Center, directs the imaging component of the Korean Obstructive Lung Disease (KOLD) cohort study, which has collected over 1000 COPD cases from 17 participating centers with repeated imaging since 2005. He also leads a national lung cancer radiomics project that has accrued 800 cases to date. In both studies, robust image registration is essential to tracking changes over time, and segmentation is an additional requirement to support automated lesion delineation for the cancer project.

Advanced image processing pipelines for MR image-guided pulmonary therapy decisions and support. Our collaborator **Grace Parraga, University of Western Ontario**, has been at the forefront of MR imaging of lung structure and function since 2005. A major challenge hampering widespread translation of current pulmonary imaging advances is the lack of precision in their interpretation, thereby complicating the planning and guiding of targeted therapies. The project's software tools will enable the development of robust analysis pipelines for the translation of *in vivo* imaging biomarkers openly across platforms and centers. This work, carried out in collaboration with industrial partners, will support patient phenotyping and stratification to therapy as well as measurement of longitudinal changes and response to therapy.

Functional MR imaging of the lungs using hyperpolarized and inert gases. Our collaborator, **Mitchell Albert, Thunder Bay Regional Research Institute**, has been advancing the use of inert fluorinated gases that can be breathed continuously in order to measure indicators of wash-in, wash-out and air trapping with dynamic imaging protocols. To compute the wash-in and wash-out time constants on a pixelwise basis, access to accurate and reliable image registration tools will be essential.

Multimodality imaging studies of pulmonary diseases. Our collaborator, **Edwin van Beek, University of Edinburgh**, has been conducting various multimodality studies, including the evaluation of pulmonary fibrosis using both gadolinium-enhanced MRI and contrast-enhanced CT perfusion imaging, and the assessment of lung nodules using PET-CT and CT perfusion imaging. These relatively new techniques would benefit from quantitative analysis of contrast enhancement, and advanced image registration and segmentation capabilities will both be necessary toward this end.

More details about the research, data, and advances enabled by the proposed software tools for each of the studies above can be found in the corresponding letter of support. *The nature and diversity of the imaging data collected for these studies will be a stringent test of the ease of use, interactivity, and flexibility of the developed processing and analysis software resources in this project. Moreover, the studies will yield valuable additions to the portfolio of use cases that serve as primary reference and instructional material.*

3(c.4) Sub-Aim 2a will disseminate the results of the project through open-source publication of the code, annotated processed data, online user support, and conduct of hands-on training workshops. ITK is the leading open-source development system for medical image analysis, and to demonstrate its endorsement of this project's value to the field, ITK will lend its infrastructure to provide long-term hosting services for the developed resources as well as incorporate ITK-Lung training into its educational programs that are offered in conjunction with major scientific (e.g., annual International Conference on Medical Image Computing and Computer Assisted Intervention) and user forums (e.g., hackathons); see Yoo letter of support. Further leveraging of ITK support will include formalized advisory input from its core development team (of which the project team is a member), and access to and promotion within its extensive outreach program. Complete dissemination details can be found in the Resource Sharing Plan.

3(c.5) Risks and alternatives While the proposed infrastructure is complex and integrates multiple cutting-edge technologies, we do not anticipate significant problems in its development and consider the risk of failure of the project to be very low. Our optimism is based on the extensive preliminary work that has been performed over a significant period of time to successfully demonstrate feasibility of every aspect of the project. Given the level of expertise and experience of our interdisciplinary team and the well-defined scope of the imaging and software engineering problems, we are highly confident in a successful outcome.

3(c.6) Timeline Aim 1: Software development will take place in Years 1-5, with Year 1 focused on refactoring of existing ANTs-based code and integration with ITK; Year 2 focused on incorporation of new methods to support expanded functionality beyond core algorithms; Year 3 focused on GUI implementation; Year 4 focused on releasing a fully functional system; and Year 5 focused on incremental improvements based on Aim 2 studies. **Aim 2:** A preliminary version of the software will be deployed at evaluation sites toward the end of Year 2, and testing will run through Year 4. Documentation and dissemination efforts will take place throughout the course of the project.

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