

# Histograms should not be used to segment hyperpolarized gas images of the lung

Nicholas J. Tustison, . . . , Jaime F. Mata

Department of Radiology and Medical Imaging, University of Virginia, Charlottesville, VA

Corresponding author:  
Nicholas J. Tustison, DSc  
Department of Radiology and Medical Imaging  
University of Virginia  
[ntustison@virginia.edu](mailto:ntustison@virginia.edu)

# Abstract

Magnetic resonance imaging using hyperpolarized gases has facilitated the novel visualization of airspaces, such as the human lung. The advent and refinement of these imaging techniques have furthered research avenues with respect to the growth, development, and pathologies of the pulmonary system. In conjunction with the improvements associated with image acquisition, multiple image analysis strategies have been proposed and developed for the quantification of hyperpolarized gas images with much research effort devoted to semantic segmentation, or voxelwise classification, into clinically-oriented categories based on functional ventilation levels. Given the functional nature of these images and the consequent complexity of the segmentation task, many of these algorithmic approaches reduce the complex spatial image intensity information to intensity-only considerations, particularly those associated with the intensity histogram. Although facilitating computational processing, this simplifying transformation results in the loss of important spatial cues for identifying salient imaging features, such as ventilation defects—an identified correlate of lung pathophysiology. In this work, we demonstrate the interrelatedness of the most common approaches for intensity-only (e.g., histogram), ventilation segmentation of hyperpolarized gas lung imaging for driving voxelwise classification. We evaluate the underlying assumptions associated with each approach and show how these assumptions lead to suboptimal performance. We then illustrate how a convolutional neural network can be constructed in a multi-scale, hierarchically feature-based (i.e., spatial) manner which circumvents the problematic issues associated with existing intensity-only approaches. Importantly, we provide the entire evaluation framework, including this newly reported deep learning functionality, as open-source through the well-known Advanced Normalization Tools (ANTs) library.

# Introduction

## Early acquisition and development

Early hyperpolarized gas pulmonary imaging research reported findings in qualitative terms.

Descriptions:

- “ $^3\text{He}$  MRI depicts anatomical structures reliably” (1)
- “hypointense areas” (2)
- “signal intensity inhomogeneities” (2)
- “wedge-shaped areas with less signal intensity” (2)
- “patchy or wedge-shaped defects” (3)
- “ventilation defects” (4)
- “defects were pleural-based, frequently wedge-shaped, and varied in size from tiny to segmental” (4)

## Historical overview of quantification

Initial attempts at quantification of ventilation images were limited to enumerating the number of “ventilation defects” or estimating ventilation defect percentage (as a percentage of total lung volume). Often these measurements were acquired on a slice-by-slice basis.

Prior to the popularization of deep learning in medical image analysis, including in the field of hyperpolarized gas imaging (5), widely used semi-automated or automated segmentation techniques were primarily based on intensity-only considerations. In order of increasing sophistication, these techniques can be categorized as follows:

- binary thresholding based on relative intensities (6, 7),

- linear intensity standardization based on global rescaling of the intensity histogram to a reference distribution based on healthy controls, i.e., “linear binning” (8, 9),
- nonlinear intensity standardization based on piecewise affine transformation of the intensity histogram using the K-means algorithm (10), and
- Gaussian mixture modeling (GMM) with Markov random field (MRF) spatial modeling (11).

The early semi-automated technique used to compare smokers and never-smokers in (6) uses manually drawn regions to determine the mean signal intensity and the standard deviation of the noise to derive a threshold value of three noise standard deviations below the mean intensity. All voxels above that threshold value were considered “ventilated” for the purposes of the study. Related approaches, which continue to be used currently (e.g., (7)), simply use a rescaled threshold value to binarize the segmentation. Similar to the histogram-only algorithms (i.e., linear binning and k-means), these approaches do not take into account the various artefacts associated with MRI such as the non-Gaussianity of the MR imaging noise (12, 13) and the intensity inhomogeneity field (14) which prevent simple intensity thresholds from distinguishing tissue types consistent with that of human experts.

To provide a more granular categorization of ventilation that tracks with clinical qualitative assessment, an increase in the number of voxel classes have been added to the various lung parcellation protocols beyond the binary categories of “ventilated” and “non-ventilated.” Linear binning is a simplified intensity standardization approach with six discrete intensity levels (or clusters). The six clusters are evenly spaced throughout the intensity range based on the mean and standard deviation values determined from a cohort of healthy controls.

Intensity rescaling for determination of segmentation clusters of lung images can be thought of as a global affine 1-D transform of the intensity histogram to a standardized 1-D reference histogram. Such a global transform does not account for MR intensity nonlinearities that have been well-studied (15–18) and can cause significant intensity variation even in the same tissue region of the same subject. As stated in (19):

Intensities of MR images can vary, even in the same protocol and the same

sample and using the same scanner. Indeed, they may depend on the acquisition conditions such as room temperature and hygrometry, calibration adjustment, slice location, B0 intensity, and the receiver gain value. The consequences of intensity variation are greater when different scanners are used.

As we demonstrate in subsequent sections, ignoring these nonlinearities can have significant consequences in the well-studied (and somewhat analogous) area of brain tissue segmentation in T1-weighted MRI (e.g., (20–22)) and we demonstrate its effect in hyperpolarized gas imaging quantification robustness. In addition, it is not a given that we have a sufficient understanding of what constitutes a “normal” in the context of mean and standard MR intensity values and whether or not those values can be combined in a linear fashion to constitute a reference standard. Of more concrete concern, though, is that the requirement for a healthy cohort for determination of algorithmic parameters introduces an (unnecessary) source of measurement variance.

Previous attempts at histogram standardization (16, 17) in light of these MR intensity nonlinearities have relied on 1-D piecewise affine mappings between corresponding structural features found within the histograms (i.e., peaks and valleys). For example, structural MRI, such as T1-weighted neuroimaging, utilizes the well-known relative intensities of major tissues types (i.e., cerebrospinal fluid, gray matter, and white matter), which characteristically correspond to visible histogram peaks, as landmarks to determine the nonlinear intensity mapping between images. However, in hyperpolarized gas imaging of the lung, no such characteristic structural features exist, generally speaking, between histograms. The approach used by some groups (10) of employing k-means as a clustering strategy (23) to minimize the within-class variance of its intensities can be viewed as an alternative optimization strategy for determining a nonlinear mapping between histograms for a clinically-based MR intensity standardization. Although manual k-means initialization is often used where representative voxels are selected for each class by the operator, linear binning can be considered a type of automated initialization. However, k-means does constitute an algorithmic approach with additional degrees of flexibility over linear binning as it employs basic prior knowledge in the

form of a generic clustering desideratum for optimizing a type of MR intensity standardization<sup>1</sup>

Histogram-based optimization is used in conjunction with spatial considerations in the approach detailed in (11). Based on a well-developed iterative approach originally used for NASA satellite image processing and subsequently appropriated for brain tissue segmentation in T1-weighted MRI (24), a GMM is used to model the intensity clusters within the histogram with class modulation in the form of probabilistic voxelwise label considerations within image neighborhoods. Initialization for this particular application is in the form of k-means clustering which, itself, is initialized automatically using evenly spaced cluster centers—similar to linear binning without the reference distribution. This has a number of advantages in that it accommodates MR intensity nonlinearities, like k-means, but in contrast to k-means and the other algorithms outlined, does not use hard intensity thresholds for distinguishing class labels. However, as we will demonstrate, this algorithm is also flawed in that it implicitly assumes, incorrectly, that meaningful structure is found, and can be characterized, within the associated image histogram in order to optimize class labeling.

Finally, we point out that N4 bias correction is used in many of these algorithms which is also histogram-based.

It should be noted that we are not claiming that these algorithms are erroneous. Much of the relevant research has been limited to quantifying differences with respect to ventilation vs. non-ventilation in various clinical categories and these algorithms have certainly demonstrated the capacity for advancing such research. However, as acquisition and analyses methodologies improve, so should the level of sophistication and performance of the measurement tools.

*In assessing these algorithms, it is important to note that human expertise leverages more than relative intensity values to identify salient, clinically relevant features in images.*

---

<sup>1</sup>The prior knowledge for histogram mapping is the general machine learning heuristic of clustering samples based on the minimizing within-class distance while simultaneously maximizing the between-class distance. In the case of k-means, this “distance” is the variance as optimizing based on the Euclidean distance is NP-hard.

**Methods**

**Results**

**Discussion**

## References

1. Bachert P, Schad LR, Bock M, et al.: Nuclear magnetic resonance imaging of airways in humans with use of hyperpolarized  $^3\text{He}$ . *Magn Reson Med* 1996; 36:192–6.
2. Kauczor HU, Hofmann D, Kreitner KF, et al.: Normal and abnormal pulmonary ventilation: Visualization at hyperpolarized  $^3\text{He}$  mr imaging. *Radiology* 1996; 201:564–8.
3. Kauczor HU, Ebert M, Kreitner KF, et al.: Imaging of the lungs using  $^3\text{He}$  mri: Preliminary clinical experience in 18 patients with and without lung disease. *J Magn Reson Imaging*; 7:538–43.
4. Altes TA, Powers PL, Knight-Scott J, et al.: Hyperpolarized  $^3\text{He}$  MR lung ventilation imaging in asthmatics: Preliminary findings. *J Magn Reson Imaging* 2001; 13:378–84.
5. Tustison NJ, Avants BB, Lin Z, et al.: Convolutional neural networks with template-based data augmentation for functional lung image quantification. *Acad Radiol* 2019; 26:412–423.
6. Woodhouse N, Wild JM, Paley MNJ, et al.: Combined helium-3/proton magnetic resonance imaging measurement of ventilated lung volumes in smokers compared to never-smokers. *J Magn Reson Imaging* 2005; 21:365–9.
7. Shammi UA, D'Alessandro MF, Altes T, et al.: Comparison of hyperpolarized  $^3\text{He}$  and  $^{129}\text{Xe}$  mr imaging in cystic fibrosis patients. *Acad Radiol* 2021.
8. He M, Driehuys B, Que LG, Huang Y-CT: Using hyperpolarized  $^{129}\text{Xe}$  mri to quantify the pulmonary ventilation distribution. *Acad Radiol* 2016; 23:1521–1531.
9. He M, Wang Z, Rankine L, et al.: Generalized linear binning to compare hyperpolarized  $^{129}\text{Xe}$  ventilation maps derived from 3D radial gas exchange versus dedicated multislice gradient echo mri. *Acad Radiol* 2020; 27:e193–e203.
10. Kirby M, Heydarian M, Svenningsen S, et al.: Hyperpolarized  $^3\text{He}$  magnetic resonance functional imaging semiautomated segmentation. *Acad Radiol* 2012; 19:141–52.



11. Tustison NJ, Avants BB, Flors L, et al.: Ventilation-based segmentation of the lungs using hyperpolarized (3)He MRI. *J Magn Reson Imaging* 2011; 34:831–41.
12. Gudbjartsson H, Patz S: The rician distribution of noisy mri data. *Magn Reson Med* 1995; 34:910–4.
13. Andersen AH: On the rician distribution of noisy mri data. *Magn Reson Med* 1996; 36:331–3.
14. Sled JG, Zijdenbos AP, Evans AC: A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Trans Med Imaging* 1998; 17:87–97.
15. Wendt RE 3rd: Automatic adjustment of contrast and brightness of magnetic resonance images. *J Digit Imaging* 1994; 7:95–7.
16. Nyúl LG, Udupa JK: On standardizing the mr image intensity scale. *Magn Reson Med* 1999; 42:1072–81.
17. Nyúl LG, Udupa JK, Zhang X: New variants of a method of mri scale standardization. *IEEE Trans Med Imaging* 2000; 19:143–50.
18. De Nunzio G, Cataldo R, Carlà A: Robust intensity standardization in brain magnetic resonance images. *J Digit Imaging* 2015; 28:727–37.
19. Collewet G, Strzelecki M, Mariette F: Influence of mri acquisition protocols and image intensity normalization methods on texture classification. *Magn Reson Imaging* 2004; 22:81–91.
20. Zhang Y, Brady M, Smith S: Segmentation of brain mr images through a hidden markov random field model and the expectation-maximization algorithm. *IEEE Trans Med Imaging* 2001; 20:45–57.
21. Ashburner J, Friston KJ: Unified segmentation. *Neuroimage* 2005; 26:839–51.
22. Avants BB, Tustison NJ, Wu J, Cook PA, Gee JC: An open source multivariate framework

- for n-tissue segmentation with evaluation on public data. *Neuroinformatics* 2011; 9:381–400.
23. Hartigan J, Wang M: A k-means clustering algorithm. *Applied Statistics* 1979; 28:100–108.
24. Vannier MW, Butterfield RL, Jordan D, Murphy WA, Levitt RG, Gado M: Multispectral analysis of magnetic resonance images. *Radiology* 1985; 154:221–4.