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Title: Convolutional Neural Networks with Template-Based Data Augmentation for Functional Lung Image Quantification

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Abstract: Rationale and Objectives: We propose an automated segmentation pipeline based on deep learning for proton lung MRI segmentation and ventilation-based quantification which improves on our previously reported methodologies in terms of computational efficiency while demonstrating accuracy and robustness. The large data requirement for the proposed framework is made possible by a novel template-based data augmentation strategy. Supporting this work is the open-source ANTsRNet—a growing repository of well-known deep learning architectures first introduced here.

Materials and Methods: Deep convolutional neural network (CNN) models were constructed and trained using a custom multilabel Dice metric loss function and a novel template-based data augmentation strategy. Training (including template generation and data augmentation) employed 205 proton MR images and 73 functional lung MRI. Evaluation was performed using data sets of size 63 and 40 images, respectively.

Results: Accuracy for proton lung MRI segmentation (in terms of Dice overlap) was left lung: 0.87 ± 0.03 , right lung: 0.88 ± 0.02 , and whole lung: 0.88 ± 0.02 . Although less accurate than our previously reported joint label fusion (JLF) approach (left lung: 0.95 ± 0.02 , right lung: 0.96 ± 0.01 , whole lung: 0.96 ± 0.01), processing time is < 1 second per subject for the proposed approach versus ~30 minutes per subject using JLF. Accuracy for quantifying ventilation defects was determined based on a consensus labeling where average accuracy (Dice overlap of ventilation defect regions plus normal region) was 0.94 for the CNN method; 0.92 for our previously reported Atropos method; and 0.90, 0.92, and 0.94 for expert readers.

Conclusions: The proposed framework yields comparable results as previously reported automated segmentation techniques. CNNs drastically reduce processing time after offline model construction and demonstrate significant future potential for facilitating quantitative analysis of functional lung MRI.

Key Words: Advanced Normalization Tools, ANTsRNet, hyperpolarized gas imaging, neural networks, U-net

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May 20, 2018

Dear Professor N. Reed Dunnick, MD,

On behalf of all the co-authors, it is with great pleasure that I submit our manuscript entitled *Convolutional Neural Networks with Template-Based Data Augmentation for Functional Lung Image Quantification*. We are submitting it (class Pulm Funct Imaging) at the invitation of Dr. Rahim Rizi of the University of Pennsylvania who is guest editing a special issue for *Academic Radiology*.

In this manuscript, we detail three main contributions: structural/functional lung segmentation using convolution neural networks, the introduction of a novel template-based data augmentation strategy for training deep learning architectures, and ANTsRNet---a growing open-source repository for well-known deep learning architectures for image classification, segmentation, and object detection. Given the content and the open science nature of our work in terms of both software and data, we strongly believe strongly that this is a very important contribution to be considered by *Academic Radiology*.

We sincerely hope that you consider our manuscript for review.

Sincerely,



Nicholas J. Tustison

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Results: Accuracy for CNN-based proton lung MRI segmentation (in terms of Dice overlap) was left lung: 0.87 ± 0.03 , right lung: 0.88 ± 0.02 , and whole lung: 0.88 ± 0.02 . Although less accurate than our previously reported joint label fusion (JLF) approach (left lung: 0.95 ± 0.02 , right lung: 0.96 ± 0.01 , whole lung: 0.96 ± 0.01), processing time is < 1 second per subject for the proposed approach versus ~ 30 minutes per subject using JLF. Accuracy for quantifying ventilation defects was determined based on a consensus labeling where average accuracy (Dice multilabel overlap of ventilation defect regions plus normal region) was 0.94 for the CNN method; 0.92 for our previously reported method; and 0.90, 0.92, and 0.94 for expert readers.

Conclusions: The proposed framework yields accurate automated quantification in near real time. CNNs drastically reduce processing time after offline model construction and demonstrate significant future potential for facilitating quantitative analysis of functional lung MRI.

Key Words: Advanced Normalization Tools, ANTsRNet, hyperpolarized gas imaging, neural networks, proton lung MRI, U-net

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INTRODUCTION

Probing lung function under a variety of conditions and/or pathologies has been significantly facilitated by the use of hyperpolarized gas imaging and corresponding quantitative image analysis methodologies. Such developments have provided direction and opportunity for current and future research trends [1]. Computational techniques targeting these imaging technologies permit spatial quantification of localized ventilation with potential for increased reproducibility, resolution, and robustness over traditional spirometry and radiological readings [2, 3].

One of the most frequently used image-based biomarkers for the study of pulmonary development and disease is based on the quantification of regions of limited ventilation, also known as *ventilation defects* [4]. These features have been shown to be particularly salient in a clinical context. For example, ventilation defect volume to total lung volume ratio has been shown to outperform other image-based features in discriminating asthmatics vs. non-asthmatics [5]. Ventilation defects have also demonstrated discriminative capabilities in chronic obstructive pulmonary disease (COPD) [6] and asthma [7]. These findings, along with related research, has motivated the development of multiple automated (and semi-automated) segmentation algorithms which have been proposed in the literature (e.g., [8–12]) and are currently used in a variety of clinical research investigations (e.g., [13]).

Despite the enormous methodological progress with existing quantification strategies, recent developments in machine learning (specifically “deep learning” [14]) have generated new possibilities for quantification with improved capabilities in terms of accuracy, robustness, and computational efficiency. The outgrowth of research, in conjunction with advances in computational hardware, has resulted in significant developments in various image research areas including classification, segmentation, and object localization and has led to co-optation by the medical imaging analysis community [15].

In this work, we develop and evaluate a convolutional neural network segmentation framework, based on the U-net architecture [16], for functional lung imaging using hyperpolarized gas. As part of this framework we include a deep learning analog to earlier work from our group targeting segmentation of proton lung MRI [17]. This is motivated by common use case scenarios in which proton

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4 images are used for quantifying corresponding ventilation images (i.e., masking regions of interest a
5 la [8–10]).
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8 One of the practical constraints to adopting deep learning techniques is the large data requirements
9 for the training process oftentimes necessitating ad hoc strategies for simulating additional data from
10 available data—a process termed *data augmentation* [18]. While common approaches to data aug-
11 mentation include the application of randomized simulated linear (e.g., translation, rotation and
12 affine) or elastic transformations and intensity adjustments (e.g., brightness and contrast), we ad-
13 vocate a tailored paradigm to commonly encountered medical imaging scenarios in which data is
14 limited but is assumed to be characterized by a population-wide spatial correspondence. In the pro-
15 posed approach, an optimal shape-based template is constructed from a subset of the available data.
16 Subsequent pairwise image registration between all training data and the resulting template permits
17 a “pseudo-geodesic” transformation [19] of each image to every other image thus potentially con-
18 verting a data set of size N to an augmented data set of size N^2 . In this way, transformations are
19 constrained to the shape space representing the population of interest.
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22 To enhance relevance to the research community, we showcase this work in conjunction with the
23 introduction of *ANTsRNet*—a growing open-source repository of well-known deep learning archi-
24 tectures which interfaces with the Advanced Normalization Tools (ANTs) package [20] and its R
25 package, ANTsR [21]. This permits the public distribution of all code, data, and models for external
26 reproducibility which can be found on the GitHub repository corresponding to this manuscript [22].
27 This allows other researchers to apply the developed models and software to their data and/or use
28 the models to initialize their own model development tailored to specific studies.
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31 In the work described below, we first provide the acquisition protocols for both the proton and ven-
32 tilation MR images followed by a discussion of the analysis methodologies for the proposed segmen-
33 tation framework. This is contextualized with a brief overview of existing quantification methods
34 (including that previously proposed by our group and used for the evaluative comparison). We also
35 summarize the key contributions of this work viz., the template-based data augmentation and the
36 current feature set of ANTsRNet.
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4 **MATERIALS AND METHODS**
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8 ***Image acquisition***
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11 Both proton and ventilation images used for this study were taken from current and previous studies
12 from our group. Ventilation images comprised both Helium-3 and Xenon-129 acquisitions as our
13 current segmentation processing does not distinguish between ventilation gas acquisition protocols
14 and we expected similar agnosticism for the proposed approach.
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17 Hyperpolarized MR image acquisition was performed under an Institutional Review Board (IRB)-
18 approved protocol with written informed consent obtained from each subject. In addition, all imaging
19 studies was performed under Food and Drug Administration (FDA)-approved physician's Investi-
20 gational New Drug applications for hyperpolarized gas (either Helium-3 and Xenon-129). MRI
21 data were acquired on a 1.5 T whole-body MRI scanner (Siemens Sonata, Siemens Medical Solu-
22 tions, Malvern, PA) with broadband capabilities and corresponding hyperpolarized-gas chest ra-
23 diofrequency coils (Rapid Biomedical, Rimpar, Germany; IGC Medical Advances, Milwaukee, WI;
24 or Clinical MR Solutions, Brookfield, WI).
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26

27 Two imaging protocols were used to acquire the MR images. Both of them are combined hyperpo-
28 larized gas (helium-3 or xenon-129) and proton imaging acquisitions. Protocol 1 uses 3-D balanced
29 steady-state free-precession or spoiled gradient-echo pulse sequences with isotropic resolution =
30 3.9 mm, TR = 1.75–1.85 ms, TE = 0.78–0.82 ms, flip angle= 9–10°, bandwidth per pixel=1050–1100
31 Hz/Pixel, total duration = 10–20 seconds. Protocol 2 uses a contiguous, coronal, 2-D gradient-echo
32 pulse sequence with interleaved spiral sampling scheme, in-plane resolution = 2–4 mm, slice thick-
33 ness = 15 mm, TR = 8–8.5 ms, TE = 0.8–1.0 ms, flip angle = 20° interleaves = 12–20 (plus 2 for field
34 map), total duration = 3–8 seconds. All subjects provided written informed consent and the data
35 were de-identified prior to analysis.
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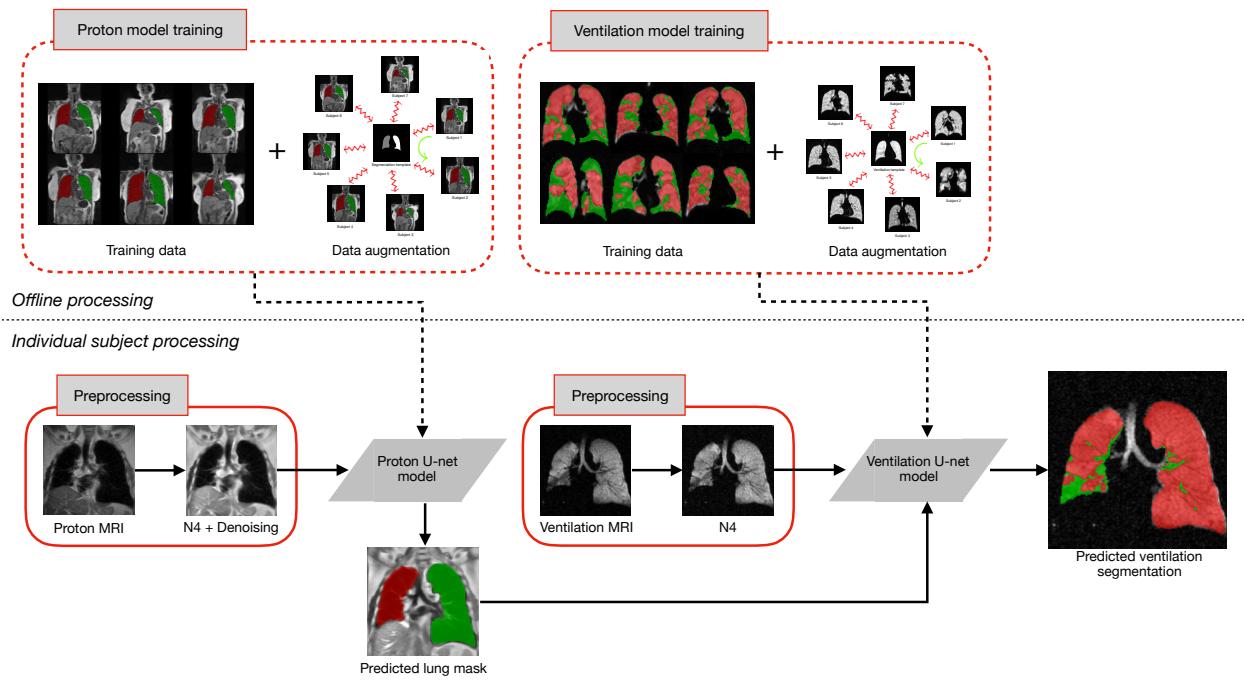


Figure 1: Illustration of the proposed workflow. Training the U-net models for both proton and ventilation imaging includes template-based data augmentation. This offline training is computationally intensive but is only performed once. Subsequent individual subject preprocessing includes MR denoising and bias correction. The proton mask determined from the proton U-net model is included as a separate channel (in deep learning software parlance) for ventilation image processing.

Image processing and analysis

We first review our previous contributions to the segmentation of proton and hyperpolarized gas MR images [8, 17] as we use these previously described techniques for evaluative comparison. We then describe the deep learning analogs (including preprocessing) extending earlier work and discuss the proposed contributions which include:

- convolution neural networks for structural/functional lung segmentation,
- template-based data augmentation, and
- open-source availability.

An overview of the resulting framework is provided in Figure 1. The most computationally intensive portion is the offline processing for model training for both structural and functional imaging. However, once that is complete, individual processing consists of a couple of preprocessing steps followed

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4 by application of the models which has minimal computational requirements.
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9 **Previous approaches from our group for lung and ventilation-based segmentation** 10

11 The automated ventilation-based segmentation, described in [8], employs a Gaussian mixture model
12 with a Markov random field (MRF) spatial prior optimized via the Expectation-Maximization algo-
13 rithm. The resulting software, called Atropos, has been used in a number of clinical studies (e.g.,
14 [7, 23]). Briefly, the intensity histogram profile of the ventilation image is modeled using Gaussian
15 functions with optimizable parameters (i.e., mean, standard deviation, and normalization factor) de-
16 signed to model the intensities of the individual ventilation classes. At each iteration the resulting
17 estimated voxelwise labels are refined based an MRF spatial regularization. The parameters of the
18 class-specific Gaussians are then re-estimated. This iterative process continues until convergence.
19 We augment this segmentation step by iterating the results with application of N4 bias correction
20 [24]. Unlike other methods which rely solely on intensity distributions which discards spatial infor-
21 mation, (e.g., K-means variants [9, 11] and histogram rescaling and thresholding [10]), our technique
22 employs both spatial and intensity information for probabilistic classification.
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25 Because of our dual structural/functional acquisition protocol [25], we also previously formulated a
26 joint label fusion (JLF)-based framework [26] for segmenting the left and right lungs in proton MRI
27 as well as estimating the lobar volumes [17]. This permits us to first identify the lung mask in the
28 proton MRI. This information is transferred to the space of the corresponding ventilation MR image
29 via image registration. The JLF method relies on a set of atlases (proton MRI plus lung labels) which
30 is spatially normalized to an unlabeled image where a weighted consensus of the normalized images
31 and labels is used to determine each voxel label. Although the method yields high quality results
32 which are fully automated, one of the drawbacks is the time and computational resources required
33 to perform the image registration for each member of the atlas set and the subsequent voxelwise label
34 consensus estimation.

35 Note that we have provided self-contained examples for both of these segmentation algorithms using
36 ANTs tools: lung and lobe estimation [27] and lung ventilation [28]. However, given the previously
37 outlined benefits of deep learning approaches to these same applications, we expect that adoption
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4 by other groups will be greatly facilitated by the proposed algorithms described below.
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9 Preprocessing

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11 Because of the low-frequency imaging artifacts introduced by confounds such as radiofrequency coil
12 inhomogeneity, we perform a retrospective bias correction on both proton and ventilation images
13 using the N4 algorithm [29]. These are included in our previously proposed ventilation [8] and
14 structural [17] segmentation frameworks. Since the initial release of these pipelines we have also
15 adopted an adaptive, patch-based denoising algorithm specific to MR [30] which we have reimple-
16 mented in the ANTs toolkit. The effects of these data cleaning techniques on both the proton images
17 and ventilation images are shown in Figure 2.
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24 U-net architecture for structural/functional lung segmentation

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26 Deep learning, a term denoting neural network architectures with multiple hidden layers, has seen
27 recent renewed research development and application. In the field of image analysis and computer
28 vision, deep learning with convolution neural networks (CNNs) has been particularly prominent in
29 recent years due, in large part, to the annual ImageNet Large Scale Visual Recognition Challenge
30 [31]. Specifically, one of the participating groups in the 2012 ImageNet challenge was the earliest
31 adopter of CNNs. The resulting architecture, colloquially known as “AlexNet” [32], surpassed any
32 approach that had been proposed previously and laid the groundwork for future CNN-based architec-
33 tures for image classification such as VGG [33] and GoogLeNet [34]. The recent successes of CNNs
34 are historically rooted in the pioneering work of LeCun et al. [35] and Fukushima [36] and others
35 which drew inspiration from earlier work on the complex arrangement of cells within the feline vi-
36 sual cortex [37]. CNNs are characterized by common components (i.e., convolution, pooling, and
37 activation functions) which can be put together in various arrangements to perform such tasks as
38 image classification and voxelwise segmentation.
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41 The U-net architecture was introduced in [16] which extended the fully convolutional neural network
42 (FCN) approach introduced by Long, Shelhamer, and Darrel [38]. U-net augments the “encoding
43 path” (see left side of Figure 3) common to such architectures as VGG and FCN with a symmetric
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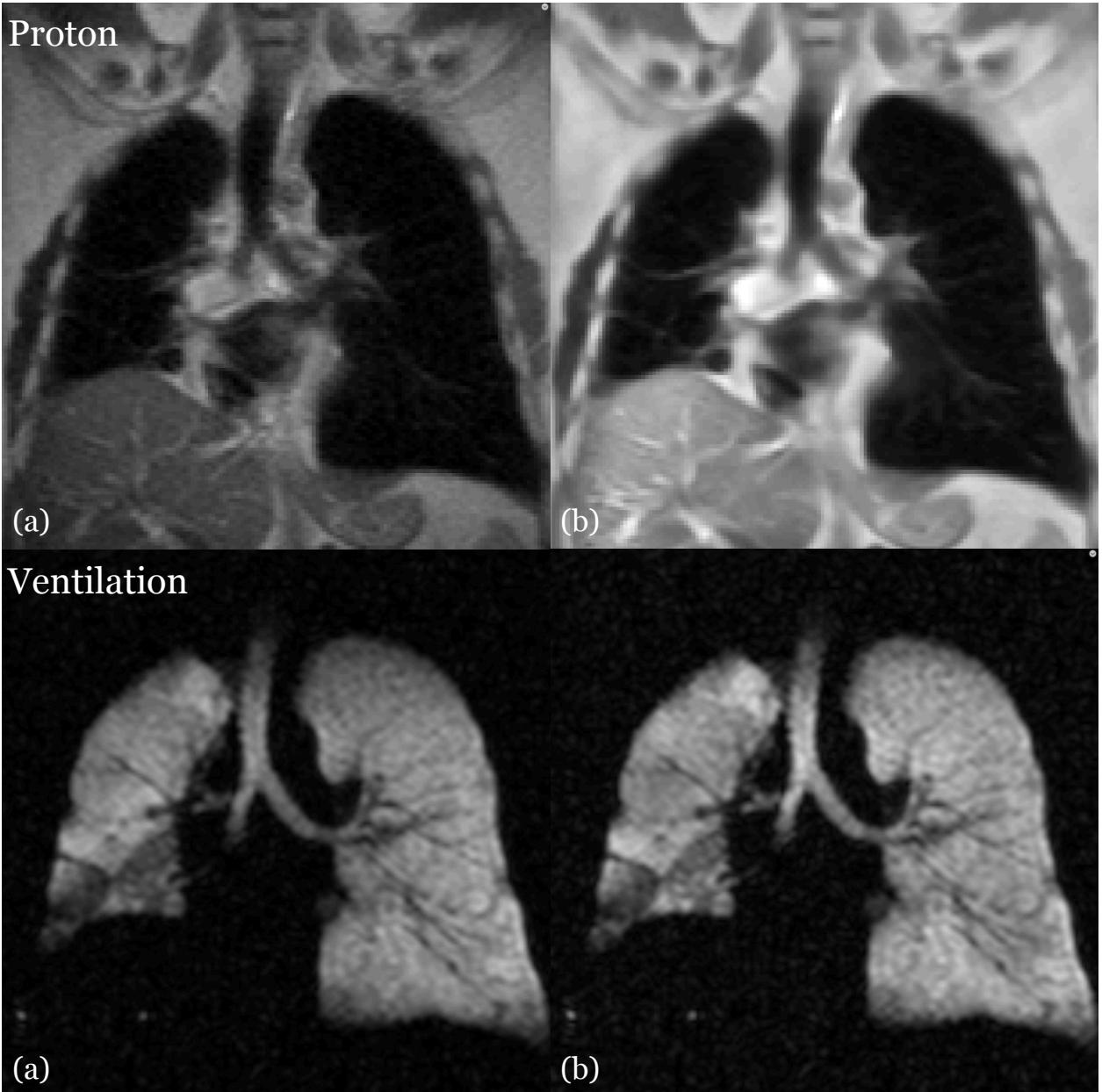


Figure 2: Side-by-side image comparison showing the effects of preprocessing on the proton (top) and ventilation (bottom) MRI. (a) Uncorrected image showing MR field inhomogeneity and noise. (b) Corresponding corrected image in which the bias effects have been ameliorated.

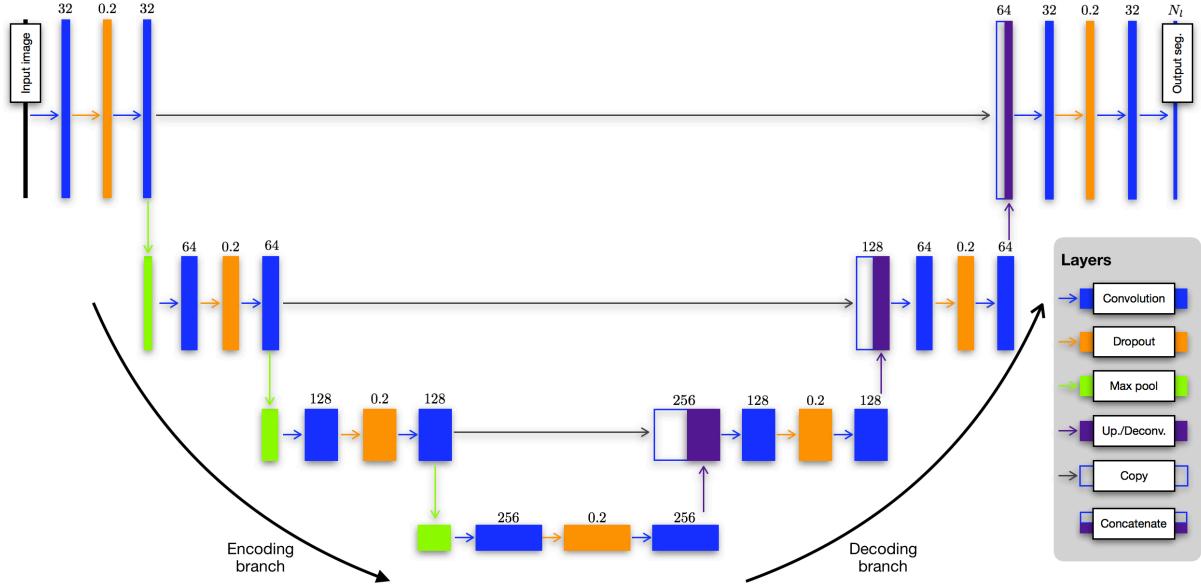


Figure 3: The modified U-net architecture for both structural and functional lung segmentation (although certain parameter values, specifically the number of filters per convolution layer, are specific to the functional case). Network layers are represented as boxes with arrows designating connections between layers. The main parameter value for each layer is provided above the corresponding box. Each layer of the descending (or “encoding”) branch of the network is characterized by two convolutional layers. Modification of the original architecture includes an intermediate dropout layer for regularization (dropout rate = 0.2). A max pooling operation produces the feature map for the next series. The ascending (or “decoding”) branch is similarly characterized. A convolutional transpose operation is used to upsample the feature map following a convolution → dropout → convolution layer series until the final convolutional operation which yields the segmentation probability maps.

decoding path where the corresponding encoding/decoding layers are linked via skip paths for enhanced feature detection. The nomenclature reflects the descending/ascending aspect of its architecture. Each series in both encoding and decoding branches is characterized by two convolutional layers sandwiching an optional dropout layer. This latter modification from the original is meant to provide additional regularization for over-fitting prevention [39]. Output consists of a segmentation probability image for each label from which a segmentation map can be generated.

We used the U-net architecture to build separate models for segmenting both structural and functional lung images. For cases where dual acquisition provides both images, we use the structural images to provide a mask for segmentation of the ventilation image. We used an open-source implementation written by our group and provided with the ANTsRNet R package [40] which is described

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4 in greater detail below. We also implemented a multi-label dice coefficient loss function along with
5 specific batch generators for generating augmented image data on the fly.
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10 **Template-based data augmentation**
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13 The need for large training data sets is a well-known limitation of deep learning algorithms. Whereas
14 the architectures developed for such tasks as the ImageNet competition have access to millions of an-
15 nnotated images for training, such data availability is atypical in medical imaging. In order to achieve
16 data set sizes necessary for learning functional models, various data augmentation strategies have
17 been employed [18]. These include application of intensity transformations, such as brightening
18 and enhanced contrast. They might also include spatial transformations such as arbitrary rotations,
19 translations, and even simulated elastic deformations. Such transformations might not be ideal if
20 they do not represent shape variation within the range within the population under study.
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23 We propose a template-based data augmentation approach whereby image data sampled from the
24 population is used to construct a representative template that is optimal in terms of shape and/or
25 intensity [41]. In addition to the representative template, this template-building process yields the
26 transformations to/from each individual image to the template space. This permits a propagation
27 of the training data to the space of each individual image. In the simplest case, the training data
28 is used to construct the template and then each individual training image and corresponding labels
29 are propagated to the space of every other image. In this way, a training data set of size N can be
30 expanded to a data set of size N^2 (see Figure 4). A slight variation to this would be to build a template
31 from M data sets (where $M > N$). Transformations between the training data and the template are
32 then used to propagate the training data to the spaces of the individual members of the template-
33 generating data for an augmented data set size of $M \times N$.
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ANTsRNet

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55 In addition to the contributions previously described, we also introduce ANTsRNet [40] to the re-
56 search community which not only contains the software to perform the operations specific to struc-
57 tural and functional lung image segmentation but also performs a host of other deep learning tasks
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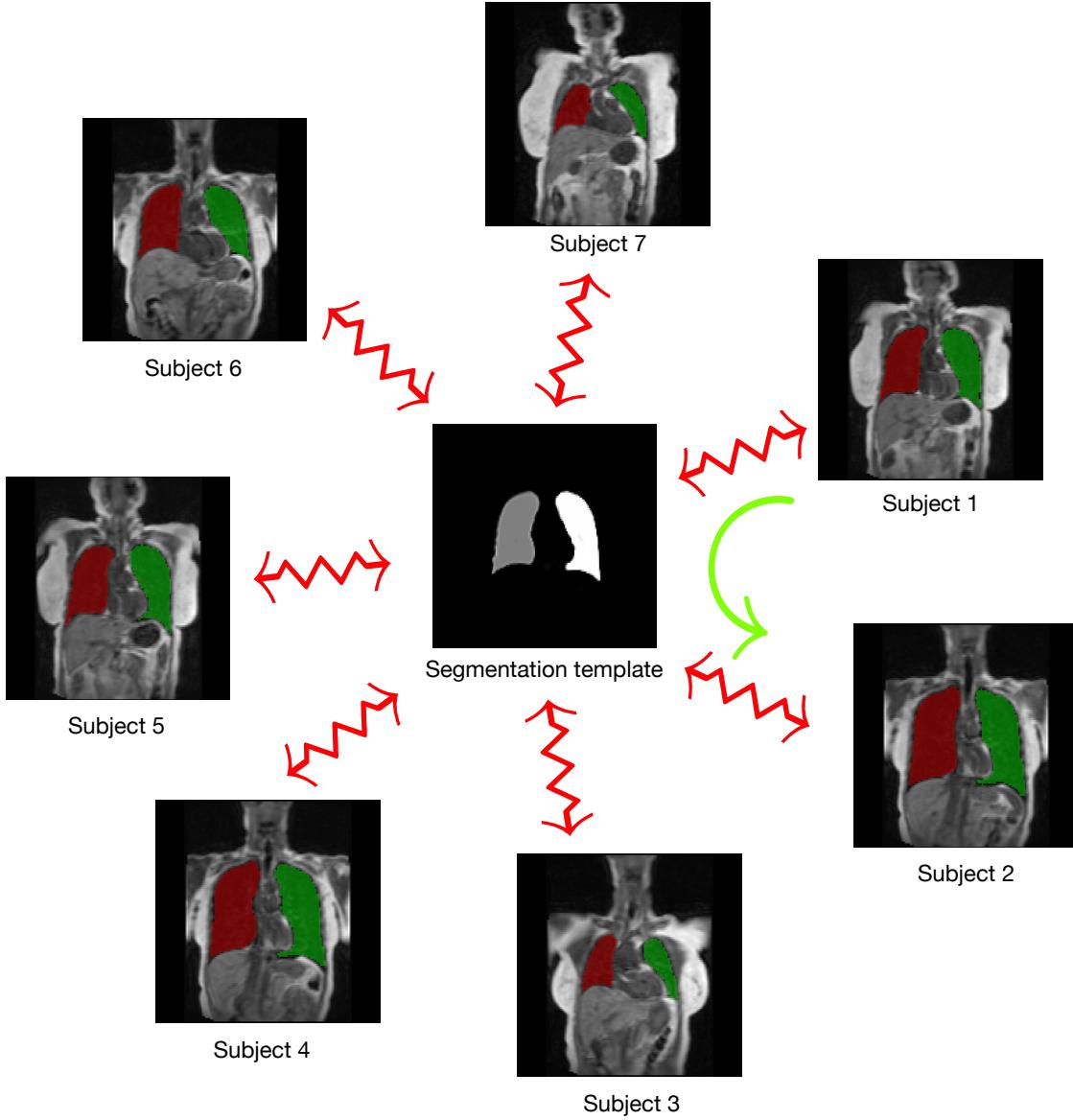


Figure 4: We introduce a novel data augmentation strategy for medical images using ANTs-based template construction. Shown here is proton lung segmentation example where a template is created from the training data segmentation images where the foreground designates the left and right lungs. This avoids the lack of internal correspondence while generating plausible global shape variations when mapping between individual training data. We used 60+ images to create such a template permitting $60^2 = 3600$ possible deformable shapes which can be further augmented by more conventional strategies (e.g., brightness transformations, translations, etc.).

wrapped in a thoroughly documented and well-written R package. The recent interest in deep learning techniques and the associated successes with respect to a variety of applications has motivated adoption of such techniques. Basic image operations such as classification, object identification, and segmentation (as well as more focused techniques) have significant potential for facilitating basic medical research. ANTsRNet is built using the Keras neural network library (available through R) and is highly integrated with the ANTsR package, the R interface of the ANTs toolkit. Consistent with our other software offerings, ongoing development is currently carried out on GitHub using a well-commented coding style, thorough documentation, and self-contained working examples [40].

It should be noted that various implementations of different deep learning architectures exist and are largely available to the public. However, we feel that ANTsRNet fills an unmet need. Based on our own search, many publicly available implementations, while functional, are not developed with large-scale distribution and application as end goals. There is little, if any, coding consistency between the various implementations leading to non-standardized APIs and difficulties in code navigation for debugging and/or didactic reasons. In addition, the vast majority employ the Python language which is understandable given its widespread usage by data scientists. However, this work makes these powerful new developments available through a major platform heavily used by statisticians and data scientists. In addition, the R-based interface to the ANTs toolkit allows for preprocessing and data augmentation strategies specific to medical imaging.

Several architectures have been implemented for both 2-D and 3-D images spanning the broad application areas of image classification, object detection, and image segmentation (cf. Table 1). It should be noted that most reporting in the literature has dealt exclusively with 2-D implementations. This is understandable due to memory and computational speed constraints limiting practical 3-D applications on current hardware. However, given the importance that 3-D data has for medical imaging and the rapid progress in hardware, we feel it worth the investment in implementing corresponding 3-D architectures. Each architecture is accompanied by one or more self-contained examples for testing and illustrative purposes. In addition, we have made novel data augmentation strategies available to the user and illustrated them with Keras-specific batch generators.

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4 **Table 1:** Current ANTsRNet capabilities comprising architectures for applications in image segmentation,
5 image classification, and object localization. Self-contained examples with data are also provided to demon-
6 strate usage for each of the architectures. Although the majority of neural network architectures are originally
7 described for 2-D images, we generalized the work to 3-D implementations where possible.
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ANTsRNet		
Image segmentation		
U-net [15]	(2-D)	Extends fully convolutional neural networks by including an upsampling decoding path with skip connections linking corresponding encoding/decoding layers.
V-net [45]	(3-D)	3-D extension of U-net which incorporates a customized Dice loss function.
Image classification		
AlexNet [32]	(2-D, 3-D)	Convolutional neural network that precipitated renewed interest in neural networks.
VGG16/VGG19 [33]	(2-D, 3-D)	Also known as 'OxfordNet'. VGG architectures are much deeper than AlexNet. Two popular styles are implemented.
GoogLeNet [34]	(2-D)	A 22-layer network formed from <i>inception blocks</i> meant to reduce the number of parameters relative to other architectures.
ResNet [46]	(2-D, 3-D)	Characterized by specialized <i>residualized blocks</i> (and skip connections).
ResNeXt [48]	(2-D, 3-D)	A variant of ResNet distinguished by a hyper-parameter called <i>cardinality</i> defining the number of independent paths.
DenseNet [49]	(2-D, 3-D)	Based on the observation that performance is typically enhanced with shorter connections between the layers and the input.
Object localization		
SSD300/SSD512 [50]	(2-D, 3-D)	The Multibox Single-Shot Detection (SSD) algorithm for determining bounding boxes around objects of interest.
SSD7	(2-D, 3-D)	Lightweight SSD variant which increases speed by slightly sacrificing accuracy. Training size requirements are smaller.

54 **Processing specifics**
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56 205 proton MR images each with left/right lung segmentations and 73 ventilation MR images with
57 masks were used for the separate U-net model training. These images were denoised and bias cor-
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4 rected offline (as described above) and required < 1 minute for both steps per image using single-
5 threading although both preprocessing steps are multi-threading capable. An R script was used to
6 read in the images and segmentations (available in our GitHub repo [22]), create the model, desig-
7 nate model parameters, and initialize the batch generator.
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12 For the proton data we built a 3-D U-net model to take advantage of the characteristic 3-D shape of
13 the lungs. This limited the possible batch size as our GPU (Titan Xp) is limited to 12 GB although this
14 can be revisited in the future with additional computational resources. We built a 2-D U-net model
15 for the ventilation images as the functional image segmentation does not take advantage of obvious
16 anatomical factors.
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19 Image size was not identical across both image cohorts so we settled on a common resampled image
20 size of $128 \times 128 \times 64$ for the proton images and 128×128 for the ventilation images. Resampling of
21 each image and segmentation was handled internally by the batch generator after transformation to
22 the reference image using ANTsR functions [21]. Additionally, during data augmentation for proton
23 model optimization, a digital “coin flip” was used to randomly vary the intensity profile of the warped
24 proton images between their original profiles and the intensity profile of the randomly selected ref-
25 erence image. The latter intensity transformation is the histogram matching algorithm of Nyul et
26 al. [42] implemented in the Insight Toolkit. Specific parameters for the U-net architecture for both
27 models are as follows (3-D parameters are included in parentheses):
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- 30 • Adam optimization:
31 – proton model learning rate = 0.00001
32 – ventilation model learning rate = 0.0001
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34 • Number of epochs: 150
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36 • Training/validation data split: 80/20
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38 • Convolution layers
39 – kernel size: $5 \times 5 (\times 5)$
40 – activation: rectified linear units (ReLU) [43]
41 – number of filters: doubled at every layer starting with $N = 16$ (proton) and $N = 32$
42 (ventilation)
43
44 • Dropout layers

- rate: 0.2
- Max pooling layers
 - size: $2 \times 2 (\times 2)$
 - stride length: $2 \times 2 (\times 2)$
- Upsampling/transposed convolution (i.e., deconvolution) layers
 - kernel size: $5 \times 5 (\times 5)$
 - stride length: $2 \times 2 (\times 2)$
 - activation: rectified linear units (ReLU) [43]

Training took approximately 10 hours for both models. After model construction, prediction per image (after preprocessing) takes < 1 second per image. Both model construction and prediction utilized a NVIDIA Titan Xp GPU.

RESULTS

Proton MRI lung segmentation

203 proton MRI with corresponding left/right lung segmentations were used to build the 3-D U-net model described in the previous section. These data were split into 80% “training” and 20% “validation” sets. Batch size was 8 images with 150 epochs with 16 steps per epoch.

After constructing the model, we applied it to the evaluation data consisting of the same 62 proton MRI used in [8]. We performed a direct comparison with the joint label fusion (JLF) method of [8] with an adopted modification that we currently use in our studies. Instead of using the entire atlas set (which would require a large number of pairwise image registrations), we align the center of the image to be segmented with each atlas image and compute a neighborhood cross-correlation similarity metric [20]. We then select the 10 atlas images that are most similar for use in the JLF scheme. The resulting performance numbers (in terms of Dice overlap) are similar to what we obtained previously and are given in Figure 5 along with the Dice overlap numbers from the CNN-based approach. Accuracy for the latter was left lung: 0.87 ± 0.03 , right lung: 0.88 ± 0.02 , and whole lung: 0.88 ± 0.02 . The analogous JLF numbers were more accurate (left lung: 0.95 ± 0.02 , right lung: 0.96

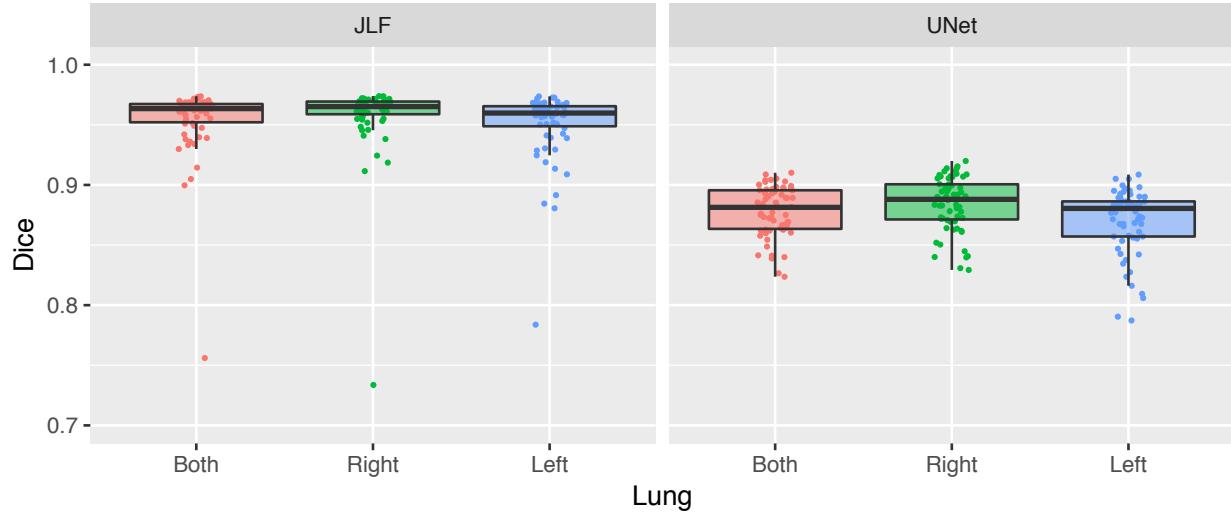


Figure 5: The Dice overlap coefficient for the left and right lungs (and their combination) between the updated joint label fusion technique (left) and our deep learning approach (right). Although slightly less accurate, the latter requires significantly less computation time.

± 0.01 , whole lung: 0.96 ± 0.01) although the processing time is significantly greater—less than 1 second per subject for the proposed approach versus ~ 25 minutes per subject using JLF using 4 CPU threads running 8 parallel pairwise registrations per evaluation image.

Ventilation MRI lung segmentation

The U-net ventilation model was generated from 73 ventilation MRI. The smaller data set size was a result of data pruning to ensure class balance. Given the smaller data set size, the availability of lung masks, and the intuitive lack of utility of morphological cues in ventilation-based segmentation, we used 2-D modeling for ventilation-based segmentation. The template-based data augmentation scheme was also used here. After transforming a randomly selected 3-D source ventilation image to the reference space, we randomly sampled slices in the coronal direction using a specified sampling rate ($= 0.5$). Once the model was complete, we performed prediction on the evaluation data slice-by-slice and then collated the slices for a single subject into probability volumetric images. We then converted these probability images into a single segmentation image which were then compared with the manual segmentation results and Atropos results from our previous work [8] using the same data. Note that the Otsu thresholding and K-means thresholding were omitted as they were the

poorest performers and, as mentioned previously, discard spatial information in contrast to both computational methods and the human readers.

In the absence of ground truth, the STAPLE algorithm [44] was used to create a consensus labeling. The Dice overlap coefficient was used to quantify agreement between each of the segmentation raters and the consensus labeling as an indicator performance. The results are shown in Figure 6. Mean values (\pm standard deviation) were as follows (total, normal lung, ventilation defect):

Reader 1: 0.89 ± 0.07 , 0.91 ± 0.06 , 0.6 ± 0.3 ; Reader 2: 0.92 ± 0.05 , 0.94 ± 0.04 , 0.57 ± 0.3 ; Reader 3: 0.94 ± 0.03 , 0.96 ± 0.03 , 0.63 ± 0.3 ; Atropos: 0.92 ± 0.03 , 0.94 ± 0.03 , 0.71 ± 0.3 ; and U-net: 0.94 ± 0.03 , 0.96 ± 0.03 , 0.70 ± 0.3 . Computational time for processing was slightly less than a minute per subject for Atropos, between 30–45 for the human readers, and less than a second for the U-net model.

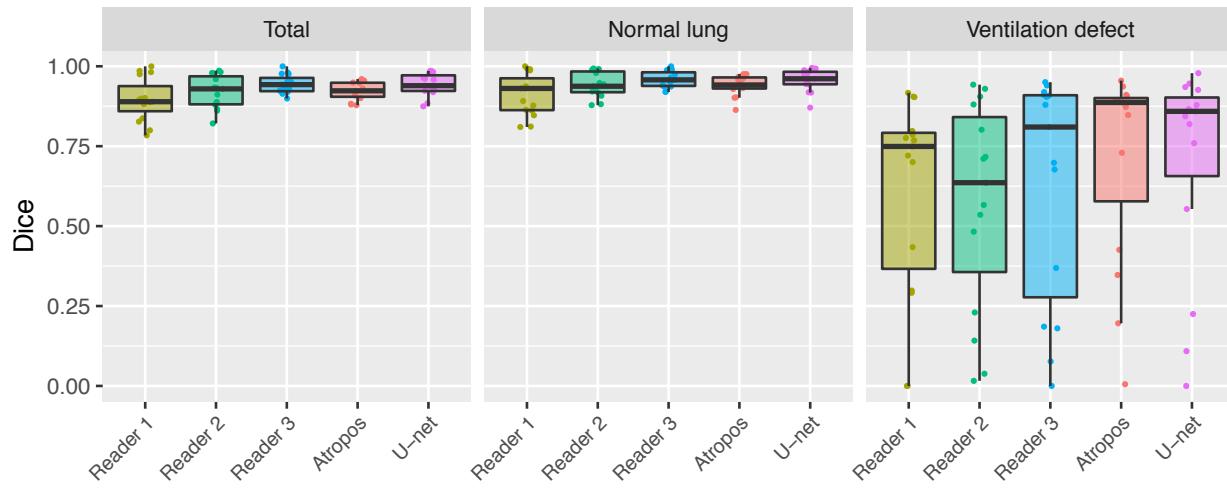


Figure 6: The Dice overlap coefficient for total, normal lung, and ventilation defect regions for segmentation of the evaluation data set.

DISCUSSION

Significant progress has been made from earlier quantification approaches in which human labelers manually identified areas of poor ventilation or applied simple thresholding techniques. More sophisticated automated and semi-automated techniques have advanced our ability to investigate

the use of hyperpolarized gas imaging as quantitative image-based biomarkers. Deep learning techniques can further enhance these methodologies by potentially increasing accuracy, generalizability, and computational efficiency. In this work, we provided a deep learning framework for segmentation of structural and functional lung MRI for quantification of ventilation. This framework is based on the U-net architecture and implemented using the Keras API available through the R statistical project.

There are several limitations to the proposed framework. The most obvious is that it only leverages the full 3-D nature of the image data collected for the proton segmentation. The trained models for ventilation image segmentation were based on 2-D coronal slices and therefore subsequent prediction is limited to those views. Even though good results were achieved in this study, even better results might be achieved by training 3-D models for the latter. Also, evaluative comparison was made using manually-refined segmentations which is certainly useful but additional evaluations using various clinical measures would also be helpful in determining the relative utility of various segmentation approaches. For example, how does the performance of the various methods translate into utility as an imaging biomarker for lung function?

Despite these limitations of the proposed framework, there are also limitations of previously reported methods. For example, in addition to the significant time requirements for JLF of lung images, shown in 7 is an example where difficult pairwise image registration scenarios can cause algorithmic failures. In contrast, the trained U-net model is capable of learning features which can potentially circumvent registration failures. Similarly, the online feature capabilities of deep learning can overcome some of the drawbacks to more conventional segmentation approaches of ventilation lung images. A well-known artifact for these approaches are partial voluming effects which can confound unsophisticated intensity-based segmentation approaches. Although spatial regularization (e.g., Markov random fields) can reduce some of these effects, these are based on relatively simplistic assumptions and it is possible that more complicated modeling can reduce these effects (see Figure 8).

Future research will certainly look into these issues as potential improvements to the existing framework. As a surrogate for full 3-D models, we are looking into developing additional 2-D U-net models for the axial and sagittal views. Since slice-by-slice processing is computationally efficient in the deep

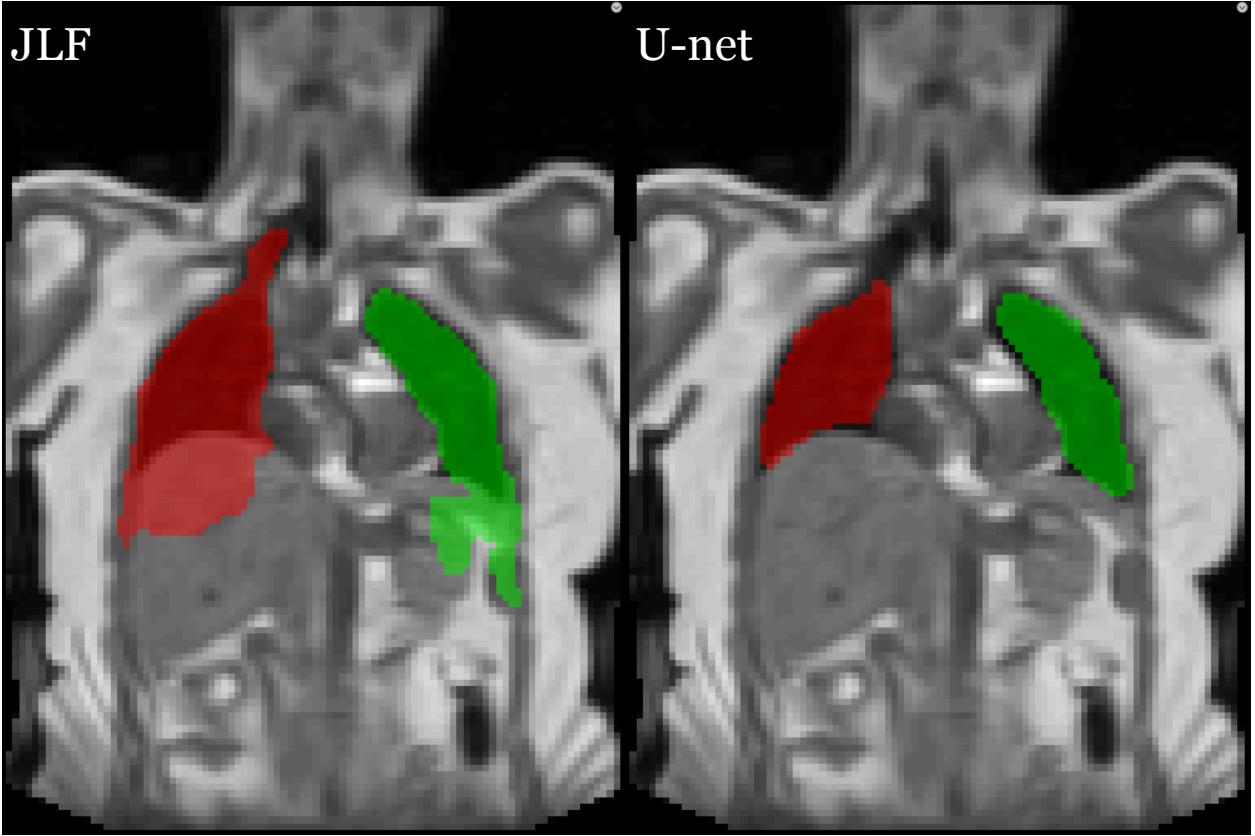


Figure 7: Problematic case showing potential issues with the JLF approach (left) for proton lung segmentation where a difficult pairwise image registration caused segmentation failure. In contrast, by learning features directly, the U-net approach (right) avoids possible registration difficulties.

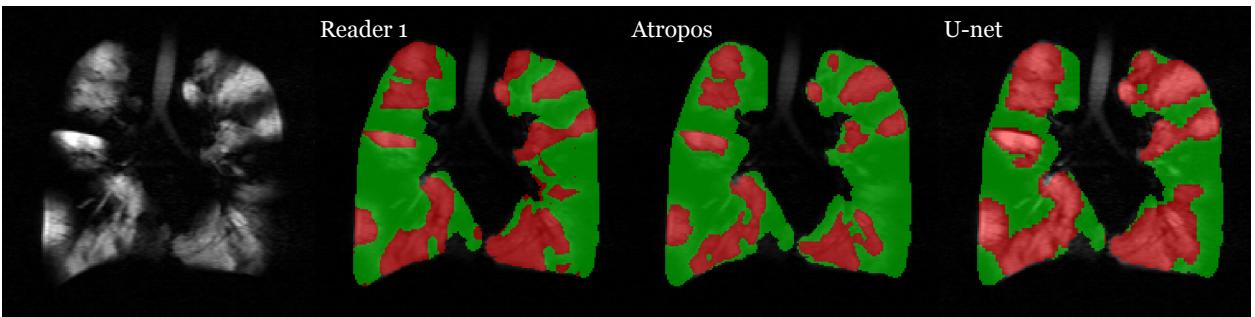


Figure 8: Ventilation segmentation comparison between a human reader and the two computational approaches. Notice the effects of the partial voluming at the apex of the lungs which are labeled as ventilation defect by the Atropos approach whereas U-net and the human reader correctly label this region.

learning paradigm, we can process 3-D images along the three canonical axes and combined the results for increased accuracy. More broadly, it would be of potential interest to investigate the use of image classification techniques (e.g., VGG [33]) for classifying lung disease phenotype directly from the images.

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REFERENCES

1. Liu, Z., Araki, T., Okajima, Y., Albert, M., and Hatabu, H. “**Pulmonary Hyperpolarized Noble**
2 **Gas MRI: Recent Advances and Perspectives in Clinical Application**” *Eur J Radiol* 83, no.
3 7 (2014): 1282–1291. doi:10.1016/j.ejrad.2014.04.014
4. Roos, J. E., McAdams, H. P., Kaushik, S. S., and Driehuys, B. “**Hyperpolarized Gas MR Imag-**
5 **ing: Technique and Applications**” *Magn Reson Imaging Clin N Am* 23, no. 2 (2015): 217–29.
6 doi:10.1016/j.mric.2015.01.003
7. Adamson, E. B., Ludwig, K. D., Mumby, D. G., and Fain, S. B. “**Magnetic Resonance Imaging**
8 **with Hyperpolarized Agents: Methods and Applications**” *Phys Med Biol* 62, no. 13 (2017):
9 R81–R123. doi:10.1088/1361-6560/aa6be8
10. Svenningsen, S., Kirby, M., Starr, D., Coxson, H. O., Paterson, N. A. M., McCormack, D. G.,
11 and Parraga, G. “**What Are Ventilation Defects in Asthma?**” *Thorax* 69, no. 1 (2014): 63–71.
12 doi:10.1136/thoraxjnl-2013-203711
13. Tustison, N. J., Altes, T. A., Song, G., Lange, E. E. de, Mugler, J. P., 3rd, and Gee, J. C. “**Feature**
14 **Analysis of Hyperpolarized Helium-3 Pulmonary MRI: A Study of Asthmatics Versus**
15 **Nonasthmatics**” *Magn Reson Med* 63, no. 6 (2010): 1448–55. doi:10.1002/mrm.22390
16. Kirby, M., Pike, D., Coxson, H. O., McCormack, D. G., and Parraga, G. “**Hyperpolarized**
17 **(3)He Ventilation Defects Used to Predict Pulmonary Exacerbations in Mild to Mod-**
18 **erate Chronic Obstructive Pulmonary Disease**” *Radiology* 273, no. 3 (2014): 887–96.
19 doi:10.1148/radiol.14140161
20. Altes, T. A., Mugler, J. P., 3rd, Ruppert, K., Tustison, N. J., Gersbach, J., Szentpetery, S.,
21 Meyer, C. H., Lange, E. E. de, and Teague, W. G. “**Clinical Correlates of Lung Ventila-**
22 **tion Defects in Asthmatic Children**” *J Allergy Clin Immunol* 137, no. 3 (2016): 789–96.e7.
23 doi:10.1016/j.jaci.2015.08.045
24. Tustison, N. J., Avants, B. B., Flors, L., Altes, T. A., Lange, E. E. de, Mugler, J. P., 3rd, and Gee,
25 J. C. “**Ventilation-Based Segmentation of the Lungs Using Hyperpolarized (3)He MRI**” *J*
26 *Magn Reson Imaging* 34, no. 4 (2011): 831–41. doi:10.1002/jmri.22738

- 1
2
3
4 9. Kirby, M., Heydarian, M., Svenningsen, S., Wheatley, A., McCormack, D. G., Etemad-Rezai, R.,
5 and Parraga, G. “**Hyperpolarized ^3He Magnetic Resonance Functional Imaging Semiau-**
6 **tomated Segmentation**” *Acad Radiol* 19, no. 2 (2012): 141–52. doi:10.1016/j.acra.2011.10.007
7
8 10. He, M., Kaushik, S. S., Robertson, S. H., Freeman, M. S., Virgincar, R. S., McAdams,
9 H. P., and Driehuys, B. “**Extending Semiautomatic Ventilation Defect Analysis for**
10 **Hyperpolarized $(^{129}\text{Xe}$ Ventilation MRI**” *Acad Radiol* 21, no. 12 (2014): 1530–41.
11 doi:10.1016/j.acra.2014.07.017
12
13 11. Zha, W., Niles, D. J., Kruger, S. J., Dardzinski, B. J., Cadman, R. V., Mummy, D. G., Nagle, S. K.,
14 and Fain, S. B. “**Semiautomated Ventilation Defect Quantification in Exercise-Induced**
15 **Bronchoconstriction Using Hyperpolarized Helium-3 Magnetic Resonance Imaging: A**
16 **Repeatability Study**” *Acad Radiol* 23, no. 9 (2016): 1104–14. doi:10.1016/j.acra.2016.04.005
17
18 12. Hughes, P. J. C., Horn, F. C., Collier, G. J., Biancardi, A., Marshall, H., and Wild, J. M. “**Spatial**
19 **Fuzzy c-Means Thresholding for Semiautomated Calculation of Percentage Lung Ven-**
20 **tilated Volume from Hyperpolarized Gas and ^1H MRI**” *J Magn Reson Imaging* 47, no. 3
21 (2018): 640–646. doi:10.1002/jmri.25804
22
23 13. Trivedi, A., Hall, C., Hoffman, E. A., Woods, J. C., Gierada, D. S., and Castro, M. “**Using**
24 **Imaging as a Biomarker for Asthma**” *J Allergy Clin Immunol* 139, no. 1 (2017): 1–10.
25 doi:10.1016/j.jaci.2016.11.009
26
27 14. LeCun, Y., Bengio, Y., and Hinton, G. “**Deep Learning**” *Nature* 521, (2015): 436–444.
28
29 15. Litjens, G., Kooi, T., Bejnordi, B. E., Setio, A. A. A., Ciompi, F., Ghafoorian, M., Laak, J. A. W. M.
30 van der, Ginneken, B. van, and Sánchez, C. I. “**A Survey on Deep Learning in Medical Image**
31 **Analysis**” *Med Image Anal* 42, (2017): 60–88. doi:10.1016/j.media.2017.07.005
32
33 16. Ronneberger, O., Fischer, P., and Brox, T. “**U-Net: Convolutional Networks for Biomed-**
34 **ical Image Segmentation**” *Proceedings of the international conference on medical image comput-*
35 *ing and computer-assisted intervention* 9351, (2015): 234–241.
36
37 17. Tustison, N. J. and Herrera, J. M. “**Two Luis Miguel Fans Walk into a Bar in Nagoya —**
38 **> (Yada, Yada, Yada) —> an ITK-Implementation of a Popular Patch-Based Denoising**

1
2
3
4 **Filter” *Insight Journal* (2016):**
5
6
7 18. Taylor, L. and Nitschke, G. “**Improving Deep Learning Using Generic Data Augmen-**
8 **tation” *CoRR* abs/1708.06020, (2017): Available at <http://arxiv.org/abs/1708.06020>**
9
10
11 19. Tustison, N. J. and Avants, B. B. “**Explicit B-Spline Regularization in Diffeomorphic Im-**
12 **age Registration” *Front Neuroinform* 7, (2013): 39. doi:10.3389/fninf.2013.00039**
13
14
15 20. Avants, B. B., Tustison, N. J., Song, G., Cook, P. A., Klein, A., and Gee, J. C. “**A Reproducible**
16 **Evaluation of ANTs Similarity Metric Performance in Brain Image Registration” *Neuro-***
17 *image* 54, no. 3 (2011): 2033–44. doi:10.1016/j.neuroimage.2010.09.025
18
19
20
21
22 21. Available at <https://github.com/stnav/ANTsR>
23
24
25 22. Available at <https://github.com/ntustison/DeepVentNet>
26
27
28 23. Altes, T. A., Johnson, M., Fidler, M., Botfield, M., Tustison, N. J., Leiva-Salinas, C., Lange, E.
29 E. de, Froh, D., and Mugler, J. P., 3rd. “**Use of Hyperpolarized Helium-3 MRI to Assess Re-**
30 **sponse to Ivacaftor Treatment in Patients with Cystic Fibrosis” *J Cyst Fibros* 16, no. 2**
31 (2017): 267–274. doi:10.1016/j.jcf.2016.12.004
32
33
34
35 24. Tustison, N. J., Avants, B. B., Cook, P. A., Zheng, Y., Egan, A., Yushkevich, P. A., and Gee, J. C.
36 “**N4ITK: Improved N3 Bias Correction” *IEEE Trans Med Imaging* 29, no. 6 (2010): 1310–20.**
37 doi:10.1109/TMI.2010.2046908
38
39
40
41 25. Qing, K., Altes, T. A., Tustison, N. J., Feng, X., Chen, X., Mata, J. F., Miller, G. W., Lange, E.
42 E. de, Tobias, W. A., Cates, G. D., Jr, Brookeman, J. R., and Mugler, J. P., 3rd. “**Rapid Acquisi-**
43 **tion of Helium-3 and Proton Three-Dimensional Image Sets of the Human Lung in a**
44 **Single Breath-Hold Using Compressed Sensing” *Magn Reson Med* 74, no. 4 (2015): 1110–5.**
45 doi:10.1002/mrm.25499
46
47
48
49
50
51
52 26. Wang, H., Suh, J. W., Das, S. R., Pluta, J., Craige, C., and Yushkevich, P. A. “**Multi-Atlas**
53 **Segmentation with Join Label Fusion” *IEEE Trans Pattern Analysis and Machine Intelligence***
54 (2013):
55
56
57
58 27. Available at <https://github.com/ntustison/LungAndLobeEstimationExample>
59
60
61
62
63
64
65

- 1
2
3
4
5
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7
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46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
28. Available at <https://github.com/ntustison/LungVentilationSegmentationExample>
29. Tustison, N. J., Avants, B. B., Cook, P. A., Zheng, Y., Egan, A., Yushkevich, P. A., and Gee, J. C. “**N4ITK: Improved N3 Bias Correction**” *IEEE Trans Med Imaging* 29, no. 6 (2010): 1310–20. doi:10.1109/TMI.2010.2046908
30. 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
31. Russakovsky, O., Deng, J., Su, H., Krause, J., Satheesh, S., Ma, S., Huang, Z., Karpathy, A., Khosla, A., Bernstein, M., Berg, A. C., and Fei-Fei, L. “**ImageNet Large Scale Visual Recognition Challenge**” *International Journal of Computer Vision* 115, no. 3 (2015): 211–252.
32. Krizhevsky, A., Sutskever, I., and Hinton, G. E. “**ImageNet Classification with Deep Convolutional Neural Networks**” *Commun. ACM* 60, no. 6 (2017): 84–90. doi:10.1145/3065386, Available at <http://doi.acm.org/10.1145/3065386>
33. Simonyan, K. and Zisserman, A. “**Very Deep Convolutional Networks for Large-Scale Image Recognition**” *CoRR* abs/1409.1556, (2014): Available at <http://arxiv.org/abs/1409.1556>
34. Szegedy, C., Vanhoucke, V., Ioffe, S., Shlens, J., and Wojna, Z. “**Rethinking the Inception Architecture for Computer Vision**” *CoRR* abs/1512.00567, (2015): Available at <http://arxiv.org/abs/1512.00567>
35. LeCun, Y., Bottou, L., Bengio, Y., and Haffner, P. “**Gradient-Based Learning Applied to Document Recognition**” *Proceedings of the IEEE* 86, no. 11 (1998): 2278–2324.
36. Fukushima, K. “**Neocognitron: A Self Organizing Neural Network Model for a Mechanism of Pattern Recognition Unaffected by Shift in Position**” *Biol Cybern* 36, no. 4 (1980): 193–202.
37. Hubel, D. H. and Wiesel, T. N. “**Receptive Fields, Binocular Interaction and Functional Architecture in the Cat’s Visual Cortex**” *J Physiol* 160, (1962): 106–54.
38. Shelhamer, E., Long, J., and Darrell, T. “**Fully Convolutional Networks for Semantic Segmentation**” *IEEE Trans Pattern Anal Mach Intell* 39, no. 4 (2017): 640–651.

1
2
3
4 doi:10.1109/TPAMI.2016.2572683
5
6

7 39. Srivastava, N., Hinton, G., Krizhevsky, A., Sutskever, I., and Salakhutdinov, R. “**Dropout: A**
8 **Simple Way to Prevent Neural Networks from Overfittin**” *Journal of Machine Learning Re-*
9 *search* 15, no. 1 (2014): 1929–1958.
10
11

12 40. Available at <https://github.com/ANTsX/ANTsRNet>
13
14

15 41. Avants, B. B., Yushkevich, P., Pluta, J., Minkoff, D., Korczykowski, M., Detre, J., and Gee, J. C.
16 “**The Optimal Template Effect in Hippocampus Studies of Diseased Populations**” *Neu-*
17 *roimage* 49, no. 3 (2010): 2457–66. doi:10.1016/j.neuroimage.2009.09.062
18
19

20 42. Nyúl, L. G., Udupa, J. K., and Zhang, X. “**New Variants of a Method of MRI Scale Stan-**
21 **dardization**” *IEEE Trans Med Imaging* 19, no. 2 (2000): 143–50. doi:10.1109/42.836373
22
23

24 43. Nair, V. and Hinton, G. E. “**Rectified Linear Units Improve Restricted Boltzmann Ma-**
25 **chines**” *Proceedings of the 27th international conference on machine learning* (2010):
26
27

28 44. Warfield, S. K., Zou, K. H., and Wells, W. M. “**Simultaneous Truth and Performance Level**
29 **Estimation (STAPLE): An Algorithm for the Validation of Image Segmentation**” *IEEE*
30 *Trans Med Imaging* 23, no. 7 (2004): 903–21. doi:10.1109/TMI.2004.828354
31
32

33 45. Milletari, F., Navab, N., and Ahmadi, S. “**V-Net: Fully Convolutional Neural Networks**
34 **for Volumetric Medical Image Segmentation**” *CoRR* abs/1606.04797, (2016): Available at
35 <http://arxiv.org/abs/1606.04797>
36
37

38 46. Krizhevsky, A., Sutskever, I., and Hinton, G. E. “**ImageNet Classification with Deep Con-**
39 **volutional Neural Networks**” *Proceedings of the 25th international conference on neural infor-*
40 *mation processing systems - volume 1* (2012): 1097–1105. Available at <http://dl.acm.org/citation.cfm?id=2999134.2999257>
41
42

43 47. He, K., Zhang, X., Ren, S., and Sun, J. “**Deep Residual Learning for Image Recognition**”
44 *CoRR* abs/1512.03385, (2015): Available at <http://arxiv.org/abs/1512.03385>
45
46

47 48. Xie, S., Girshick, R. B., Dollár, P., Tu, Z., and He, K. “**Aggregated Residual Transforma-**
48 **tions for Deep Neural Networks**” *CoRR* abs/1611.05431, (2016): Available at <http://arxiv.org/abs/1611.05431>
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

- 1
2
3
4 49. Huang, G., Liu, Z., and Weinberger, K. Q. “**Densely Connected Convolutional Networks**”
5
6 *CoRR* abs/1608.06993, (2016): Available at <http://arxiv.org/abs/1608.06993>
7
8
9 50. Liu, W., Anguelov, D., Erhan, D., Szegedy, C., Reed, S. E., Fu, C., and Berg, A. C. “**SSD: Single**
10 **Shot Multibox Detector**” *CoRR* abs/1512.02325, (2015): Available at [http://arxiv.org/abs/1512.](http://arxiv.org/abs/1512.02325)
11
12
13
14
15
16
17
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Convolutional Neural Networks with Template-Based Data Augmentation for Functional Lung Image Quantification

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