

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].

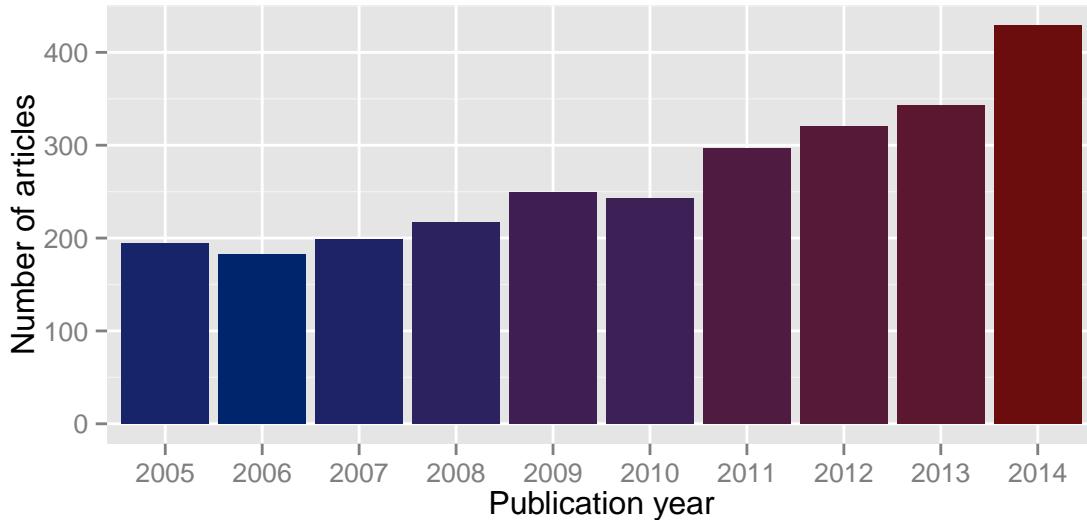


Figure 1: Number of articles per year which cite publicly available neuroimaging analysis packages (specifically, FreeSurfer, AFNI, FSL, and SPM). Although the benefits seem clear for the neuroscience community, analogous efforts within the pulmonary community have yet to be undertaken despite consensus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

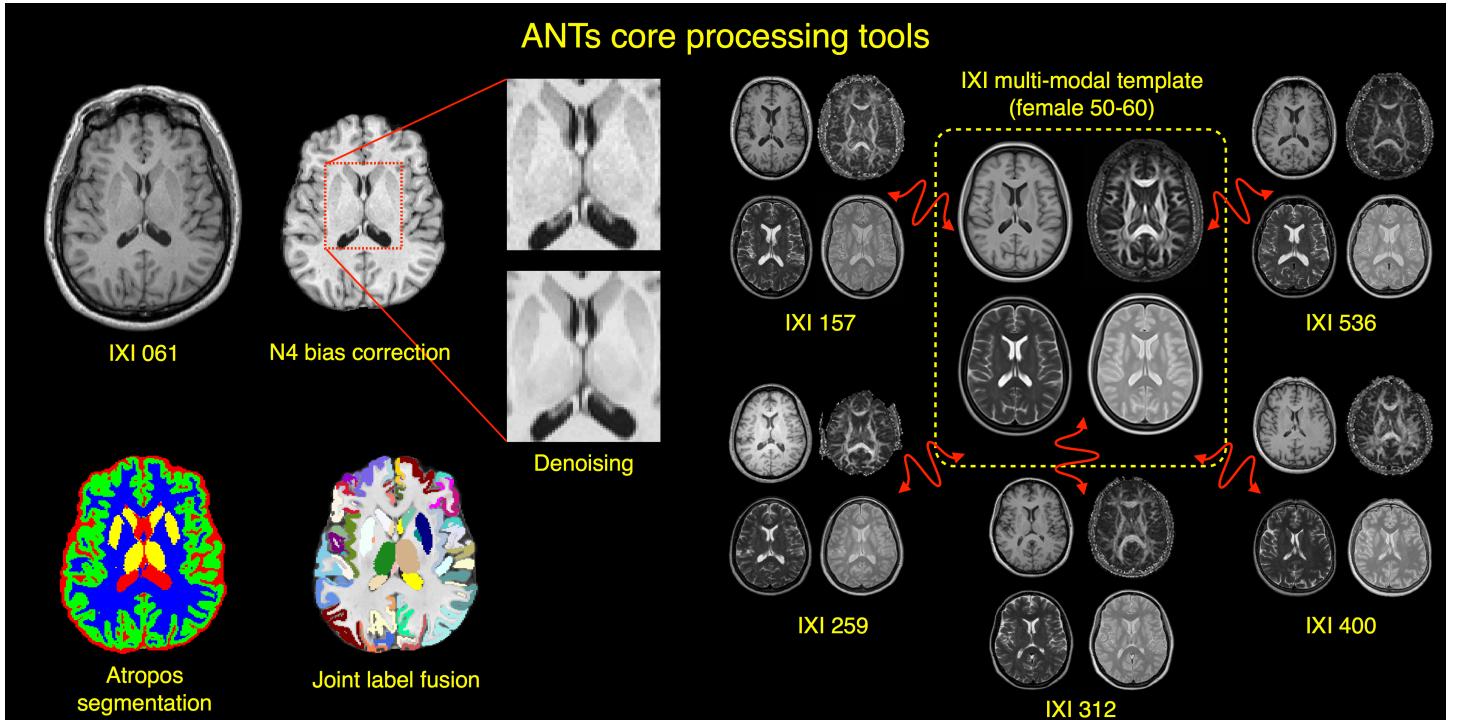


Figure 2: Core processing tools that have made the ANTs package one of the most popular neuroimaging toolkits. Fundamental processing tasks such as image registration, template generation, bias correction, denoising, intensity-based segmentation, and joint label fusion are extremely well-performing software 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.

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

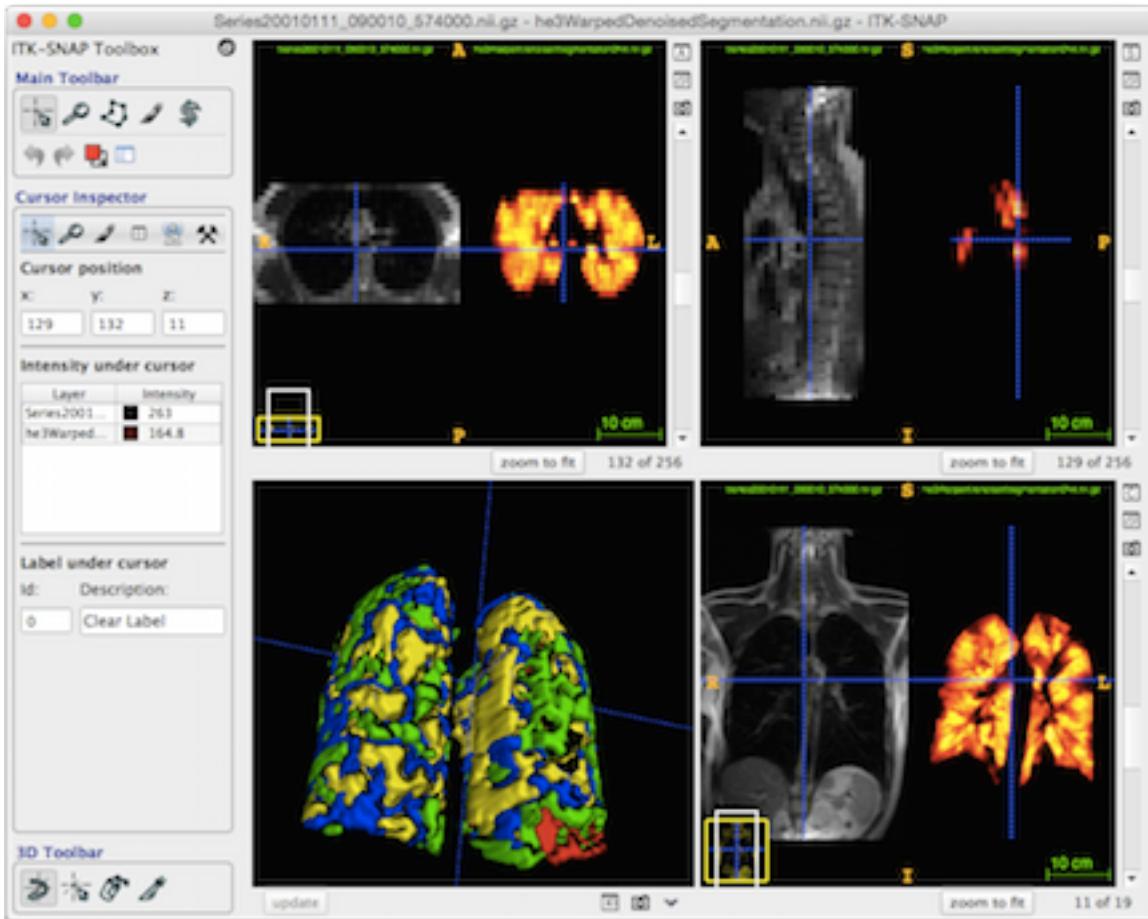


Figure 3: Screenshot of the well-known ITK-SNAP open source tool showing co-registered 1H (left) and 3He MRI (right). The spatially normalized images permits extraction of anatomical information (i.e., lung and lobar regions) and functional information in terms of ventilation. Shown in the bottom left panel is the surface rendering of the ventilation-based segmentation.

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

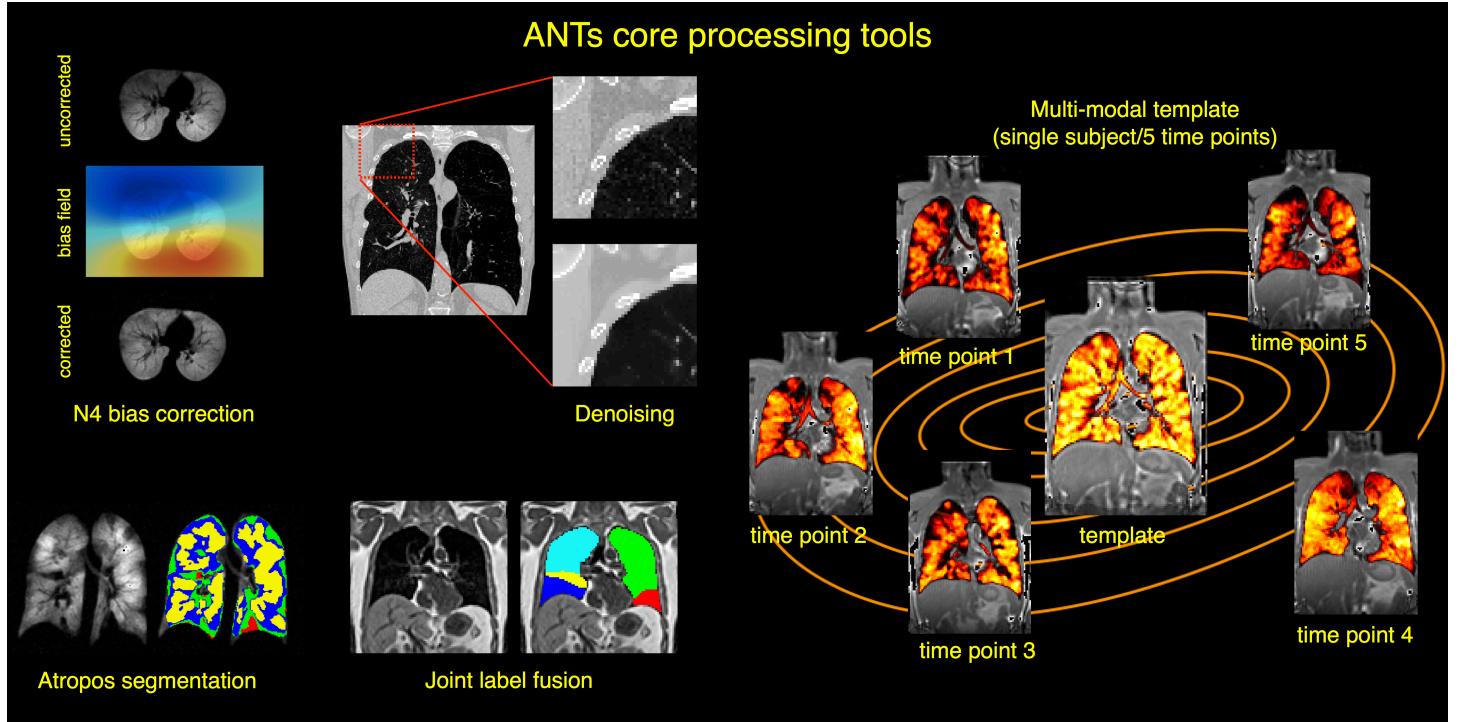


Figure 4: Using ANTs core processing tools, our team has developed several lung-specific extensions such as ventilation-based segmentation, lung and lobe estimation, and multi-modal pulmonary template building. Although each of these extensions requires significant additional development and tuning, 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 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 seg-

Functionality	CT	¹ H 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.

mentation 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 2).

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 ³He and ¹²⁹Xe 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].

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

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.

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 ^{3}He 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 ^{3}He 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.

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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