

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

## 2 Specific Aims

One of the most significant hurdles to leveraging imaging innovations 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 computational image 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 general software exists for multi-modality pulmonary imaging analysis. The primary goal of this project is to develop a robust, open-source image analysis toolkit and dissemination platform specifically targeted at the pulmonary research community. Given the significant efforts to make lung imaging datasets publicly available (such as LIDC, RIDER, COPDGene, and IELCAP), this contribution would be innovative as it would meet a critical need through a first-of-its-kind software package for multi-modality lung image analysis.

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 is often 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 limits accessibility to researchers.

As a corrective alternative, this project brings together leading expertise in lung imaging research at the University of Pennsylvania (Penn), the University of Virginia (UVa), and the University of Iowa to develop, evaluate and deploy under community support an open-source software toolkit targeted for multi-modality pulmonary imaging research. Specifically, we plan to provide core algorithms for specific pulmonary image analysis tasks across multiple modalities, many of which we have included with previous publications. These basic tasks include intra- and inter-modal pulmonary image registration, template building for cross-sectional and longitudinal (i.e., respiratory cycle) analyses, functional and structural lung image segmentation, perfusion analysis, and computation of quantitative image indices as potential imaging biomarkers. These efforts would facilitate other NIH-sponsored projects which interface specific pulmonary algorithms (e.g., CT nodule detection) with clinical and research applications. In addition to the software, we will provide scripts, documentation, and tutorial materials consistent with open-science principles. Formally, this project is defined by the following specific aims:

- **Specific Aim 1: Develop ITK-Lung, a set of open-source software tools for CT, PET, and MRI pulmonary computational analysis.** These open-source software tools based on selected algorithms will specifically target pulmonary image analysis and comprise core application functions such as inspiratory/expiratory and multi-modality registration, ventilation-based segmentation, lung and lobe estimation, airway and vessel segmentation, perfusion analysis, and calculation of clinical indices for characterization of lung development and pathology. As a complement to these software development efforts, CT and 1H MRI multi-atlas libraries will be provided as open data, complete with the corresponding lung, airway, vessel and lobe segmentations, according to modality, to facilitate the employment of atlas-based algorithms on user data sets. In addition, we will generate optimal intensity/shape templates from each library for use as common coordinate frameworks for more localized (i.e., voxelwise) analyses. All data will be provided with the scripts used to produce them in order to permit user-reproduction of the results. As principal developers of the popular, open-source ANTs, ITK-SNAP and ITK packages for image segmentation and registration, we know firsthand that the impact of a particular technological innovation greatly depends on the availability of an easily accessible software implementation. The proposed software framework will tie together all of the capabilities of the project’s developed methodology in the form of programmable workflows as well as provide a seamless user experience through a full featured graphical user interface. Interactive functionality will extend beyond the ability to steer segmentation and registration pipelines to include tools for evaluation and visualization of processed results.
- **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 proposed framework within the real-world context of pulmonary research being carried out at Penn and UVa in addition to various partner sites serving as secondary beta testers. We will disseminate the results of the project through open-source distribution of the software, atlases and documentation, online user support, and conduct of hands-on training workshops.

### 3 Research Strategy

#### 3(a) Significance

**3(a.1) The importance of analysis tools for research and clinical \textcolor{red}{imaging} 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].

**3(a.2) Open-source as an essential attribute of high-impact image analysis toolkits.** Well-vetted and publicly available software have transformed targeted research fields. 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.

*However, despite the important implications for the pulmonary imaging community, no such analogous set of tools exist for multi-modal pulmonary-specific research. Such an original software package would potentially have an immediate and significant impact.* Indeed, a recent review [8] of CT- and MRI-derived biomarkers for pulmonary clinical investigation highlighted the lack of universally available multi-modality image analysis software—despite the existence of an extensive and continually growing literature—as one of the major impediments to more widespread usage of the unique applications offered by each modality and the use of multi-modality imaging to gain a broader understanding of the etiology of lung disease. This project would thus be transformative in providing both a solution for this critical unmet need and a publically available set of multi-modality software approaches that can be built upon further.

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) do not exist despite the vast number of algorithms that have been proposed in the literature (most of which are not available to the public).<sup>1</sup> Importantly, the goals of this project would significantly support the National Library of Medicine's (NLM) open-source directives in that all software proposed in the project 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 (ITK) as we have done in the past; textcolor{red}{see Yoo letter of support}. NLM's position on open-source stems from the documented benefits within the targeted communities for which such software is developed and supported. In addition to increase in research output, open-source permits trainees 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(a.3) The challenging dynamic nature of the multi-modality lung imaging environment demands tools with comprehensive capabilities.** There is need for continued improvement of imaging acquisition technologies for the lung; nevertheless, the current state-of-the-art permits effective quantitation of pulmonary structural and functional parameters in multi-modality studies. The major caveat, however, is that sophisticated and extensive pre- and post-processing of the images may be required depending on the type and degree of distortions and artifacts introduced in their acquisition. Enabling the ability to carry out such processing is one of the major goals of this project. To achieve this objective, given the additional complexity introduced by the heterogeneity of applications and equipment in lung imaging, flexible and tunable (i.e., open and programmable) tools are needed, with manifold capabilities carefully curated to cover essential analysis and processing tasks, all of which ideally integrated within a single coherent toolbox—this is the overall goal and deliverable of the proposed project.

#### 3(b) Innovation

**3(b.1) Open-source pulmonary imaging algorithmic innovation.** Given the lack of open-source solutions for multi-modality pulmonary image analysis, this project would produce the first-of-its-kind processing and analytic platform for performing such research. Similar to the brain-specific algorithms provided in our ANTs (Advanced Normalization Tools) toolkit [11], our project would include several essential algorithms for analyzing lung images from different modalities, including CT, PET, and MRI. A large number of algorithms have been proposed in various technical venues, but these are mostly in the form of textual descriptions without accompanying software. In contrast, we will provide well-vetted and easy-to-use implementa-

<sup>1</sup>Several competitions have been held in recent years focused on the processing and analysis of lung image data (e.g., VOLCANO09—nodule detection, EMPIRE10—registration and motion estimation, LOLA11—lung and lobe segmentation, and VESSEL12—vasculature segmentation). To the best of our knowledge, the vast majority of the proposed algorithms are not publicly available. Other pulmonary imaging efforts, such as LIDC and RIDER, have amassed large amounts of imaging data but available software support is limited to organizational tasks specific to those databases. In contrast, the COPDGene study has given rise to the Chest Imaging Platform software, which does not yet appear to be fully available to the public and whose focus and scope (CT imaging primarily of COPD) are significantly more narrow than those for this project.

Functionality	Papers
registration and normalization	[21, 45, 73, 74]
template generation	[29]
lung segmentation	[50]
lobe segmentation	[50]
airway segmentation	[82]
functional segmentation	[29, 38, 41]
feature indices	[97, 98]

**Table 1:** Research contributions from our group demonstrating pulmonary multi-modal image domain expertise.

tions of specific robust methodologies for pulmonary 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. We recognize that the methodological depth of the field is extensive and have therefore carefully selected algorithms for implementation in the project that 1) provide coverage of essential functionality, 2) have been rigorously discussed in the literature, and 3) have delivered consistently excellent performance in our clinical collaborations. The availability of these implementations will offer a unique clinical utility to the community in addition to a performance benchmark and baseline platform for application and algorithm developers.

**3(b.2) Use case studies with leading pulmonary research scientists.** Another innovative component of the project is the inclusion of an extensive set of use cases from leading pulmonary research groups with regression testing performed using different image acquisition protocols, equipment, etc. to ensure quality and robustness of the processed data. The use of separate, independent testing sites will increase the value of the tools produced by ensuring that their success is not specific to the particular source of data. This will increase the generality of the developed resources and thus ease dissemination to the wider community. Toward this end, the 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. Tutorial materials, data, and example scripts drawn from these studies will be provided to the public for any interested researcher to apply to their 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 our publications (e.g., see previous similar offerings from our group [12, 13]). A clinically-based evaluation of these tools will not only provide insight into the specifics of certain pulmonary pathologies but also offer a reproducible mechanism for using the tools created in this project.

### 3(c) Research design

#### 3(c.1) Preliminary data

Major progress toward the proposed platform, demonstrating project feasibility, has already been reported by our group (cf Table 1). These publications not only document methodological novelty of the work but also describe their subsequent usage for clinical research studies of small to large cohorts. Much of this innovation has been encoded in prototypical form in the ANTs processing toolkit, as described below, to allow for continued use, potential future improvements, and reproducibility.

**3(c.1.1) Generic ANTs core tools for image analysis and processing.** The Advanced Normalization Tools (ANTs) package is a state-of-the-art, open-source software toolkit for image registration, segmentation, and other basic medical image analysis functionality [11]. Several core programs comprising portions of the proposed pulmonary imaging analysis software framework have been created and made available within ANTs (and either simultaneously or subsequently made available in ITK). However, these programs have more general application and require pulmonary-specific tuning for the tasks targeted by this project. The following list comprises available functionality proposed 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 innovations in medical image analysis is the development of image registration techniques capable of mapping the highly complex 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 [14–16]. 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 for lung [17], brain [18], and cardiac imaging [19]. ANTs not only encodes the most advanced results in registration research, notably the Symmetric Normalization (SyN) algorithm for diffeomorphisms [20], 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 [12]. This evaluation utilized multiple publicly available, annotated 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 in this project, these scripts were extensively modified to serve as a follow-up entry into the EMPIRE10 lung image registration challenge where B-spline SyN performed better than its original counterpart on pulmonary data [21], which had been the official

*top ranked entry since the inception of the challenge.*

**Multi-modality template generation.** Given the variability in anatomical shape across populations, generating population- or subject-specific optimal shape/intensity templates significantly enhances study potential [22, 23]. First, an average template is estimated via a voxelwise 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 1 for a cohort-specific multi-modality brain template for females in the age range 50–60 years. This functionality has proven to be a highly valued component of the ANTs toolkit, with significant community adoption, for performing neuroimaging research (e.g., [13, 24–28]). *The same technology specialized to lung imaging will accelerate the translation to the pulmonary domain of voxelwise studies that have transformed the neuroimaging field, and may prove equally valuable and impactful to the pulmonary research community* [29].

**Bayesian segmentation with spatial and Markov Random Field priors.** Early statistically-based segmentation work appropriated NASA satellite image processing software for classification of head tissues in 2-D MR images [30]. Following this work, many researchers adopted statistical methods for  $n$ -tissue anatomical brain segmentation. The Expectation-Maximization (EM) framework is natural [31] 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 [32, 33] and the use of Markov Random Field (MRF) modeling [34] for regularizing the classification results [35]. Spatial prior probability maps of anatomical structures of interest are also employed within this framework [36, 37]. Although this particular segmentation framework has significant application in the neuroimaging domain, it is also relevant to other domains including functional ventilation of the lung [38]. *However, despite the numerous developments which have been proposed over the years within this area, there are only a few actual software implementations. This deficit inspired us to create our own Bayesian segmentation framework* [39] (denoted as Atropos), which we have made publicly available within ANTs and has proven highly effective in quantification of functional lung imaging data [38, 40–42].

**N4 MRI 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 [43], as part of their standard processing protocol [44]. In [45], we introduced “N4,” which incorporates both an enhanced fitting routine (including multi-resolution capabilities) and a modified optimization formulation that produces a significant improvement over N3 in performance and convergence behavior on a variety of data. N4 has since become the new standard in the field.

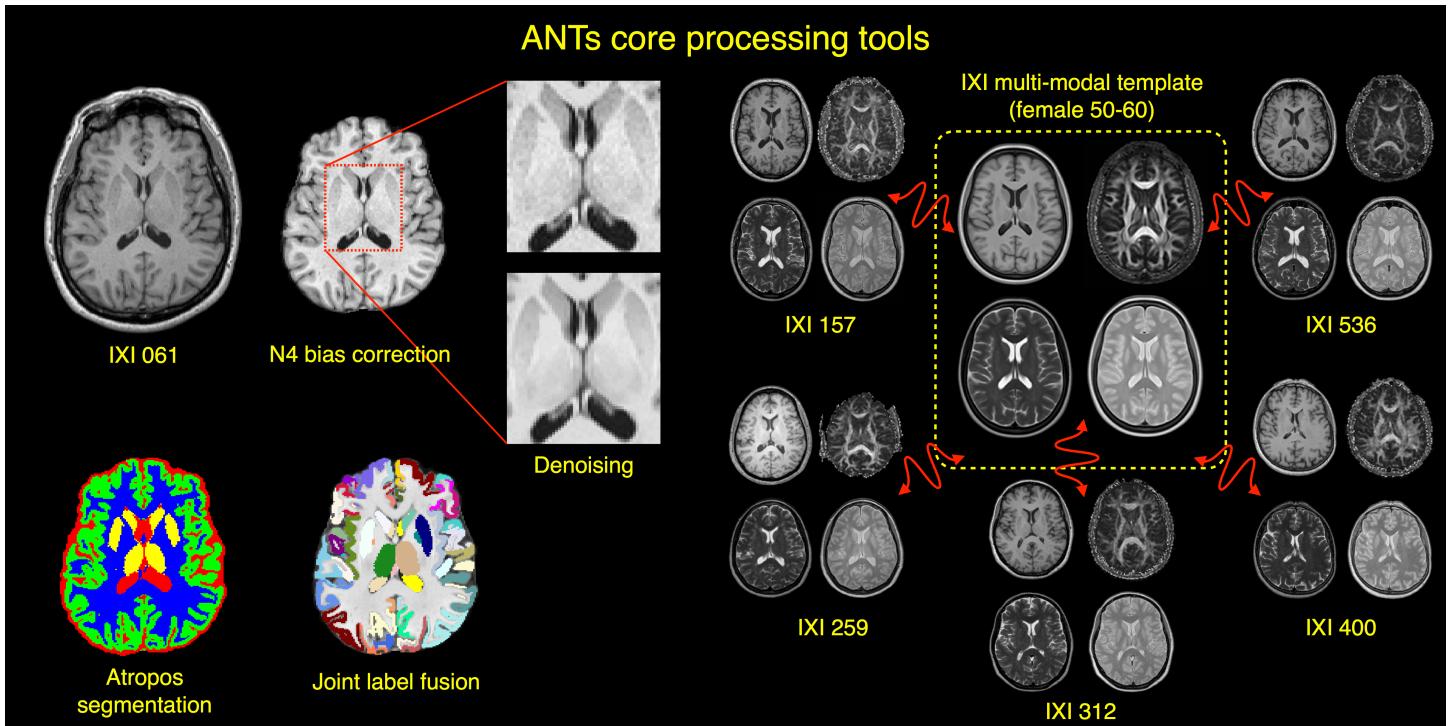
**Joint label fusion for multi-atlas segmentation.** Joint label fusion (JLF) is the current state-of-the-art for propagating expert labelings from a reference atlas library onto new instances of unlabeled data. Image registration is used to align the atlas library (images plus segmentations) to a common 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 label fusion (JLF) algorithm of [46, 47] from our group is widely recognized as among the best performing, having placed first in the MICCAI Grand Challenge. JLF is capable of predicting anatomical labels with accuracy that rivals expert anatomists [48] and has proven its effectiveness in multiple domains [13, 49]. Importantly, we have successfully extended JLF to the challenging problem of applying prior-based information to lung and lobe segmentation [50].

**Spatially adaptive denoising.** Denoising is essential for data “cleaning” prior to subsequent processing such as segmentation or spatial normalization. ANTs implements a state-of-the-art spatially adaptive version to patch-based denoising recently proposed in [51].

**Field-leading open-source implementations.** The previously described core software functionality, 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 advancements 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 programming library (<http://www.itk.org>), the leading open-source platform for medical image analysis. *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 [18].
- SyN also competed in the Evaluation of Methods for Pulmonary Image REgistration 2010 (EMPIRE10) challenge [17], 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 [46, 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 [23].
- A B-spline variant of the SyN algorithm [12] won the best paper award at the STACOM 2014 workshop for cardiac motion estimation [19].



**Figure 1:** 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 **first-in-class** 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.*

**3(c.1.2) Neuroimaging with ANTs as a model for the pulmonary community.** ANTs takes advantage of the mature Insight Toolkit in providing a powerful framework for building scripts and programs to facilitate processing of large neuroimaging studies. In particular, ANTs has developed a very large user base by making openly available a complete suite of fundamental processing capabilities, covering brain normalization [55, 56], brain template generation [22], skull-stripping or brain extraction [57], prior-based brain tissue segmentation [39], cortical thickness estimation [13, 58], brain tumor segmentation [23], and cortical labeling [46, 47]. These tools have been wrapped in easy-to-use, well-documented shell scripts that are accompanied by online self-contained examples with developer-tuned parameters and are compatible with the major cluster systems (e.g., SLURM, SGE, and PBS). This project will implement a similar strategy to support the lung imaging community, as demonstrated by the following software utilities that have already begun to find widespread use among pulmonary research groups:

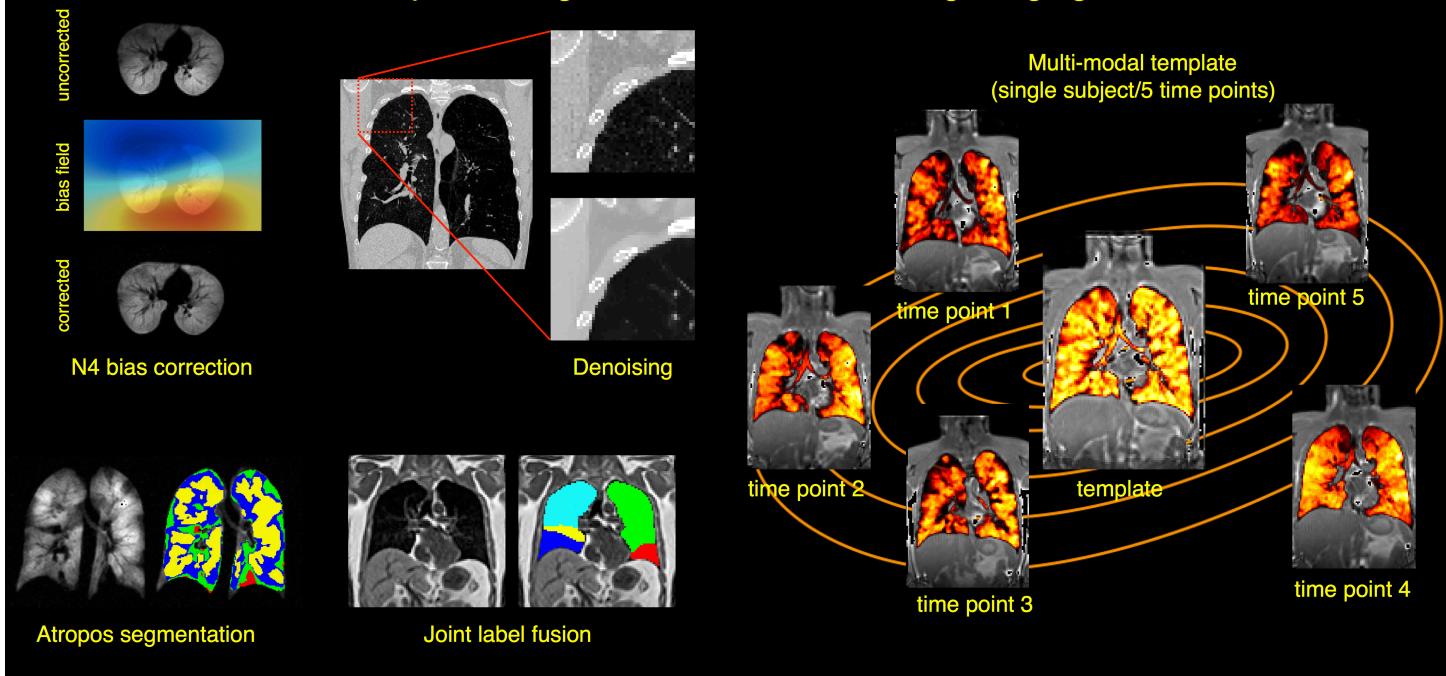
- intra-modal lung registration [12] (<https://github.com/ntustison/antsCtLungRegistrationExample>),
- inter-modal lung registration [12] (<https://github.com/ntustison/ProtonCtLungMaskRegistration>),
- functional lung segmentation [38] (<https://github.com/ntustison/He3LongitudinalAnalysis>), and
- lung and lobe segmentation [50] (<https://github.com/ntustison/LungAndLobeEstimationExample>).

### **3(c.2) Specific Aim 1: To develop ITK-Lung, a set of open-source software tools for CT, PET, and MRI pulmonary computational analysis**

The envisioned open-science tool set for pulmonary image analysis consists of software, processed data to illustrate the use of the software, and the ability to evaluate and visualize user-generated results. With this comprehensive offering, the goal of this project is to help the pulmonary imaging research community on a much deeper level than simply providing a set of programs. In order to facilitate engagement on the part of the community, we are proposing a multi-faceted approach with ITK-Lung. The main component will be the core **software** tool set described in Sub-Aim 1a which would permit large-scale processing of multi-modal pulmonary image data. To illustrate the use of the software, allow for processing of other public and private data sets, and provide baseline data for algorithmic comparison, **the second component will involve the release of CT and 1H MRI annotated atlas libraries, corresponding templates, and data-generating scripts as described below.** The third component will be significant extensions to the well-known ITK-SNAP software for an enhanced user experience through a full featured graphical user interface to support interactive **tuning of parameters and interrogation of processed results**.

### **3(c.2.1) Sub-Aim 1a will expand the ITK/ANTs open-source libraries by implementing currently unavailable**

## ANTs core processing tools for multi-modal lung imaging studies



**Figure 2:** ANTs core processing tools for multi-modal lung imaging studies. Using ANTs processing tools, our team has developed several lung-specific extensions such as ventilation-based segmentation, lung and lobe estimation, and multi-modality pulmonary template building. Although each of these extensions requires significant additional development and tuning, a robust and generic software foundation ensures that these prototypes are of high quality and are readily adapted to the pulmonary image domain.

**lung-specific algorithms.** Many important algorithmic categories implementing fundamental lung image analysis tasks do not currently exist in any comprehensive, publicly available package. This is despite 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 [59] 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 key problem in the pulmonary image analysis community is that the lack of publicly available tools translates directly into a paucity of baseline performance standards with which researchers can compare their own algorithms [60]. This project constitutes a specific and overdue response to this major deficiency in the field.

Toward this end, a select set of tools with a track record of good performance, spanning the range of core functionality and designed to facilitate expansion, will serve the pulmonary research community as a well-vetted quantitative resource and baseline for future algorithmic development. Table 2 comprises the proposed functionality for multi-modal lung image analysis that would be incorporated into ITK-Lung in addition to further enhancements to the registration and segmentation capabilities described in preliminary work. Using ANTs core tools with lung-specific modifications, we have produced prototypical implementations complete with preliminary documentation and github examples for several of the proposed processing capabilities as described below.

**Atlas-based lung segmentation.** Identification of anatomical structure in lung images is often a crucial preprocessing step for quantification of morphological features or ventilation information from functional images. Quantitative regional analysis typically requires the delineation of lung and lobar anatomy. Although much algorithmic research for lung segmentation has been reported in the CT literature [61], co-opting such technologies is complicated in MRI by 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 [50]. Multi-atlas approaches to segmentation have proven highly successful in multiple domains [46, 52], and these methods translate readily to pulmonary applications. 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 2). The evaluation of our proposed method [50] demonstrated excellent performance with Jaccard overlap for the left and right lungs measuring  $0.966 \pm 0.018$  and  $0.970 \pm 0.016$ , respectively. Further work for this project includes extension to CT datasets with a particular emphasis on segmentation in the presence of lung pathology that will incorporate the data from the proposed multi-atlas CT library.

Functionality	CT	1H MRI	3He MRI	PET
registration and normalization	[12,21,56]	[12,56]	[12,56]	[12,56]
template generation	[22,23]	[22,23,29]	[22,23,29]	[22,23]
lung segmentation	[50]	[50]	–	–
lobe segmentation	[50]	[50]	–	–
airway segmentation	[80, 82]	–	–	–
vessel segmentation	[83]	–	–	–
functional segmentation	[38]	–	[38]	–
feature indices	[97, 98]	–	–	–

**Table 2:** Core functionality proposed for development and evaluation in the project 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 subsequently added to the functionality developed and offered as part of this project. It should also be noted that some modality-specific modifications will be required. For example, our lobe estimation approach works well for 1H MRI where no internal anatomical features are available for refinement. This lobe estimation strategy can be directly applied to CT in providing spatial prior maps for subsequent subject-specific refinement. In response to reviewer suggestion, nodule detection has been removed from the project to avoid redundancy with the Chest Imaging Platform software that has this capability as a major development focus.

**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. Nevertheless, 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). Specifically, to generate the lobe segmentation in a target 1H or CT lung image, we register the same-modality atlas set to the target image (given the general increased robustness of intra-modality vs. inter-modality image registration) using the B-spline SyN registration approach described earlier [12]. Subsequently, we warp the set of lobe label images to the target image using the atlas-to-target transformation. This process will be illustrated publicly as part of the project using the open-data multi-atlas CT and 1H atlas libraries created as part of Sub-Aim 1b. Since there is no intensity information inside the target lung mask and CT atlas lung masks, a simple majority voting strategy is used to generate the consensus labeling for the target image. Following this step, we remove any labelings outside the lung mask and assign any unlabeled voxels with the label closest in distance to that voxel. Additional details can be found in [50], where we showed that lobar overlap measures in 1H MRI were on par with methods for CT images in which fissure information is actually visible (left upper:  $0.882 \pm 0.059$ , left lower:  $0.868 \pm 0.06$ , right upper:  $0.852 \pm 0.067$ , right middle:  $0.657 \pm 0.130$ , right lower:  $0.873 \pm 0.063$ ). We will extend this framework to pulmonary CT in providing spatial prior probability maps derived from image-specific CT data features such as fissures, airways, and blood vessels for data-driven, subject-specific lobe segmentation [62]. With the simultaneous acquisition of functional (i.e., PET and 3He images) and anatomical (i.e., 1H and CT) images, the availability of lobe anatomy estimation in anatomical lung images facilitates the calculation of regional functional measures which is difficult to directly obtain from the functional images.

**Ventilation quantification.** The ability to classify areas of varying degrees of ventilation represents a basic need in pulmonary functional analysis. In [38], we presented an automated algorithmic pipeline for ventilation-based partitioning of the lungs in hyperpolarized 3He and 129Xe MRI. Given a whole lung mask (see **Atlas-based lung segmentation**), the original pipeline performs MR inhomogeneity correction followed by Bayesian segmentation with an MRF prior. Without ground truth data for evaluation, we used a consensus labeling approach [63] to simultaneously estimate the true segmentation from given “raters” and the performance of those raters with respect to that estimation. In this evaluation, “raters” refers to the segmentation from our automated approach and the manual tracings of three trained individuals. In terms of combined specificity and sensitivity, our algorithm demonstrated superior performance with the added benefit of being reproducible and less time-consuming. Future enhancements to this pipeline will include the incorporation of 1) an iterative bias-correction/segmentation scheme that should yield improved optimization solutions and 2) a better performing denoising protocol based on the patch-based method described in [51].

**Multi-modality lung template construction.** Because the template construction algorithm described in [22] was originally developed for proton MRI and neuroimaging applications, it will be modified in this project to additionally admit CT and PET data and further adapted for specialized use in studies of the lung. The latter development will build on our recent innovations in diffeomorphic registration technology that has led to a Symmetric Normalization B-spline variant which will be extended and refined to include patch-based similarity metrics suitable for minimizing the computational footprint of problems involving very large images of the kind commonly encountered in lung studies while at the same time providing accurate normalizations [12] for pulmonary data [21]. For functional lung imaging data (i.e., PET and 3He), this step generates the statistical coordinate system which could be used for subsequent voxelwise analyses to determine local correlation with clinical measures.

**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 ground-glass opacities and fractal and connectivity approaches to differentiate centrilobular from panlobular emphysema. The available indices for CT image analysis can roughly be divided into those that characterize the pulmonary parenchyma: volumetric tissue (e.g., [64, 65]), distribution of low attenuation areas (LAA) (e.g., [66, 67]), cooccurrence and run-length matrix features (e.g., [68, 69]), attenuation statistics (e.g., [70, 71]), deformation measures (e.g., [72, 73]), and stochastic fractal dimension features (e.g., [68, 71]); and those that characterize the airways (e.g., [74–76]). The former are important for subjects with an emphysematous component of disease, whereas the latter are important for subjects with a bronchitic **disease** component. *An important benefit of this project's multi-modality scope is that many of these measurements can also be directly applied to discriminative analysis using <sup>3</sup>He MRI and PET for a variety of lung diseases.* Moreover, recent work has demonstrated [77] these indices can **additionally** be studied not only at any particular single time point, but also for changes with time.

**Airway segmentation.** Lung airway morphology has been previously utilized as a biomarker for disease characterization but there are many other potential uses motivating the inclusion of airway segmentation in any pulmonary image analysis toolkit. In an evaluation of 15 airway segmentation algorithms [78] for the Extraction of Airways from CT challenge held in 2009, the top 2 performers were the algorithms of [79] and [80] with the latter being one of the more conservative algorithms and the former being more prone to false positives. Our plan is to provide an implementation of [79] which employs a sharpening of the airway branching edges and **the use of** adaptive cuboid volumes to **realize** a region-growing airway segmentation approach. We **will then** augment this functionality with complementary aspects of our previous work [81] for removing leakage path candidates.

**Vessel segmentation.** In contrast to much of what is described in the literature, there exist key contributions for pulmonary vessel segmentation available to the public, specifically the algorithms described in [82]. Similar to much of the research for enhancement of vessel-like morphology in different anatomies, the authors employed Hessian-based filters for deriving a “vesselness” function. Their approach ranked consistently among the top performers in the VESSEL12 challenge organized in conjunction with the IEEE International Symposium on Biomedical Imaging (ISBI 2012). Given that the first author is a regular ITK contributor, the corresponding code will be easily integrated into our platform.

**Perfusion analysis.** A nonparametric deconvolution technique for quantifying cerebral blood flow was first presented in [83] and subsequently extended for use in assessing pulmonary blood flow [84, 85]. This deconvolution strategy was recently implemented by our group for a separate lung imaging study but will be modified for this project to automatically select the arterial input region and volume of interest.

**Graphics processing unit acceleration.** In preliminary work, we have successfully used OpenGL shader language to perform image processing operations, such as computation of similarity metrics between images or extraction of features from images, on the graphics processing unit (GPU) at real-time speed. GPU requirements for ITK-Lung will be very modest and would be met by virtually any mid-range desktop computer sold today (e.g., a mid-range iMac). We plan to integrate both affine and deformable registration with GPU acceleration into ANTs. The three components of diffeomorphic deformable registration in ANTs that account for over 95% of computation time are: 1) computation of the gradient of the similarity metric (e.g., mutual information, cross-correlation); 2) smoothing of the gradient using Gaussian kernels; and 3) image and vector field interpolation. All three components are highly parallelizable, and we will write OpenGL shader code for performing these operations on the GPU, analogous to the code currently used for metric computation in GPU-based affine registration in ANTs.

**Computational power.** With the proposed GPU acceleration of image registration, we expect that even the most complex registration-dependent problems will be possible to solve on a desktop computer in under 10 minutes. **This estimate is based on** preliminary work **in which** we have developed a CPU-based accelerated version of the ANTs deformable registration algorithm that is approximately 15 times faster in typical problems than the version currently in use. This means that on a typical 8-core CPU, the same registration of  $512 \times 512 \times \sim 500$  voxel images can be **completed in under 20 minutes instead of the 1-2 hours it would take on a single CPU core using the current production version of ANTs.** This dramatic improvement was made primarily through 1) use of more efficient metric gradient computation algorithms, 2) use of single instruction multiple data (SIMD) parallelization on Intel CPUs, and 3) extensive code profiling and optimization. With the move to the GPU, we expect to speed up registration by another factor of 4–5 times. Therefore, the vast majority of ITK-Lung users will not need to have access to high-performance computing clusters or other expensive hardware.

However, for power users with very large datasets or datasets that require more compute-demanding parameters or higher-resolution registration, we will also provide an alternative offline processing mode, in which the registration tasks are executed on an external high-performance computing resource. In this mode, the ITK-Lung GUI (see Sub-Aim 1c) will provide a user interface front-end to **available processing pipelines** running remotely. It will send data to the external resource over the network, monitor and control pipeline execution, and receive results when processing is complete. This remote pipeline execution mode will additionally support other highly computationally intensive tasks **as well as** other data processing tasks that may be added in the future. The external resource may be either a physical Linux cluster or a virtual one hosted on the Amazon Web Services (AWS) cloud. For AWS, we will use the MIT StarCluster software (<http://star.mit.edu/cluster>) to launch a virtual cluster directly from the ITK-Lung GUI on demand. We will take advantage of the GPU enabled AWS instances, **which would allow** the speed-ups described above to be combined with parallel execution across multiple hosts. The advantage of using AWS is

that a power user would not need to purchase and configure expensive hardware—they just register for an AWS account. While this would incur costs for computational time used, these costs would be a fraction of the cost of the required hardware. For instance, even with the most demanding datasets and parameters, it is hard to envision a processing task that would require more than an hour when distributed across 40 GPUs on AWS, the cost of which is currently \$26. Data transfer to AWS will incur negligible costs (\$0.01 per GB), particularly since data may be uploaded at reduced resolutions sufficient for many processing tasks.

**3(c.2.2) Sub-Aim 1b will provide two annotated multi-atlas libraries, one for CT and another for 1H MRI.** The corresponding group templates will also be provided along with the scripts to produce the results using ITK-Lung. As a complement to the open-source software provided in Sub-Aim 1a, we will generate atlas libraries for both CT and 1H MRI acquisitions. As indicated above, the availability of such atlases as anatomical priors is prerequisite to application of the current state-of-the-art in robust and accurate lung and lobe segmentation within their respective modalities. Additionally, the accompanying annotations provide an open-data platform for quantitatively assessing other lung and lobe segmentation algorithms. Both libraries will consist of  $n = 30$  different subjects to represent a range of lung size and shape. The CT atlas library will include lung, lobe, airway and vessel segmentations, whereas the 1H MRI atlas library will include left/right lung segmentations and lobar estimations [50]. Along with the annotated data we will provide the scripts and documentation to allow independent reproduction of the ITK-Lung results. Finally, optimal group templates [22] for the two atlas libraries will be generated and made openly available to be utilized as common coordinate frameworks to support voxelwise analyses.

**3(c.2.3) Sub-Aim 1c will develop a graphical user interface (GUI) for running ITK-Lung on user data and evaluating processed results.** ANTs will be the workhorse toolkit for the registration development effort in Aim 1, and the creation of a user-friendly GUI enabling interactive access for the first time to ANTs functionality will be a critical innovation toward a comprehensive registration solution for multi-modality imaging studies of the lung. The existence of the GUI will not only open ANTs to users without programming experience—which is expected to greatly expand its already considerable user base and in turn further increase its impact on the field—but will also significantly enhance the power of ANTs by allowing human/expert input to interactively tune parameters and intelligently initialize as well as steer the registration toward the solution that best satisfies both user and algorithmic constraints. Equally important, the GUI will permit qualitative and quantitative assessment of the results produced by ITK-Lung as well as potentially other software, another much needed capability not currently available to the general community. Taking these considerations into account, we propose to base the GUI front-end to ITK-Lung on the ITK-SNAP multi-platform, open-source tool for interactive user-guided medical image segmentation and data visualization [86], the development of which is led by project investigator Paul Yushkevich. ITK-SNAP provides an effective combination of semi-automatic segmentation functionality based on active contours [87] and manual delineation functionality, put together into a compact and easy-to-learn GUI, that perfectly complements the automated segmentation functionality proposed for development in this project. ITK-SNAP design 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 [86] has been cited over 1400 times (Google Scholar) in the context of various biomedical domains. ITK-SNAP will also be used in this project for manual labeling of the proposed lung 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.

Several features will be added to ITK-SNAP to enhance visualization and quantitation for the registration and segmentation results of the lung-specific algorithms developed in the project. Users will be able to edit and annotate these segmentations, modify registration transforms, and extract quantities both globally and regionally. Transforms will be modifiable via manual annotations (clicking corresponding landmarks, tracing curves, and/or painting regions) or by directly modifying transform parameters. Quantitative parameters, such as volumes and strain tensors, will be available through the ITK-SNAP interface. Finally, existing ITK-SNAP functionality for segmentation visualization will be expanded to support evaluation of registration quality, including a dashboard of performance metrics, linked cursors identifying corresponding positions in multi-window configurations, and fused data displays with adjustable blending. These proposed enhancements to the software will be extremely useful to the general imaging research community and not just those investigators targeted in this project. Thus, the impact of this work will be both immediate and broad on pulmonary-driven science and research.

**3(c.2.4) 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; and 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 [11, 89]. A similar infrastructure will be developed for the software resources proposed in Aim 1.

### **3(c.3) 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 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. Two evaluation groups will serve as primary and secondary beta testers, respectively: institutional and external collaborators. For the former, the development team will be embedded in the labs of project co-investigators, providing training to lab personnel and assisting with the creation of customized analysis pipelines. These experiences will be used to develop tutorial materials and processing examples that our external collaborators will independently test by processing their own data in-house with beta versions of the proposed software and data resources. Similarly, the dissemination and user support mechanisms outlined in the Resource Sharing Plan will be refined by employing these as much as possible to communicate and interact with the external collaborator group.

#### **Institutional collaborators**

**3(c.3.1) Novel imaging biomarkers for Chronic Obstructive Pulmonary Disease (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 [90–92]. This project plans to establish connectivity between these advanced HXe MRI imaging signatures and important clinical outcomes of COPD to advance HXe MRI as a novel clinical diagnostic tool. 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. HXe MRI has potential to detect pathologic changes present in COPD patients with high sensitivity and specificity previously unattainable by the 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 thus provide new insights into the 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 ventilation-based segmentation functionality in ITK-Lung [38]. In order to determine lobar values of HXe MRI, this study will utilize the recently proposed lobar estimation algorithm [50] that will be available for both proton MRI and CT.

**3(c.3.2) 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 [93]. Furthermore, improvements in image processing and signal intensity analysis have made possible accurate measurements of lung volume compartments [38]. 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 [94] or hand counts of visual defects were used to estimate the ventilation defect volume [95]. 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 in this project. For example, our ventilation-based segmentation method is already being used to determine volumetric compartments based on lung function. Additional “cleaning” necessary for these data include denoising techniques [51] implemented and made available in ANTs. Lobe estimation will be possible by refining the techniques originally described in [50].

**3(c.3.3) Characterization of COPDGene cohort by hyperpolarized gas (HP) MRI.** Co-investigator **Rahim Rizi** is leading a study of lung function and structure in 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, PAO<sub>2</sub>), 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. They 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 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: a) to develop imaging markers that better identify early COPD; b) to develop tests that predict health deterioration due to COPD; c) to determine if specific patterns of disease progression are associated with genetic markers identified in the larger COPDGene study; and d) 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 (PAO<sub>2</sub>), 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-based 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)

**3(c.3.4) 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 FEV<sub>1</sub>) 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 more advanced, fully 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 [96, 97] 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 **that** would capture not only attenuation maps but also regional deformation and texture based features. In combination, this would 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.

**3(c.3.5) Novel PET/CT biomarkers for early prediction of treatment response and survival in patients with non small cell lung cancer (NSCLC).** PET and CT have traditionally played important roles in diagnosis, staging, and predicting treatment response in NSCLC [98–100]. Although many studies have demonstrated diagnostic and prognostic value of tumor metabolic burden and morphological information derived from PET/CT imaging measures [100, 101], current ability to predict treatment response and survival following radiation therapy in NSCLC is far from satisfactory [102]. The poor performance of existing methods may be due to a number of reasons: first, most studies have been limited to primary tumor lesions and ignored the information available in other lesions/regions [103]; second, many investigations have focused on global image measures of tumors, such as those derived from standardized uptake value (SUV) of PET images and tumor morphological information, which may not be sufficient for capturing subtleties of tumor characteristics and tumor heterogeneity [104, 105]; and finally, group-level statistical analysis strategies are typically adopted to evaluate imaging markers, which may not be effective for personalized prediction [106].

To improve prediction of radiation therapy treatment response and survival in patients with NSCLC based on PET/CT imaging data, co-investigator **David Mankoff** and collaborators are developing methods to adaptively extract image features from the data that are then input into a multi-task learning framework constructed to jointly model (and leverage potential statistical correlations between) the problems of predicting treatment response and survival. The proposed software tools will fulfill essential pre-processing needs of the study: PET/CT data will be co-registered and a wealth of image features calculated using ITK-Lung.

### **External collaborators**

**3(c.3.6) Comparison of automated multi-modality registration methodologies to manual registration for assessing 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.

**3(c.3.7) Validation of voxel-based ventilation CT.** Our collaborator **Jim Wild**, **University of Sheffield**, has been active in the field of methods development for quantitative pulmonary imaging and its clinical translation for more than a decade. Relevant to this project, his group requires advanced registration capabilities to validate a novel CT technique for obtaining high-resolution images of pulmonary ventilation. In addition, there is need within his research for multi-modality registration of pulmonary CT and MRI images as well as segmentation of key lung structures as part of standard processing workflows.

**3(c.3.8) 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.

**3(c.3.9) 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.

**3(c.3.10) 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 in an open and consistent manner 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.

**3(c.3.11) 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.

**3(c.3.12) 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.

**3(c.3.13) Computational imaging biomarkers for diverse thoracic malignancies.** Our collaborator **Yoshiharu Ohno, Kobe University**, leads a comprehensive program of multi-modality imaging (CT, MRI, PET, molecular imaging) research on lung cancer, COPD, ILD, and pulmonary infectious diseases. His myriad image analysis needs include quantitative characterization of: lung parenchyma and airway changes; regional perfusion, ventilation, and metabolism from whole-lung perfusion and multi-modality metabolic imaging studies; ultra-short TE MRI data; and regional and global kinematics.

More details about the research, data, and advances enabled by the proposed software tools for each of the extramural partner 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 for the software.*

**3(c.3.14) 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 in recognition 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.4) 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 software development and engineering problems, we are highly confident in a successful outcome.

#### **3(c.5) 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 ITK-SNAP-based GUI implementation; Year 4 focused on releasing a fully functional system; and Year 5 focused on incremental improvements based on Aim 2 studies. Data collection and annotation (lung and lobes) for the multi-atlas libraries will take place in Years 1-2, followed by segmentations (vessels and airways) and template building in Year 3. **Aim 2:** A preliminary version of the software will be deployed at evaluation sites toward the end of Year 2 (**with quarterly software updates thereafter**), and testing will run through Year 4. Documentation and dissemination efforts will take place throughout the course of the project.

## References

1. Wang, Y.-X. and Deng, M. “**Medical Imaging in New Drug Clinical Development**” *J Thorac Dis* 2, no. 4 (2010): 245–52. doi:[10.3978/j.issn.2072-1439.2010.11.10](https://doi.org/10.3978/j.issn.2072-1439.2010.11.10)
2. Zhao, B., Tan, Y., Bell, D. J., Marley, S. E., Guo, P., Mann, H., Scott, M. L. J., Schwartz, L. H., and Ghiorghiu, D. C. “**Exploring Intra- and Inter-Reader Variability in Uni-Dimensional, Bi-Dimensional, and Volumetric Measurements of Solid Tumors on CT Scans Reconstructed at Different Slice Intervals**” *Eur J Radiol* 82, no. 6 (2013): 959–68. doi:[10.1016/j.ejrad.2013.02.018](https://doi.org/10.1016/j.ejrad.2013.02.018)
3. McErlean, A., Panicek, D. M., Zabor, E. C., Moskowitz, C. S., Bitar, R., Motzer, R. J., Hricak, H., and Ginsberg, M. S. “**Intra- and Interobserver Variability in CT Measurements in Oncology**” *Radiology* 269, no. 2 (2013): 451–9. doi:[10.1148/radiol.13122665](https://doi.org/10.1148/radiol.13122665)
4. Fischl, B. “**FreeSurfer**” *Neuroimage* 62, no. 2 (2012): 774–81. doi:[10.1016/j.neuroimage.2012.01.021](https://doi.org/10.1016/j.neuroimage.2012.01.021)
5. Jenkinson, M., Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W., and Smith, S. M. “**FSL**” *Neuroimage* 62, no. 2 (2012): 782–90. doi:[10.1016/j.neuroimage.2011.09.015](https://doi.org/10.1016/j.neuroimage.2011.09.015)
6. Cox, R. W. “**AFNI: What a Long Strange Trip It’s Been**” *Neuroimage* 62, no. 2 (2012): 743–7. doi:[10.1016/j.neuroimage.2011.08.030](https://doi.org/10.1016/j.neuroimage.2011.08.030)
7. Ashburner, J. “**SPM: A History**” *Neuroimage* 62, no. 2 (2012): 791–800. doi:[10.1016/j.neuroimage.2011.10.025](https://doi.org/10.1016/j.neuroimage.2011.10.025)
8. Hoffman, E. A., Lynch, D. A., Barr, R. G., Beek, E. J. R. van, Parraga, G., and IWPFI Investigators. “**Pulmonary CT and MRI Phenotypes That Help Explain Chronic Pulmonary Obstruction Disease Pathophysiology and Outcomes**” *J Magn Reson Imaging* (2015): doi:[10.1002/jmri.25010](https://doi.org/10.1002/jmri.25010)
9. Yunwen, Y. and Kishida, K. “**Toward an Understanding of the Motivation of Open Source Software Developers**” *Software engineering, 2003. proceedings. 25th international conference on* (2003): 419–429. doi:[10.1109/ICSE.2003.1201220](https://doi.org/10.1109/ICSE.2003.1201220)
10. (2008): Available at <http://fsmsh.com/2845>
11. Available at <http://picsl.upenn.edu/software/ants/>
12. Tustison, N. J. and Avants, B. B. “**Explicit B-Spline Regularization in Diffeomorphic Image Registration**” *Front Neuroinform* 7, (2013): 39. doi:[10.3389/fninf.2013.00039](https://doi.org/10.3389/fninf.2013.00039)
13. Tustison, N. J., Cook, P. A., Klein, A., Song, G., Das, S. R., Duda, J. T., Kandel, B. M., Strien, N. van, Stone, J. R., Gee, J. C., and Avants, B. B. “**Large-Scale Evaluation of ANTs and FreeSurfer Cortical Thickness Measurements**” *Neuroimage* 99, (2014): 166–79. doi:[10.1016/j.neuroimage.2014.05.044](https://doi.org/10.1016/j.neuroimage.2014.05.044)
14. Bajcsy, R. and Broit, C. “**Matching of Deformed Images**” *Sixth international conference on pattern recognition (ICPR’82)* (1982): 351–353.
15. Bajcsy, R. and Kovacic, S. “**Multiresolution Elastic Matching**” *Computer Vision, Graphics, and Image Processing* 46, no. 1 (1989): 1–21. doi:[10.1016/S0734-189X\(89\)80014-3](https://doi.org/10.1016/S0734-189X(89)80014-3), Available at [http://dx.doi.org/10.1016/S0734-189X\(89\)80014-3](http://dx.doi.org/10.1016/S0734-189X(89)80014-3)
16. Gee, J. C., Reivich, M., and Bajcsy, R. “**Elastically Deforming 3D Atlas to Match Anatomical Brain Images**” *J Comput Assist Tomogr* 17, no. 2 (): 225–36.
17. Murphy, K., Ginneken, B. van, Reinhardt, J. M., Kabus, S., Ding, K., Deng, X., Cao, K., Du, K., Christensen, G. E., Garcia, V., Vercauteren, T., Ayache, N., Commowick, O., Malandain, G., Glocker, B., Paragios, N., Navab, N., Gorbunova, V., Sporrings, J., Bruijne, M. de, Han, X., Heinrich, M. P., Schnabel, J. A., Jenkinson, M., Lorenz, C., Modat, M., McClelland, J. R., Ourselin, S., Muenzing, S. E. A., Viergever, M. A., De Nigris, D., Collins, D. L., Arbel, T., Peroni, M., Li, R., Sharp, G. C., Schmidt-Richberg, A., Ehrhardt, J., Werner, R., Smeets, D., Loeckx, D., Song, G., Tustison, N., Avants, B., Gee, J. C., Staring, M., Klein, S., Stoel, B. C., Urschler, M., Werlberger, M., Vandemeulebroucke, J., Rit, S., Sarrut, D., and Pluim, J. P. W. “**Evaluation of Registration Methods on Thoracic CT: The EMPIRE10 Challenge**” *IEEE Trans Med Imaging* 30, no. 11 (2011): 1901–20. doi:[10.1109/TMI.2011.2158349](https://doi.org/10.1109/TMI.2011.2158349)
18. Klein, A., Andersson, J., Ardekani, B. A., Ashburner, J., Avants, B., Chiang, M.-C., Christensen, G. E., Collins, D. L., Gee, J., Hellier, P., Song, J. H., Jenkinson, M., Lepage, C., Rueckert, D., Thompson, P., Vercauteren, T., Woods, R. P., Mann, J. J., and Parsey, R. V. “**Evaluation of 14 Nonlinear Deformation Algorithms Applied to Human Brain MRI Registration**” *Neuroimage* 46, no. 3 (2009): 786–802. doi:[10.1016/j.neuroimage.2008.12.037](https://doi.org/10.1016/j.neuroimage.2008.12.037)
19. Tustison, N. J., Yang, Y., and Salerno, M. “**Advanced Normalization Tools for Cardiac Motion Correction**” *Statistical atlases and computational models of the heart - imaging and modelling challenges* 8896, (2015): 3–12. doi:[10.1007/978-3-319-14678-2\\_1](https://doi.org/10.1007/978-3-319-14678-2_1), Available at [http://dx.doi.org/10.1007/978-3-319-14678-2\\_1](http://dx.doi.org/10.1007/978-3-319-14678-2_1)
20. Avants, B. B., Epstein, C. L., Grossman, M., and Gee, J. C. “**Symmetric Diffeomorphic Image Registration with Cross-Correlation: Evaluating Automated Labeling of Elderly and Neurodegenerative Brain**” *Med Image Anal* 12, no. 1 (2008): 26–41. doi:[10.1016/j.media.2007.06.004](https://doi.org/10.1016/j.media.2007.06.004)
21. Tustison, N. J., Song, G., Gee, James C, and Avants, B. B. “**Two Greedy SyN Variants for Pulmonary Image Regis-**

- tration” Evaluation of methods for pulmonary image registration (EMPIRE10) (2012):**
22. Avants, B. B., Yushkevich, P., Pluta, J., Minkoff, D., Korczykowski, M., Detre, J., and Gee, J. C. “**The Optimal Template Effect in Hippocampus Studies of Diseased Populations**” *Neuroimage* 49, no. 3 (2010): 2457–66. doi:[10.1016/j.neuroimage.2009.09.062](https://doi.org/10.1016/j.neuroimage.2009.09.062)
23. Tustison, N. J., Shrinidhi, K. L., Wintermark, M., Durst, C. R., Kandel, B. M., Gee, J. C., Grossman, M. C., and Avants, B. B. “**Optimal Symmetric Multimodal Templates and Concatenated Random Forests for Supervised Brain Tumor Segmentation (Simplified) with ANTsR**” *Neuroinformatics* (2014): doi:[10.1007/s12021-014-9245-2](https://doi.org/10.1007/s12021-014-9245-2)
24. Avants, B. B., Duda, J. T., Kilroy, E., Krasileva, K., Jann, K., Kandel, B. T., Tustison, N. J., Yan, L., Jog, M., Smith, R., Wang, Y., Dapretto, M., and Wang, D. J. J. “**The Pediatric Template of Brain Perfusion**” *Sci Data* 2, (2015): 150003. doi:[10.1038/sdata.2015.3](https://doi.org/10.1038/sdata.2015.3)
25. Datta, R., Lee, J., Duda, J., Avants, B. B., Vite, C. H., Tseng, B., Gee, J. C., Aguirre, G. D., and Aguirre, G. K. “**A Digital Atlas of the Dog Brain**” *PLoS One* 7, no. 12 (2012): e52140. doi:[10.1371/journal.pone.0052140](https://doi.org/10.1371/journal.pone.0052140)
26. McMillan, C. T., Avants, B. B., Cook, P., Ungar, L., Trojanowski, J. Q., and Grossman, M. “**The Power of Neuroimaging Biomarkers for Screening Frontotemporal Dementia**” *Hum Brain Mapp* 35, no. 9 (2014): 4827–40. doi:[10.1002/hbm.22515](https://doi.org/10.1002/hbm.22515)
27. Cook, P. A., McMillan, C. T., Avants, B. B., Peelle, J. E., Gee, J. C., and Grossman, M. “**Relating Brain Anatomy and Cognitive Ability Using a Multivariate Multimodal Framework**” *Neuroimage* 99, (2014): 477–86. doi:[10.1016/j.neuroimage.2014.09.040](https://doi.org/10.1016/j.neuroimage.2014.09.040)
28. Tustison, N. J., Avants, B. B., Cook, P. A., Kim, J., Whyte, J., Gee, J. C., and Stone, J. R. “**Logical Circularity in Voxel-Based Analysis: Normalization Strategy May Induce Statistical Bias**” *Hum Brain Mapp* 35, no. 3 (2014): 745–59. doi:[10.1002/hbm.22211](https://doi.org/10.1002/hbm.22211)
29. Tustison, N. J., Contrella, B., Altes, T. A., Avants, B. B., Lange, E. E. de, and Mugler, J. P. “**Longitudinal Assessment of Treatment Effects on Pulmonary Ventilation Using <sup>1</sup>H/<sup>3</sup>He MRI Multivariate Templates**” *Proc. SPIE 8672, medical imaging 2013: Biomedical applications in molecular, structural, and functional imaging* (2013):
30. Vannier, M. W., Butterfield, R. L., Jordan, D., Murphy, W. A., Levitt, R. G., and Gado, M. “**Multispectral Analysis of Magnetic Resonance Images**” *Radiology* 154, no. 1 (1985): 221–4. doi:[10.1148/radiology.154.1.3964938](https://doi.org/10.1148/radiology.154.1.3964938)
31. Dempster, A., Laird, N., and Rubin, D. “**Maximum Likelihood Estimation from Incomplete Data Using the EM Algorithms**” *Journal of the Royal Statistical Society* 39, (1977): 1–38.
32. Cline, H. E., Lorensen, W. E., Kikinis, R., and Jolesz, F. “**Three-Dimensional Segmentation of MR Images of the Head Using Probability and Connectivity**” *J Comput Assist Tomogr* 14, no. 6 (): 1037–45.
33. Kikinis, R., Shenton, M. E., Gerig, G., Martin, J., Anderson, M., Metcalf, D., Guttmann, C. R., McCarley, R. W., Lorensen, W., and Cline, H. “**Routine Quantitative Analysis of Brain and Cerebrospinal Fluid Spaces with MR Imaging**” *J Magn Reson Imaging* 2, no. 6 (): 619–29.
34. Geman, S. and Geman, D. “**Stochastic Relaxation, Gibbs Distributions, and the Bayesian Restoration of Images**” *IEEE Trans Pattern Anal Mach Intell* 6, no. 6 (1984): 721–41.
35. Held, K., Rota Kops, E., Krause, B. J., Wells, W. M., 3rd, Kikinis, R., and Müller-Gärtner, H. W. “**Markov Random Field Segmentation of Brain MR Images**” *IEEE Trans Med Imaging* 16, no. 6 (1997): 878–86. doi:[10.1109/42.650883](https://doi.org/10.1109/42.650883)
36. Van Leemput, K., Maes, F., Vandermeulen, D., and Suetens, P. “**Automated Model-Based Tissue Classification of MR Images of the Brain**” *IEEE Trans Med Imaging* 18, no. 10 (1999): 897–908. doi:[10.1109/42.811270](https://doi.org/10.1109/42.811270)
37. Ashburner, J. and Friston, K. J. “**Unified Segmentation**” *Neuroimage* 26, no. 3 (2005): 839–51. doi:[10.1016/j.neuroimage.2005.01.030](https://doi.org/10.1016/j.neuroimage.2005.01.030)
38. Tustison, N. J., Avants, B. B., Flors, L., Altes, T. A., Lange, E. E. de, Mugler, J. P., 3rd, and Gee, J. C. “**Ventilation-Based Segmentation of the Lungs Using Hyperpolarized (<sup>3</sup>)He MRI**” *J Magn Reson Imaging* 34, no. 4 (2011): 831–41. doi:[10.1002/jmri.22738](https://doi.org/10.1002/jmri.22738)
39. Avants, B. B., Tustison, N. J., Wu, J., Cook, P. A., and Gee, J. C. “**An Open Source Multivariate Framework for n-Tissue Segmentation with Evaluation on Public Data**” *Neuroinformatics* 9, no. 4 (2011): 381–400. doi:[10.1007/s12021-011-9109-y](https://doi.org/10.1007/s12021-011-9109-y)
40. Altes, T., Johnson, M., III, J. M., Miller, G. W., Flors, L., Mata, J., Salinas, C., Tustison, N., Lee, P.-S., Song, T., Froh, K. Y. D., and Botfield, M. “**The Effect of Ivacaftor, an Investigational CFTR Potentiator, on Hyperpolarized Noble Gas Magnetic Resonance Imaging in Subjects with Cystic Fibrosis Who Have the G551D-CFTR Mutation**” *PATHOGENESIS AND CLINICAL ISSUES IN CYSTIC FIBROSIS* B35, (2012): A2814–A2814.
41. Teague, W. G., Tustison, N. J., and Altes, T. A. “**Ventilation Heterogeneity in Asthma**” *J Asthma* 51, no. 7 (2014): 677–84. doi:[10.3109/02770903.2014.914535](https://doi.org/10.3109/02770903.2014.914535)
42. Kirby, M., Pike, D., Coxson, H. O., McCormack, D. G., and Parraga, G. “**Hyperpolarized (<sup>3</sup>)He Ventilation Defects Used to Predict Pulmonary Exacerbations in Mild to Moderate Chronic Obstructive Pulmonary Disease**” *Radiology*

- ology 273, no. 3 (2014): 887–96. doi:[10.1148/radiol.14140161](https://doi.org/10.1148/radiol.14140161)
43. Sled, J. G., Zijdenbos, A. P., and Evans, A. C. “**A Nonparametric Method for Automatic Correction of Intensity Nonuniformity in MRI Data**” *IEEE Trans Med Imaging* 17, no. 1 (1998): 87–97. doi:[10.1109/42.668698](https://doi.org/10.1109/42.668698)
44. Boyes, R. G., Gunter, J. L., Frost, C., Janke, A. L., Yeatman, T., Hill, D. L. G., Bernstein, M. A., Thompson, P. M., Weiner, M. W., Schuff, N., Alexander, G. E., Killiany, R. J., DeCarli, C., Jack, C. R., Fox, N. C., and ADNI Study. “**Intensity Non-Uniformity Correction Using N3 on 3-T Scanners with Multichannel Phased Array Coils**” *Neuroimage* 39, no. 4 (2008): 1752–62. doi:[10.1016/j.neuroimage.2007.10.026](https://doi.org/10.1016/j.neuroimage.2007.10.026)
45. Tustison, N. J., Awate, S. P., Cai, J., Altes, T. A., Miller, G. W., Lange, E. E. de, Mugler, J. P., 3rd, and Gee, J. C. “**Pulmonary Kinematics from Tagged Hyperpolarized Helium-3 MRI**” *J Magn Reson Imaging* 31, no. 5 (2010): 1236–41. doi:[10.1002/jmri.22137](https://doi.org/10.1002/jmri.22137)
46. Wang, H. and Yushkevich, P. A. “**Multi-Atlas Segmentation with Joint Label Fusion and Corrective Learning—an Open Source Implementation**” *Front Neuroinform* 7, (2013): 27. doi:[10.3389/fninf.2013.00027](https://doi.org/10.3389/fninf.2013.00027)
47. Wang, H., Suh, J. W., Das, S. R., Pluta, J. B., Craige, C., and Yushkevich, P. A. “**Multi-Atlas Segmentation with Joint Label Fusion**” *IEEE Trans Pattern Anal Mach Intell* 35, no. 3 (2013): 611–23. doi:[10.1109/TPAMI.2012.143](https://doi.org/10.1109/TPAMI.2012.143)
48. Yushkevich, P. A., Wang, H., Pluta, J., Das, S. R., Craige, C., Avants, B. B., Weiner, M. W., and Mueller, S. “**Nearly Automatic Segmentation of Hippocampal Subfields in in Vivo Focal T2-Weighted MRI**” *Neuroimage* 53, no. 4 (2010): 1208–24. doi:[10.1016/j.neuroimage.2010.06.040](https://doi.org/10.1016/j.neuroimage.2010.06.040)
49. Available at [https://masi.vuse.vanderbilt.edu/workshop2013/index.php/Main\\_Page](https://masi.vuse.vanderbilt.edu/workshop2013/index.php/Main_Page)
50. Tustison, N. J., Qing, K., Wang, C., Altes, T. A., and Mugler, J. P., 3rd. “**Atlas-Based Estimation of Lung and Lobar Anatomy in Proton MRI**” *Magn Reson Med* 76, no. 1 (2016): 315–20. doi:[10.1002/mrm.25824](https://doi.org/10.1002/mrm.25824)
51. Manjón, J. V., Coupé, P., Martí-Bonmatí, L., Collins, D. L., and Robles, M. “**Adaptive Non-Local Means Denoising of MR Images with Spatially Varying Noise Levels**” *J Magn Reson Imaging* 31, no. 1 (2010): 192–203. doi:[10.1002/jmri.22003](https://doi.org/10.1002/jmri.22003)
52. Wang, H., Suh, J. W., Das, S. R., Pluta, J., Craige, C., and Yushkevich, P. A. “**Multi-Atlas Segmentation with Joint Label Fusion**” *IEEE Trans Pattern Anal Mach Intell* (2012): doi:[10.1109/TPAMI.2012.143](https://doi.org/10.1109/TPAMI.2012.143)
53. “**MICCAI 2012 Workshop on Multi-Atlas Labeling**” (2012):
54. Asman, A., Akhondi-Asl, A., Wang, H., Tustison, N., Avants, B., Warfield, S. K., and Landman, B. “**MICCAI 2013 Segmentation Algorithms, Theory and Applications (SATA) Challenge Results Summary**,” *MICCAI 2013 challenge workshop on segmentation: Algorithms, theory and applications*. (2013):
55. Avants, B. B., Tustison, N. J., Song, G., Cook, P. A., Klein, A., and Gee, J. C. “**A Reproducible Evaluation of ANTs Similarity Metric Performance in Brain Image Registration**” *Neuroimage* 54, no. 3 (2011): 2033–44. doi:[10.1016/j.neuroimage.2010.09.025](https://doi.org/10.1016/j.neuroimage.2010.09.025)
56. Avants, B. B., Tustison, N. J., Stauffer, M., Song, G., Wu, B., and Gee, J. C. “**The Insight ToolKit Image Registration Framework**” *Front Neuroinform* 8, (2014): 44. doi:[10.3389/fninf.2014.00044](https://doi.org/10.3389/fninf.2014.00044)
57. Avants, B. B., Klein, A., Tustison, N. J., Woo, J., and Gee, J. C. “**Evaluation of Open-Access, Automated Brain Extraction Methods on Multi-Site Multi-Disorder Data**” *16th annual meeting for the organization of human brain mapping* (2010):
58. Das, S. R., Avants, B. B., Grossman, M., and Gee, J. C. “**Registration Based Cortical Thickness Measurement**” *Neuroimage* 45, no. 3 (2009): 867–79. doi:[10.1016/j.neuroimage.2008.12.016](https://doi.org/10.1016/j.neuroimage.2008.12.016)
59. Sluimer, I., Schilham, A., Prokop, M., and Ginneken, B. van. “**Computer Analysis of Computed Tomography Scans of the Lung: A Survey**” *IEEE Trans Med Imaging* 25, no. 4 (2006): 385–405. doi:[10.1109/TMI.2005.862753](https://doi.org/10.1109/TMI.2005.862753)
60. Tustison, N. J., Johnson, H. J., Rohlfing, T., Klein, A., Ghosh, S. S., Ibanez, L., and Avants, B. B. “**Instrumentation Bias in the Use and Evaluation of Scientific Software: Recommendations for Reproducible Practices in the Computational Sciences**” *Front Neurosci* 7, (2013): 162. doi:[10.3389/fnins.2013.00162](https://doi.org/10.3389/fnins.2013.00162)
61. Rikxoort, E. M. van and Ginneken, B. van. “**Automated Segmentation of Pulmonary Structures in Thoracic Computed Tomography Scans: A Review**” *Phys Med Biol* 58, no. 17 (2013): R187–220. doi:[10.1088/0031-9155/58/17/R187](https://doi.org/10.1088/0031-9155/58/17/R187)
62. Doel, T., Gavaghan, D. J., and Grau, V. “**Review of Automatic Pulmonary Lobe Segmentation Methods from CT**” *Comput Med Imaging Graph* 40, (2015): 13–29. doi:[10.1016/j.compmedimag.2014.10.008](https://doi.org/10.1016/j.compmedimag.2014.10.008)
63. Warfield, S. K., Zou, K. H., and Wells, W. M. “**Simultaneous Truth and Performance Level Estimation (STAPLE): An Algorithm for the Validation of Image Segmentation**” *IEEE Trans Med Imaging* 23, no. 7 (2004): 903–21. doi:[10.1109/TMI.2004.828354](https://doi.org/10.1109/TMI.2004.828354)
64. Coxson, H. O., Rogers, R. M., Whittall, K. P., D'yachkova, Y., Paré, P. D., Sciurba, F. C., and Hogg, J. C. “**A Quantification of the Lung Surface Area in Emphysema Using Computed Tomography**” *Am J Respir Crit Care Med* 159, no. 3 (1999):

851–6. doi:[10.1164/ajrccm.159.3.9805067](https://doi.org/10.1164/ajrccm.159.3.9805067)

65. Perez, A., 4th, Coxson, H. O., Hogg, J. C., Gibson, K., Thompson, P. F., and Rogers, R. M. “**Use of CT Morphometry to Detect Changes in Lung Weight and Gas Volume**” *Chest* 128, no. 4 (2005): 2471–7. doi:[10.1378/chest.128.4.2471](https://doi.org/10.1378/chest.128.4.2471)
66. Coxson, H. O. and Rogers, R. M. “**New Concepts in the Radiological Assessment of COPD**” *Semin Respir Crit Care Med* 26, no. 2 (2005): 211–20. doi:[10.1055/s-2005-869540](https://doi.org/10.1055/s-2005-869540)
67. Stolk, J., Putter, H., Bakker, E. M., Shaker, S. B., Parr, D. G., Piitulainen, E., Russi, E. W., Grebski, E., Dirksen, A., Stockley, R. A., Reiber, J. H. C., and Stoel, B. C. “**Progression Parameters for Emphysema: A Clinical Investigation**” *Respir Med* 101, no. 9 (2007): 1924–30. doi:[10.1016/j.rmed.2007.04.016](https://doi.org/10.1016/j.rmed.2007.04.016)
68. Uppaluri, R., Hoffman, E. A., Sonka, M., Hartley, P. G., Hunninghake, G. W., and McLennan, G. “**Computer Recognition of Regional Lung Disease Patterns**” *Am J Respir Crit Care Med* 160, no. 2 (1999): 648–54. doi:[10.1164/ajrccm.160.2.9804094](https://doi.org/10.1164/ajrccm.160.2.9804094)
69. Xu, Y., Sonka, M., McLennan, G., Guo, J., and Hoffman, E. A. “**MDCT-Based 3-D Texture Classification of Emphysema and Early Smoking Related Lung Pathologies**” *IEEE Trans Med Imaging* 25, no. 4 (2006): 464–75. doi:[10.1109/TMI.2006.870889](https://doi.org/10.1109/TMI.2006.870889)
70. Gevenois, P. A., De Vuyst, P., Sy, M., Scillia, P., Chaminade, L., Maertelaer, V. de, Zanen, J., and Yernault, J. C. “**Pulmonary Emphysema: Quantitative CT During Expiration**” *Radiology* 199, no. 3 (1996): 825–9. doi:[10.1148/radiology.199.3.8638012](https://doi.org/10.1148/radiology.199.3.8638012)
71. Hoffman, E. A., Simon, B. A., and McLennan, G. “**State of the Art. a Structural and Functional Assessment of the Lung via Multidetector-Row Computed Tomography: Phenotyping Chronic Obstructive Pulmonary Disease**” *Proc Am Thorac Soc* 3, no. 6 (2006): 519–32. doi:[10.1513/pats.200603-086MS](https://doi.org/10.1513/pats.200603-086MS)
72. Gee, J., Sundaram, T., Hasegawa, I., Uematsu, H., and Hatabu, H. “**Characterization of Regional Pulmonary Mechanics from Serial Magnetic Resonance Imaging Data**” *Acad Radiol* 10, no. 10 (2003): 1147–52.
73. Sundaram, T. A. and Gee, J. C. “**Towards a Model of Lung Biomechanics: Pulmonary Kinematics via Registration of Serial Lung Images**” *Med Image Anal* 9, no. 6 (2005): 524–37. doi:[10.1016/j.media.2005.04.002](https://doi.org/10.1016/j.media.2005.04.002)
74. Aykac, D., Hoffman, E. A., McLennan, G., and Reinhardt, J. M. “**Segmentation and Analysis of the Human Airway Tree from Three-Dimensional X-Ray CT Images**” *IEEE Trans Med Imaging* 22, no. 8 (2003): 940–50. doi:[10.1109/TMI.2003.815905](https://doi.org/10.1109/TMI.2003.815905)
75. Park, W., Hoffman, E. A., and Sonka, M. “**Segmentation of Intrathoracic Airway Trees: A Fuzzy Logic Approach**” *IEEE Trans Med Imaging* 17, no. 4 (1998): 489–97. doi:[10.1109/42.730394](https://doi.org/10.1109/42.730394)
76. Ederle, J. R., Heussel, C. P., Hast, J., Fischer, B., Van Beek, E. J. R., Ley, S., Thelen, M., and Kauczor, H. U. “**Evaluation of Changes in Central Airway Dimensions, Lung Area and Mean Lung Density at Paired Inspiratory/expiratory High-Resolution Computed Tomography**” *Eur Radiol* 13, no. 11 (2003): 2454–61. doi:[10.1007/s00330-003-1909-5](https://doi.org/10.1007/s00330-003-1909-5)
77. Lovinfosse, P., January, Z. L., Coucke, P., Jodogne, S., Bernard, C., Hatt, M., Visvikis, D., Jansen, N., Duysinx, B., and Hustinx, R. “**FDG PET/CT Texture Analysis for Predicting the Outcome of Lung Cancer Treated by Stereotactic Body Radiation Therapy**” *Eur J Nucl Med Mol Imaging* 43, no. 8 (2016): 1453–60. doi:[10.1007/s00259-016-3314-8](https://doi.org/10.1007/s00259-016-3314-8)
78. Lo, P., Ginneken, B. van, Reinhardt, J. M., Yavarna, T., Jong, P. A. de, Irving, B., Fetita, C., Ortner, M., Pinho, R., Sijbers, J., Feuerstein, M., Fabijańska, A., Bauer, C., Beichel, R., Mendoza, C. S., Wiemker, R., Lee, J., Reeves, A. P., Born, S., Weinheimer, O., Rikxoort, E. M. van, Tschirren, J., Mori, K., Odry, B., Naidich, D. P., Hartmann, I., Hoffman, E. A., Prokop, M., Pedersen, J. H., and Bruijne, M. de. “**Extraction of Airways from CT (EXACT'09)**” *IEEE Trans Med Imaging* 31, no. 11 (2012): 2093–107. doi:[10.1109/TMI.2012.2209674](https://doi.org/10.1109/TMI.2012.2209674)
79. Feuerstein, M., Kitasaka, T., and Mori, K. “**Adaptive Branch Tracing and Image Sharpening for Airway Tree Extraction in 3-d Chest CT**” *Proc. of second international workshop on pulmonary image analysis* (2009):
80. Lee, J. and Reeves, A. P. “**Segmentation of the Airway Tree from Chest CT Using Local Volume of Interest**” *Proc. of second international workshop on pulmonary image analysis* (2009):
81. Song, G., Tustison, N., and Gee, J. C. “**Airway Tree Segmentation by Removing Paths of Leakage**” *Proc. 3rd int. workshop pulmonary image analysis* (2010): 109–116.
82. Staring, M., Xiao, C., Shamounin, D. P., and Stoel, B. C. “**Pulmonary Vessel Segmentation Using Vessel Enhancement Filters**” *VESEL Segmentation in the Lung* (2012):
83. Ostergaard, L., Weisskoff, R. M., Chesler, D. A., Gyldensted, C., and Rosen, B. R. “**High Resolution Measurement of Cerebral Blood Flow Using Intravascular Tracer Bolus Passages. Part I: Mathematical Approach and Statistical Analysis**” *Magn Reson Med* 36, no. 5 (1996): 715–25.
84. Ohno, Y., Hatabu, H., Murase, K., Higashino, T., Kawamitsu, H., Watanabe, H., Takenaka, D., Fujii, M., and Sugimura, K. “**Quantitative Assessment of Regional Pulmonary Perfusion in the Entire Lung Using Three-Dimensional Ultrafast Dynamic Contrast-Enhanced Magnetic Resonance Imaging: Preliminary Experience in 40 Subjects**”

*J Magn Reson Imaging* 20, no. 3 (2004): 353–65. doi:[10.1002/jmri.20137](https://doi.org/10.1002/jmri.20137)

85. Hansch, A., Kohlmann, P., Hinneburg, U., Boettcher, J., Malich, A., Wolf, G., Laue, H., and Pfeil, A. “**Quantitative Evaluation of MR Perfusion Imaging Using Blood Pool Contrast Agent in Subjects Without Pulmonary Diseases and in Patients with Pulmonary Embolism**” *Eur Radiol* 22, no. 8 (2012): 1748–56. doi:[10.1007/s00330-012-2428-z](https://doi.org/10.1007/s00330-012-2428-z)
86. Yushkevich, P. A., Piven, J., Hazlett, H. C., Smith, R. G., Ho, S., Gee, J. C., and Gerig, G. “**User-Guided 3D Active Contour Segmentation of Anatomical Structures: Significantly Improved Efficiency and Reliability**” *Neuroimage* 31, no. 3 (2006): 1116–28. doi:[10.1016/j.neuroimage.2006.01.015](https://doi.org/10.1016/j.neuroimage.2006.01.015)
87. Caselles, V., Kimmel, R., and Sapiro, G. “**Geodesic Active Contours**” *Int J Comput Vision* 22, (1997): 61–79.
88. Zhu, S. and Yuille, A. “**Region Competition: Unifying Snakes, Region Growing, and Bayes/MDL for Multiband Image Segmentation**” *IEEE Trans Pattern Anal Mach Intell* 18, no. 9 (1996): 884–900.
89. Available at <http://www.itksnap.org>
90. Dregely, I., Mugler, J. P., 3rd, Ruset, I. C., Altes, T. A., Mata, J. F., Miller, G. W., Ketel, J., Ketel, S., Distelbrink, J., Hersman, F. W., and Ruppert, K. “**Hyperpolarized Xenon-129 Gas-Exchange Imaging of Lung Microstructure: First Case Studies in Subjects with Obstructive Lung Disease**” *J Magn Reson Imaging* 33, no. 5 (2011): 1052–62. doi:[10.1002/jmri.22533](https://doi.org/10.1002/jmri.22533)
91. Mugler, J. P., 3rd, Altes, T. A., Ruset, I. C., Dregely, I. M., Mata, J. F., Miller, G. W., Ketel, S., Ketel, J., Hersman, F. W., and Ruppert, K. “**Simultaneous Magnetic Resonance Imaging of Ventilation Distribution and Gas Uptake in the Human Lung Using Hyperpolarized Xenon-129**” *Proc Natl Acad Sci U S A* 107, no. 50 (2010): 21707–12. doi:[10.1073/pnas.1011912107](https://doi.org/10.1073/pnas.1011912107)
92. Qing, K., Mugler, J. P., 3rd, Altes, T. A., Jiang, Y., Mata, J. F., Miller, G. W., Ruset, I. C., Hersman, F. W., and Ruppert, K. “**Assessment of Lung Function in Asthma and COPD Using Hyperpolarized 129Xe Chemical Shift Saturation Recovery Spectroscopy and Dissolved-Phase MRI**” *NMR Biomed* 27, no. 12 (2014): 1490–501. doi:[10.1002/nbm.3179](https://doi.org/10.1002/nbm.3179)
93. Altes, T. A., Mata, J., Lange, E. E. de, Brookeman, J. R., and Mugler, J. P., 3rd. “**Assessment of Lung Development Using Hyperpolarized Helium-3 Diffusion MR Imaging**” *J Magn Reson Imaging* 24, no. 6 (2006): 1277–83. doi:[10.1002/jmri.20723](https://doi.org/10.1002/jmri.20723)
94. Woodhouse, N., Wild, J. M., Paley, M. N. J., Fichele, S., Said, Z., Swift, A. J., and Beek, E. J. R. van. “**Combined Helium-3/proton Magnetic Resonance Imaging Measurement of Ventilated Lung Volumes in Smokers Compared to Never-Smokers**” *J Magn Reson Imaging* 21, no. 4 (2005): 365–9. doi:[10.1002/jmri.20290](https://doi.org/10.1002/jmri.20290)
95. Altes, T. A., Powers, P. L., Knight-Scott, J., Rakes, G., Platts-Mills, T. A., Lange, E. E. de, Alford, B. A., Mugler, J. P., 3rd, and Brookeman, J. R. “**Hyperpolarized 3He MR Lung Ventilation Imaging in Asthmatics: Preliminary Findings**” *J Magn Reson Imaging* 13, no. 3 (2001): 378–84.
96. Barbosa, E. M., Jr, Song, G., Tustison, N., Kreider, M., Gee, J. C., Gefter, W. B., and Torigian, D. A. “**Computational Analysis of Thoracic Multidetector Row HRCT for Segmentation and Quantification of Small Airway Air Trapping and Emphysema in Obstructive Pulmonary Disease**” *Acad Radiol* 18, no. 10 (2011): 1258–69. doi:[10.1016/j.acra.2011.06.004](https://doi.org/10.1016/j.acra.2011.06.004)
97. Song, G., Mortani Barbosa, E., Jr, Tustison, N., Gefter, W. B., Kreider, M., Gee, J. C., and Torigian, D. A. “**A Comparative Study of HRCT Image Metrics and PFT Values for Characterization of ILD and COPD**” *Acad Radiol* 19, no. 7 (2012): 857–64. doi:[10.1016/j.acra.2012.03.007](https://doi.org/10.1016/j.acra.2012.03.007)
98. Lardinois, D., Weder, W., Hany, T. F., Kamel, E. M., Korom, S., Seifert, B., Schulthess, G. K. von, and Steinert, H. C. “**Staging of Non-Small-Cell Lung Cancer with Integrated Positron-Emission Tomography and Computed Tomography**” *N Engl J Med* 348, no. 25 (2003): 2500–7. doi:[10.1056/NEJMoa022136](https://doi.org/10.1056/NEJMoa022136)
99. Lee, H. Y., Lee, H. J., Kim, Y. T., Kang, C. H., Jang, B. G., Chung, D. H., Goo, J. M., Park, C. M., Lee, C. H., and Kang, K. W. “**Value of Combined Interpretation of Computed Tomography Response and Positron Emission Tomography Response for Prediction of Prognosis After Neoadjuvant Chemotherapy in Non-Small Cell Lung Cancer**” *J Thorac Oncol* 5, no. 4 (2010): 497–503. doi:[10.1097/JTO.0b013e3181d2efe7](https://doi.org/10.1097/JTO.0b013e3181d2efe7)
100. Horne, Z. D., Clump, D. A., Vargo, J. A., Shah, S., Beriwal, S., Burton, S. A., Quinn, A. E., Schuchert, M. J., Landreneau, R. J., Christie, N. A., Luketich, J. D., and Heron, D. E. “**Pretreatment SUVmax Predicts Progression-Free Survival in Early-Stage Non-Small Cell Lung Cancer Treated with Stereotactic Body Radiation Therapy**” *Radiat Oncol* 9, (2014): 41. doi:[10.1186/1748-717X-9-41](https://doi.org/10.1186/1748-717X-9-41)
101. Kim, K., Kim, S.-J., Kim, I.-J., Kim, Y. S., Pak, K., and Kim, H. “**Prognostic Value of Volumetric Parameters Measured by F-18 FDG PET/CT in Surgically Resected Non-Small-Cell Lung Cancer**” *Nucl Med Commun* 33, no. 6 (2012): 613–20. doi:[10.1097/MNM.0b013e328351d4f5](https://doi.org/10.1097/MNM.0b013e328351d4f5)
102. Berman, A. T., Ellenberg, S. S., and Simone, C. B., 2nd. “**Predicting Survival in Non-Small-Cell Lung Cancer Using Positron Emission Tomography: Several Conclusions from Multiple Comparisons**” *J Clin Oncol* 32, no. 15 (2014):

1631–2. doi:[10.1200/JCO.2013.54.3074](https://doi.org/10.1200/JCO.2013.54.3074)

103. Ryu, J.-S. and Hyun, I. Y. “**Prognostic Impact of [18F]fluorodeoxyglucose Positron Emission Tomography Scanning in the Era of Molecular Oncology**” *J Clin Oncol* 32, no. 15 (2014): 1630. doi:[10.1200/JCO.2013.53.6300](https://doi.org/10.1200/JCO.2013.53.6300)
104. Chicklore, S., Goh, V., Siddique, M., Roy, A., Marsden, P. K., and Cook, G. J. R. “**Quantifying Tumour Heterogeneity in 18F-FDG PET/CT Imaging by Texture Analysis**” *Eur J Nucl Med Mol Imaging* 40, no. 1 (2013): 133–40. doi:[10.1007/s00259-012-2247-0](https://doi.org/10.1007/s00259-012-2247-0)
105. Depeursinge, A., Foncubierta-Rodriguez, A., Van De Ville, D., and Müller, H. “**Three-Dimensional Solid Texture Analysis in Biomedical Imaging: Review and Opportunities**” *Med Image Anal* 18, no. 1 (2014): 176–96. doi:[10.1016/j.media.2013.10.005](https://doi.org/10.1016/j.media.2013.10.005)
106. Henderson, R. and Keiding, N. “**Individual Survival Time Prediction Using Statistical Models**” *J Med Ethics* 31, no. 12 (2005): 703–6. doi:[10.1136/jme.2005.012427](https://doi.org/10.1136/jme.2005.012427)