

Statistical Methodology for Computed Tomography Scans of the Lung

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- 1 Chapter 1: Introduction
- 2 Chapter 2: Template Creation for High Resolution Computed Tomography Scans of the Lung in R Software
- 3 Chapter 3: An Eigenvector Spatial Filtering Model for Lung Imaging Data
- 4 Chapter 4: Cluster Activation Mapping with Applications to Medical Imaging Data
- 5 Chapter 5: Conclusion

Chapter 1:

Introduction

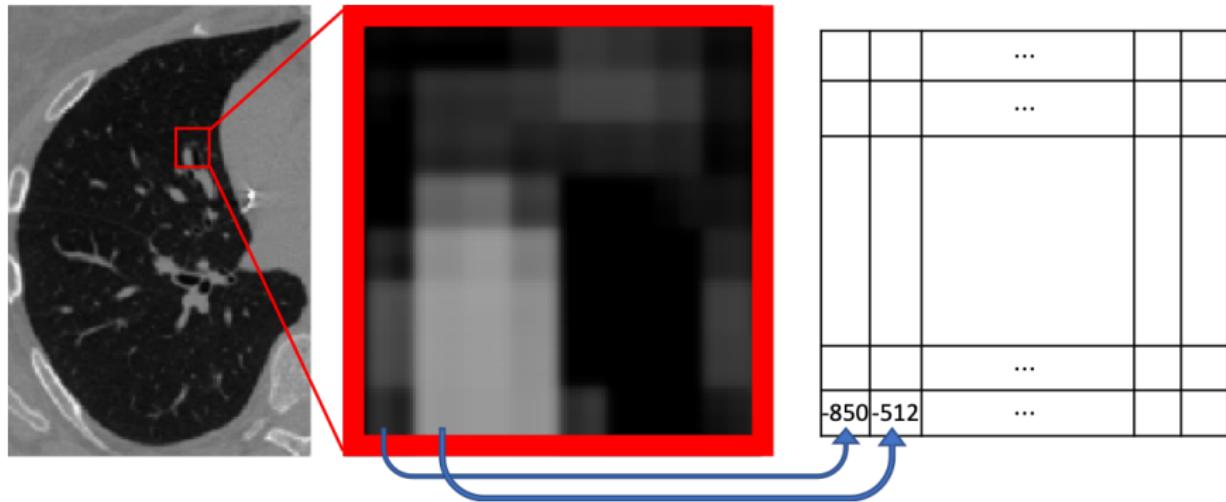
Computed Tomography (CT)

A non-invasive computerized x-ray imaging procedure which generates cross-sectional images of the body



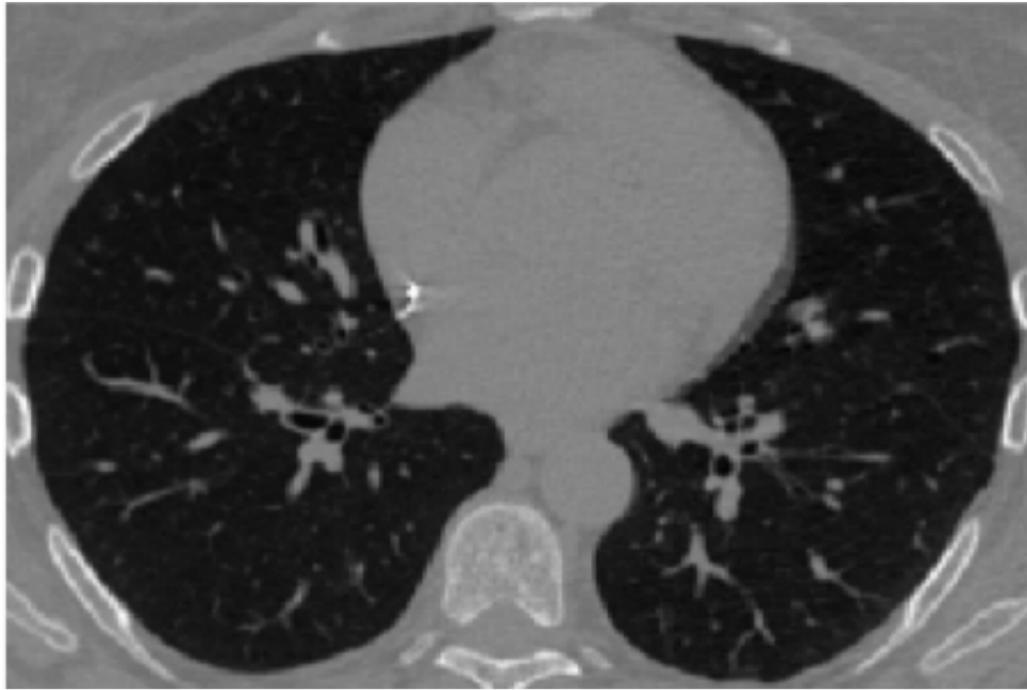
Hounsfield Unit (HU)

A measure of the radiodensity of a pixel from a CT scan

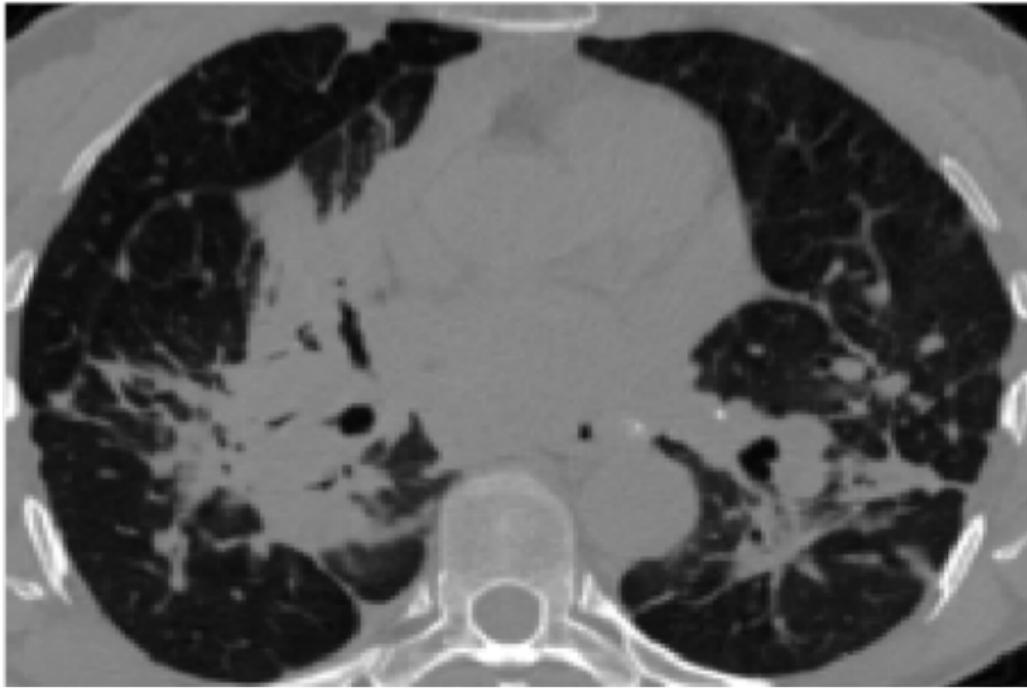


CT Scans of the Lung

Healthy Lung



Fibrotic Lung



An interstitial lung disease characterized by the formation of granulomas in the lung, resulting in compromised lung function and reduced quality of life [Nunes et al., 2005]

- Incidence rate: 8-18 per 100,000 [Baughman et al., 2016]
- Highest rates in Blacks, females

Table: Scadding staging for pulmonary sarcoidosis [Scadding, 1961]

Stage	Chest radiograph findings
0	No chest abnormality
I	Bilateral hilar lymphadenopathy (BHL)
II	BHL and parenchymal abnormality
III	Parenchymal abnormality
IV	Fibrosis with volume loss

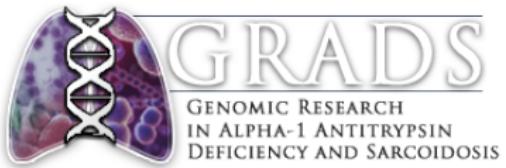


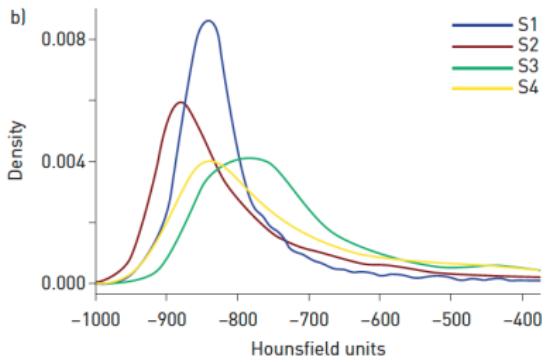
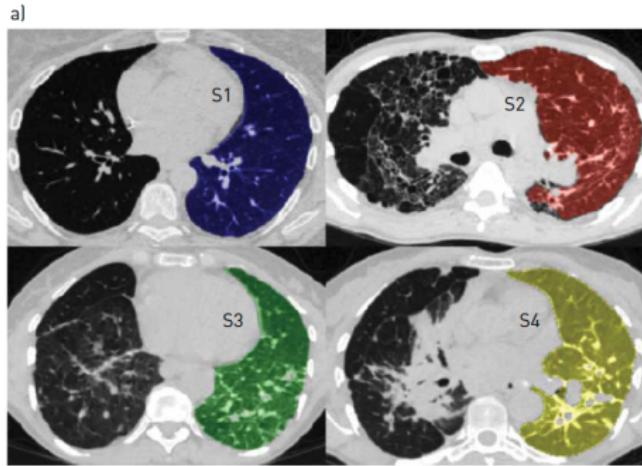
Table: GRADS characteristics

- Data: Demographics, pulmonary function testing, patient reported outcomes
- Research Chest HRCT: Siemens, standard B35f kernel, 0.75mm thickness, 0.5mm computed interval

	Overall
Sample Size	301
Male	142 (47.2)
White	218 (72.9)
Hispanic	14 (4.7)
Age (years)	52.87 (9.75)
Height (in)	67.08 (4.15)
FVC PRED	87.81 (16.75)
FEV1 PRED	84.90 (20.71)
Scadding	
0	40 (13.3)
1	59 (19.6)
2	87 (28.9)
3	43 (14.3)
4	72 (23.9)

Existing Methods for Image Analysis

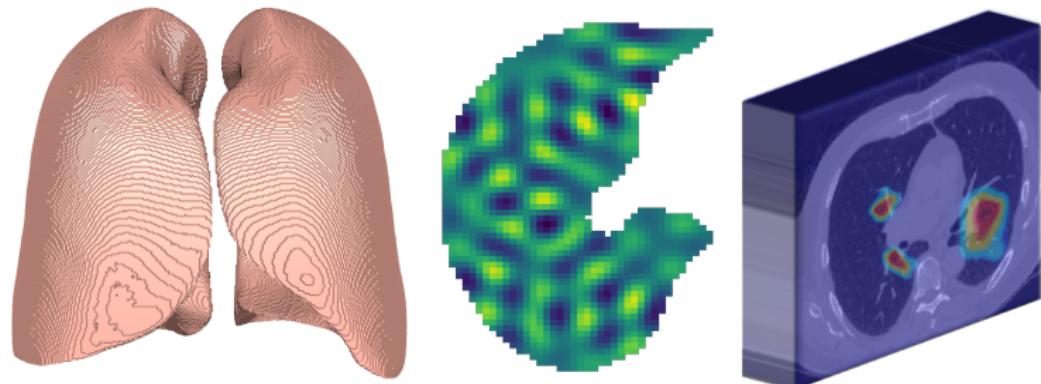
Radiomics: An emerging field in which large numbers of quantitative features are computed from medical images, providing a rapid, objective, and sensitive quantification of lung abnormalities [Ryan et al., 2019a]



Goal: Identify population-level spatial patterns for lung CT scans

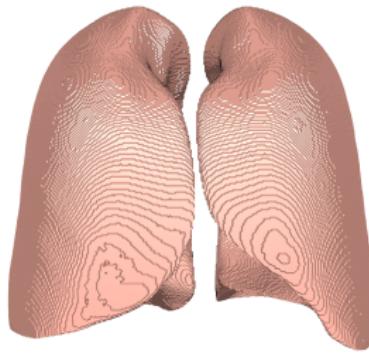
My three primary aims are:

- ① Create a coordinate system to align voxels across scans
- ② Explain the variation in HU throughout the lung using a set of covariates
- ③ Identify novel clusters of CT scans for sub-typing



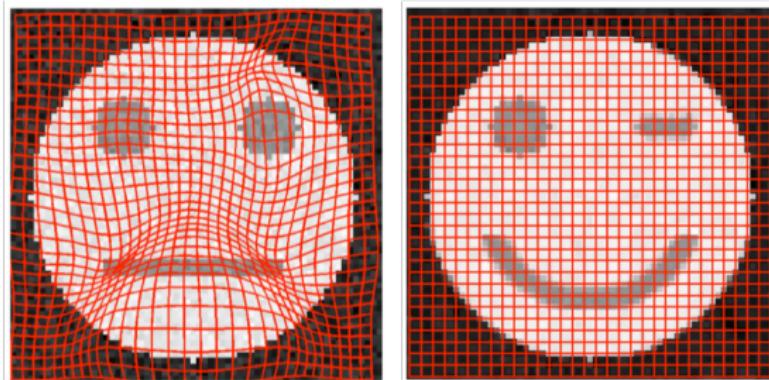
Chapter 2:

Template Creation for High Resolution Computed Tomography Scans of the Lung in R Software

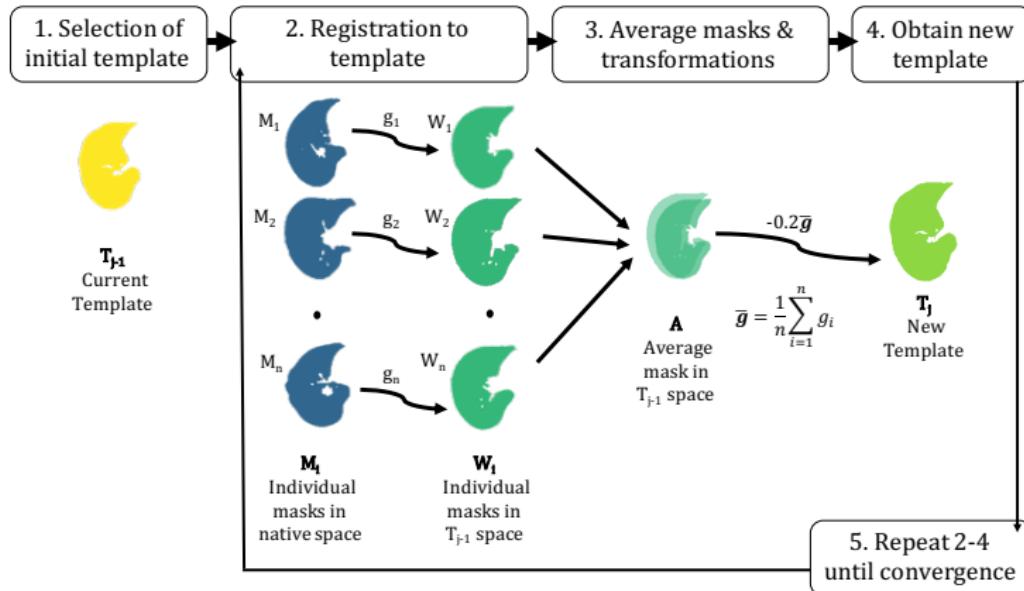


Template

- A **template** is a standardized 3D coordinate frame [Evans et al., 2012]
- By aligning each individual's image to the template, we can:
 - ▶ Identify anatomical regions that differ between groups
 - ▶ Compare findings across studies
 - ▶ Remove potential biases and technical issues related to image size and shape



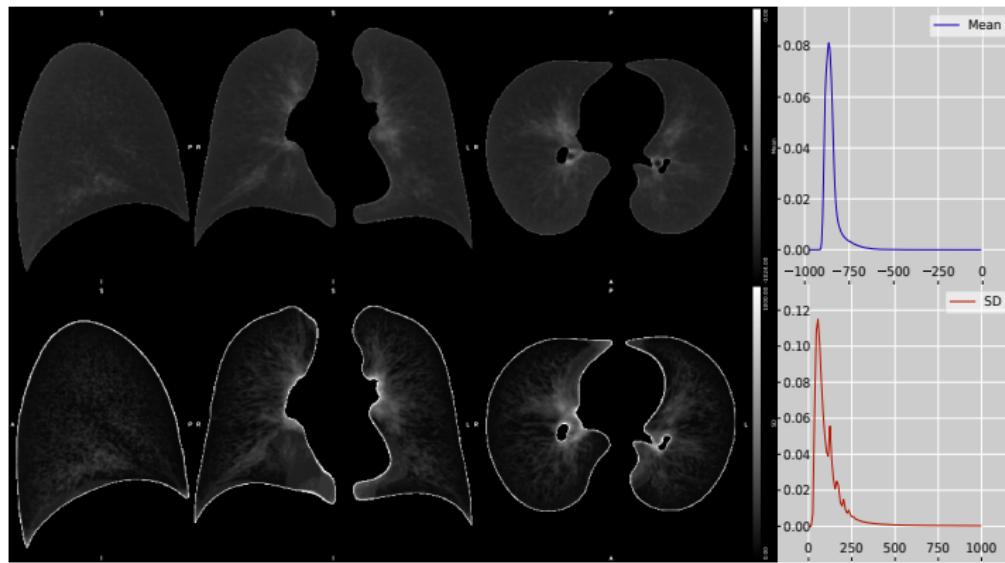
Template Creation [Ryan et al., 2019b]



- Convergence is defined using the Dice similarity coefficient

Standard Lung Template

- Applied to $N = 62$ HRCT scans from a healthy non-smoking adult population [Moller et al., 2015]
- Converged after 14 iterations to average size and shape
- Right lung ≈ 3 L, left lung ≈ 2.6 L (at full-inspiration)



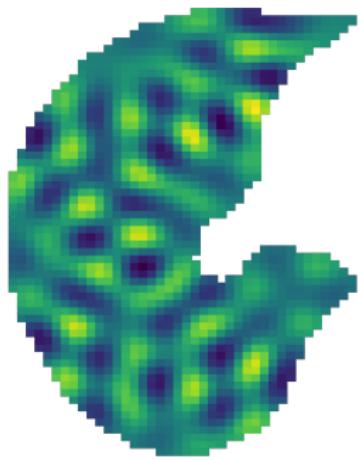
Conclusions of Chapter 2

- ① We create the first publicly available standard lung template using healthy adults, which is available for download via *lungct* [Ryan et al., 2019b]
- ② We develop a fully-automated and open-source image processing pipeline for lung CTs in R software

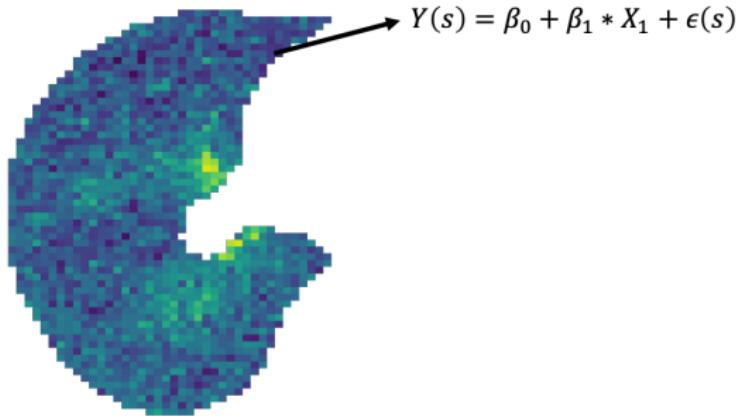


Note: For the remainder of this talk, we will assume all scans have been pre-processed, including the segmentation of the lung from the scans and registration to the lung template.

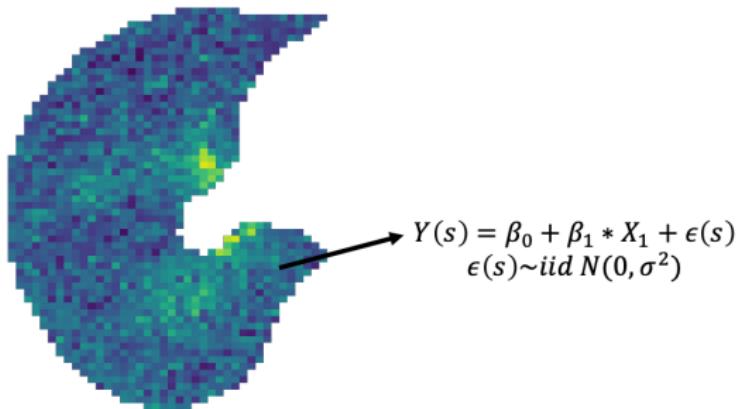
Chapter 3: An Eigenvector Spatial Filtering Model for Lung Imaging Data



- **Voxel-based morphometry (VBM)** is an approach typically used in neuroimaging to find associations between intensity values from brain scans and various covariates [Ashburner and Friston, 2000]
- Traditionally, a separate statistical test is fit on every voxel



- **Voxel-based morphometry (VBM)** is an approach, commonly used in neuroimaging, to find associations between intensity values from scans and various covariates [Ashburner and Friston, 2000]
- Traditionally, a separate statistical test is fit on every voxel



Fails to account for the spatial relationship between voxels
[Bookstein, 2001]

- Many spatial modeling approaches
 - ▶ [Friston and Penny, 2003]
 - ▶ [Smith and Fahrmeir, 2007]
 - ▶ [Brown et al., 2014]
 - ▶ [Musgrove et al., 2016]
 - ▶ [Mejia et al., 2019]
- All rely on assumptions and approximations due to high-dimensionality
- Fast, fully Bayesian spatiotemporal inference for fMRI data
[Musgrove et al., 2016]
 - ▶ Uses MCMC for estimation
 - ▶ Partitions the brain into parcels
 - ▶ Within each parcel, models spatial correlation in residuals using Moran eigenvectors

Eigenvector Spatial Filtering (ESF)

- Spatial models that use Moran eigenvectors are referred to as Eigenvector Spatial Filtering (ESF) models.
- Commonly used to model high-dimensional geographic data [Murakami et al., 2017] [Murakami and Griffith, 2019]
- ESF is a type of low rank approximation, which describes spatial variation in an outcome using a linear combination of L basis functions where $L \ll N$
- Basis functions derived from the eigen-decomposition of a row-standardized spatial correlation function
- Related to Moran's I [Moran, 1950], a common spatial summary measure

$$MC(\mathbf{y}) = \frac{N}{\mathbf{1}'\mathbf{C}\mathbf{1}} \frac{\mathbf{y}'\mathbf{M}\mathbf{C}\mathbf{M}\mathbf{y}}{\mathbf{y}'\mathbf{M}\mathbf{y}}$$

Moran Eigenvectors

- Distance matrix: ($N \times N$) dimension
- Eigenvector design matrix: ($N \times L$) dimension

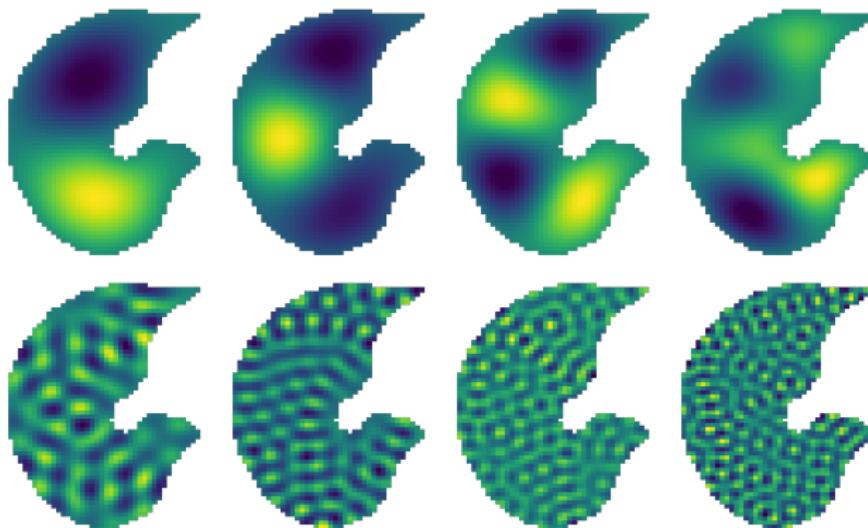
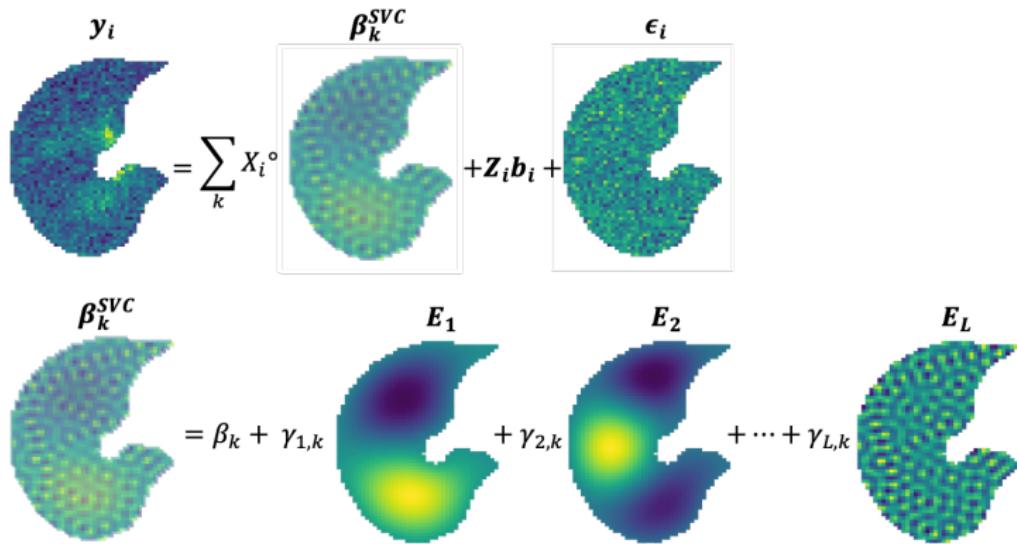


Figure: Moran eigenvectors based on the distance matrix from a 2D axial slice of the lung. The top row corresponds to the 1st - 4th eigenvectors. The bottom row corresponds to the 100th, 200th, 300th, and 397th eigenvectors.

Our spVBM Model

Our spatial voxel-based morphometry, or **spVBM**, for a single subject i is:



$$\gamma_k \sim N(\mathbf{0}, \sigma_k^2 \Lambda(\alpha_k)), \quad \mathbf{b}_i \sim N(\mathbf{0}, D), \quad \epsilon_i \sim N(0, \sigma_\epsilon^2 \mathbf{I})$$

spVBM: Reparameterization

We reparameterize so that the global term $\mathbf{X}\beta$ and spatial term $\tilde{\mathbf{E}}\gamma$ are separated, and we obtain a common variance term across the random variables following [Bates et al., 2014]:

$$\begin{aligned} \mathbf{Y} &= \mathbf{X}\beta + \tilde{\mathbf{E}}\mathbf{V}(\theta)\mathbf{u} + \mathbf{Z}\Omega(\phi)\mathbf{w} + \boldsymbol{\varepsilon}, \quad \mathbf{u}, \mathbf{w}, \boldsymbol{\varepsilon} \sim N(\mathbf{0}, \sigma^2 \mathbf{I}) \\ \tilde{\mathbf{E}} &= [\mathbf{X}_1 \circ \mathbf{E} \cdots \mathbf{X}_K \circ \mathbf{E}] \\ \mathbf{V}(\theta) &= \begin{bmatrix} \mathbf{V}(\theta_1) & & \\ & \ddots & \\ & & \mathbf{V}(\theta_K) \end{bmatrix}, \quad \Omega(\phi) = \begin{bmatrix} \Omega(\phi_1) & & \\ & \ddots & \\ & & \Omega(\phi_H) \end{bmatrix} \end{aligned}$$

where $\mathbf{V}(\theta)\mathbf{u} = \boldsymbol{\gamma}$ and $\Omega(\phi)\mathbf{w} = \mathbf{b}$

The log-likelihood of our model can be expressed as:

$$\log \text{lik}(\beta, \theta, \phi, \sigma^2) = -\frac{N}{2} \log(2\pi\sigma^2) - \log(|\mathbf{V}(\theta)|^2) - \log(|\Omega(\phi)|^2) - \frac{d(\theta, \phi)}{\sigma^2}$$

$$d(\theta, \phi) = \|\mathbf{y} - \mathbf{X}\beta - \mathbf{E}\mathbf{V}(\theta)\mathbf{u} - \mathbf{Z}\Omega(\phi)\mathbf{w}\|^2 + \|\mathbf{u}\|^2 + \|\mathbf{w}\|^2$$

Then, the best linear unbiased estimates of β , \mathbf{u} and \mathbf{w} are found by maximizing the log-likelihood:

$$\begin{bmatrix} \hat{\beta} \\ \hat{\mathbf{u}} \\ \hat{\mathbf{w}} \end{bmatrix} = \mathbf{P}^{-1} \begin{bmatrix} \mathbf{X}'\mathbf{y} \\ \mathbf{V}(\theta)\tilde{\mathbf{E}}'\mathbf{y} \\ \Omega(\phi)\mathbf{Z}'\mathbf{y} \end{bmatrix}$$

$$\mathbf{P} = \begin{bmatrix} \mathbf{X}'\mathbf{X} & \mathbf{X}'\tilde{\mathbf{E}}\mathbf{V}(\theta) & \mathbf{X}'\mathbf{Z}\Omega(\phi) \\ \mathbf{V}(\theta)\tilde{\mathbf{E}}'\mathbf{X} & \mathbf{V}(\theta)\tilde{\mathbf{E}}'\tilde{\mathbf{E}}\mathbf{V}(\theta) + \mathbf{I} & \mathbf{V}(\theta)\tilde{\mathbf{E}}'\mathbf{Z}\Omega(\phi) \\ \Omega(\phi)\mathbf{Z}'\mathbf{X} & \Omega(\phi)\mathbf{Z}'\tilde{\mathbf{E}}\mathbf{V}(\theta) & \Omega(\phi)\mathbf{Z}'\mathbf{Z}\Omega(\phi) + \mathbf{I} \end{bmatrix}$$

Variance parameters θ, ϕ, σ^2 are estimated using residual maximum likelihood estimation (REML)

- Interested in $\hat{\beta}_k^{SVC}$
- Voxel-level null hypothesis that $\hat{\beta}_k^{SVC}(s) = 0$
- Wald statistic: $W(s) = \frac{(\hat{\beta}_k^{SVC}(s)-0)^2}{Var(\hat{\beta}_k^{SVC}(s))}$
- Multiple comparisons correction: Benjamini-Hochberg (BH)
[Benjamini and Hochberg, 1995, Mejia et al., 2019]

Simulation Study

- Simulated 2D lung slices, with varying disease abnormalities
- Also varied sample size, SNR
- Compared spVBM to VBM

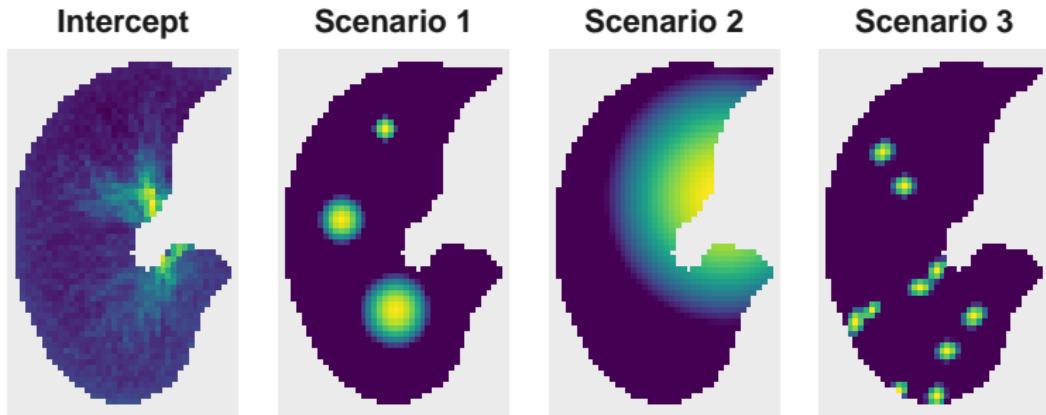


Figure: Simulated β^{SVC} for each scenario.

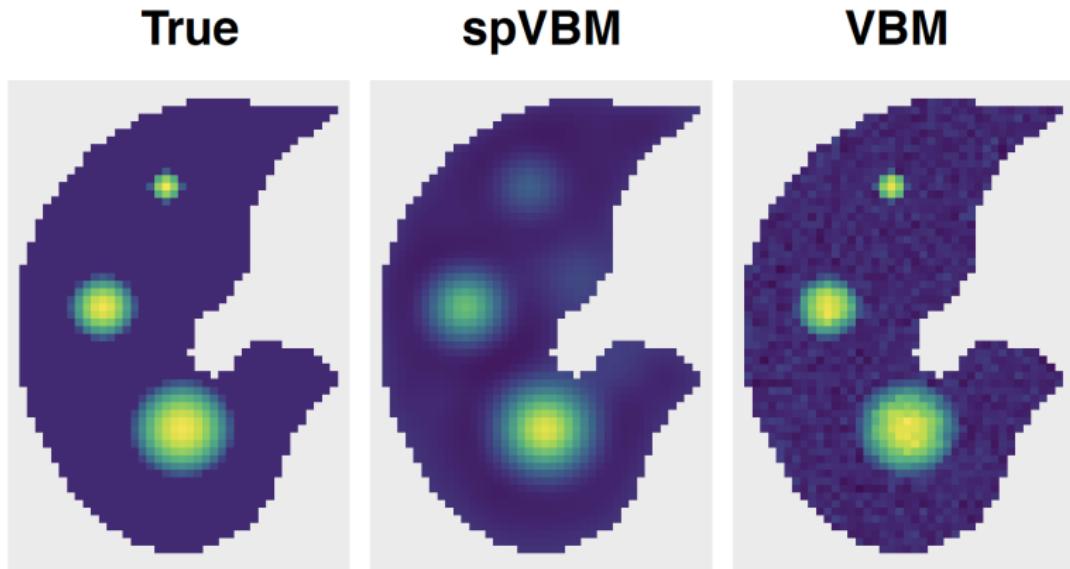


Figure: Estimated β_1^{SVC} for Simulation Scenario 1

$$\hat{\beta}_1^{SVC} > 0$$

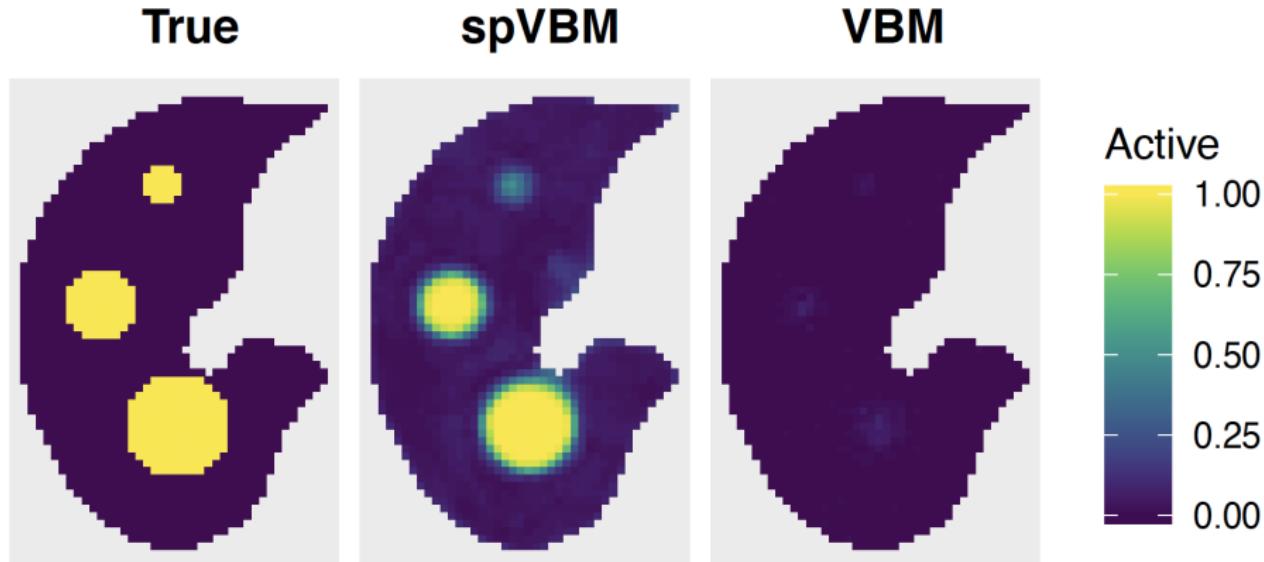


Figure: Proportion of simulations from Scenario 1 in which $\hat{\beta}_1^{SVC}(s)$ reached significance at $\alpha = 0.05$ after BH correction.

TPR: spVBM = 0.76, VBM = 0

- **Data:** GRADS
- **Methods:**
 - ▶ Pre-processing: Segmentation, Registration
 - ▶ Resampled to 3mm³ for computation (Right: 29K non-null voxels. Left: 24K non-null voxels)
 - ▶ Created eigenvector matrix (Right: 419 eigenvectors. Left: 385 eigenvectors)
- **spVBM analysis:**
 - ▶ Difference in HU between Scadding stage 4 (fibrosis) and stage 0 (healthy)
 - ▶ Association between HU and FEV1

Results

Compared to stage 0 patients (healthy), patients with stage 4 (fibrosis) have areas of significantly higher intensity near the hilar region.

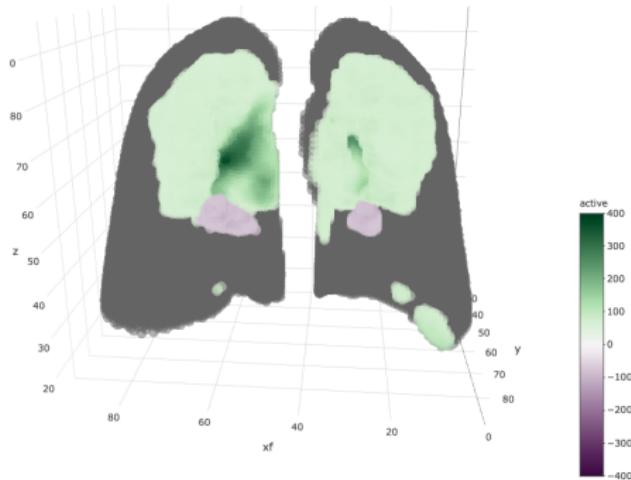


Figure: Statistical parametric map indicating the difference in HU between stage 0 and 4 Scadding, with colored values representing statistically significant effects at $|t| < 10$ after BH correction.

See in 3D

Results

FEV1 is significantly associated with HU throughout the whole lung.

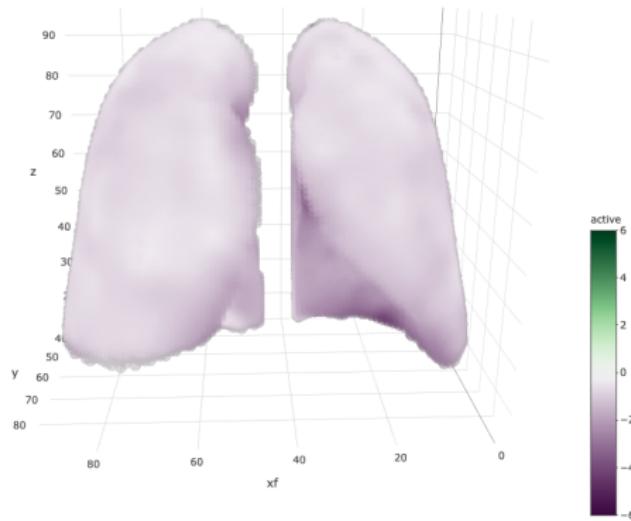
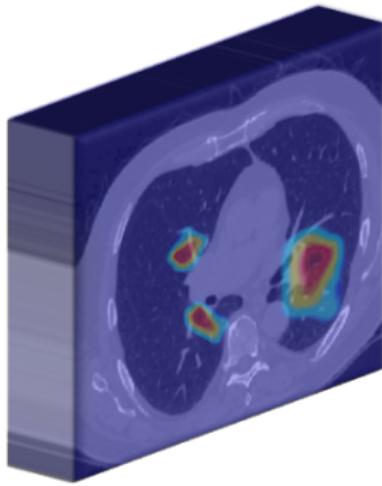


Figure: Statistical parametric map indicating the effect of FEV1 on HU, with colored values representing statistically significant effects at $p < 0.05$ after BH correction.

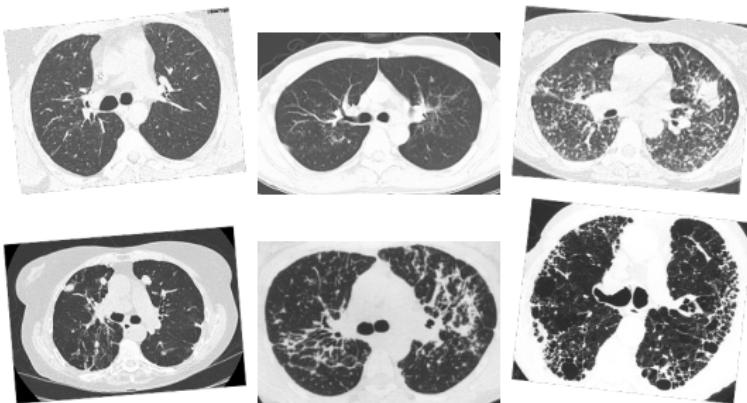
See in 3D

Chapter 4: Cluster Activation Mapping with Applications to Medical Imaging Data



Motivation

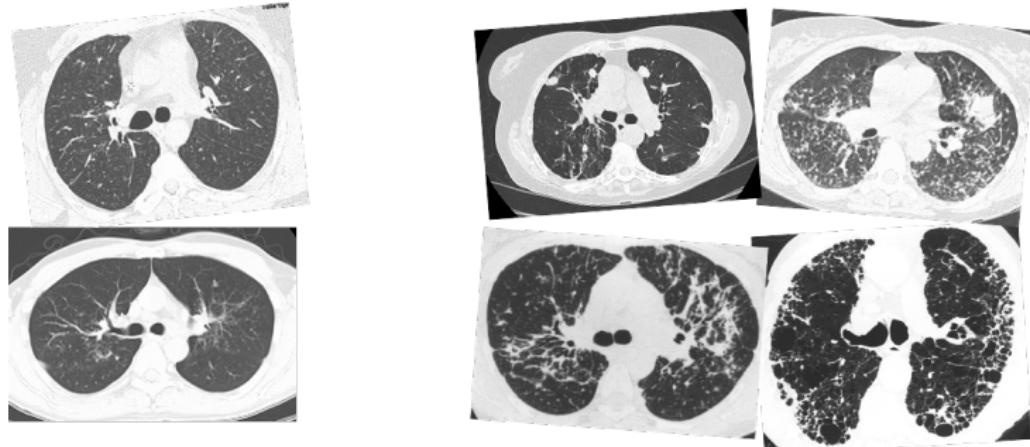
- Vast amounts of medical imaging datasets are becoming available, BUT annotation of these images is difficult
- Traditionally, we rely on visual assessment for annotation, which can be subjective, costly and slow to obtain
- This is especially true for sarcoidosis, which can have many disease manifestations on CT scans [Sluimer et al., 2006]



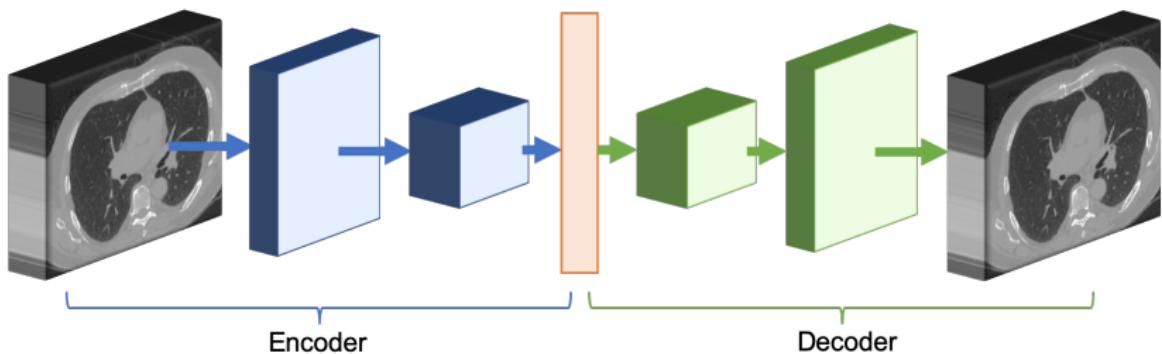
Motivation

For unlabeled or poorly labeled medical imaging datasets, such as sarcoidosis, we want to develop a data-driven method to:

- ① Assign labels to images to develop new disease subtypes
- ② Understand the reasoning behind the label, which is essential to its adoption in clinical practice

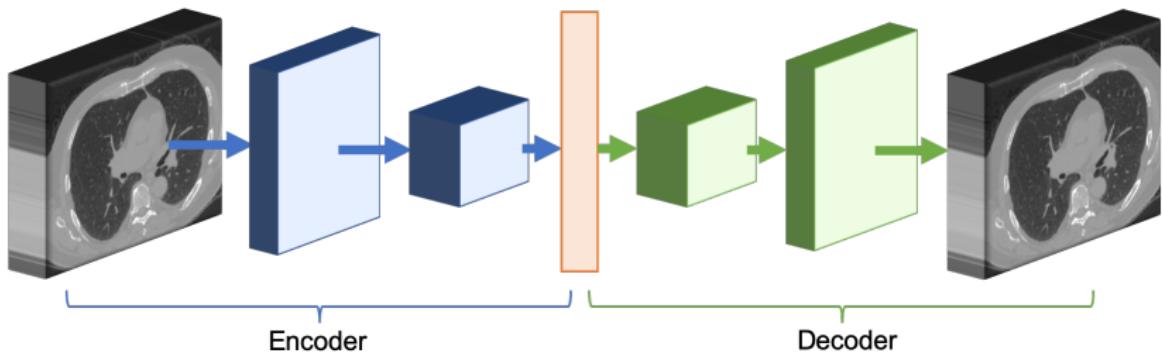


- Deep clustering is a recent methodology which assigns images into clusters using unsupervised machine learning networks, specifically autoencoders [Guo et al., 2017, Afshar et al., 2018, Masci et al., 2011, Xie et al., 2016]



Deep Clustering

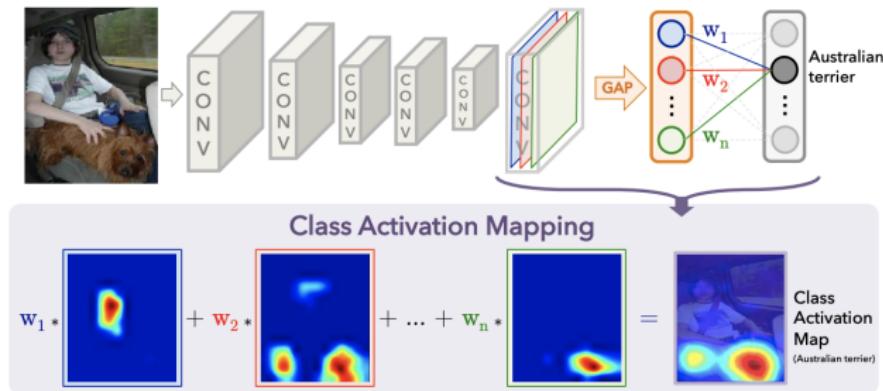
- Deep clustering is a recent methodology which assigns images into clusters using unsupervised machine learning networks, specifically autoencoders [Guo et al., 2017, Afshar et al., 2018, Masci et al., 2011, Xie et al., 2016]



- While these methods have proven successful for clustering images, they provide no understanding as to why an image is assigned to a particular cluster.

Class Activation Mapping (CAM)

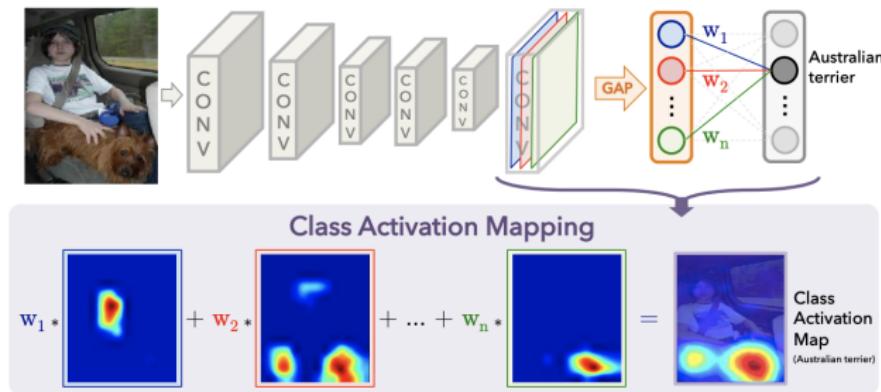
- In *supervised* machine learning, class activation maps are used to highlight the discriminative region from the original image used by the neural network to identify that category [Zhou et al., 2016]



- Other methods include: GradCAM, GradCAM++, Score-CAM [Selvaraju et al., 2017, Wang et al., 2019]

Class Activation Mapping (CAM)

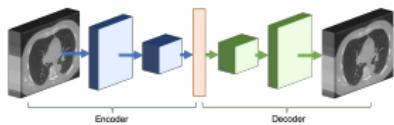
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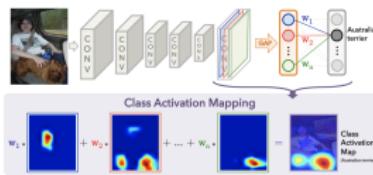
- No comparable methods exist in the *unsupervised* setting, such as in clustering

Our Methodology

Deep Clustering



Class Activation Mapping



Cluster Activation Mapping (CLAM)

CLuster Activation Mapping (CLAM)

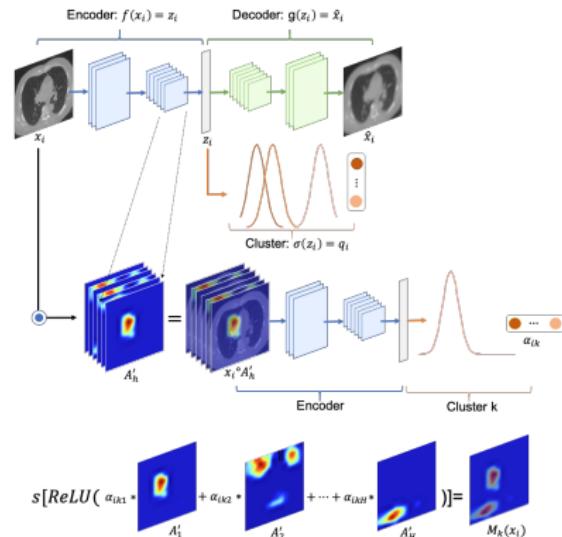
To create a CLAM for a particular image, we perform the following:

① Training

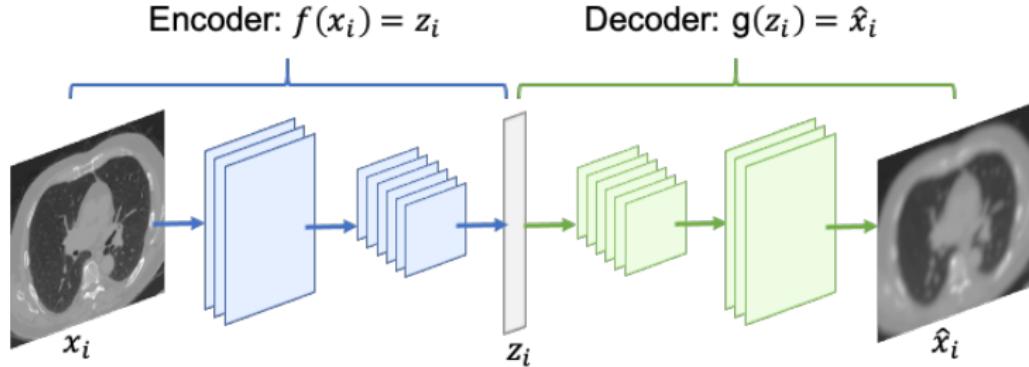
② Clustering

③ Weighting

④ Combining

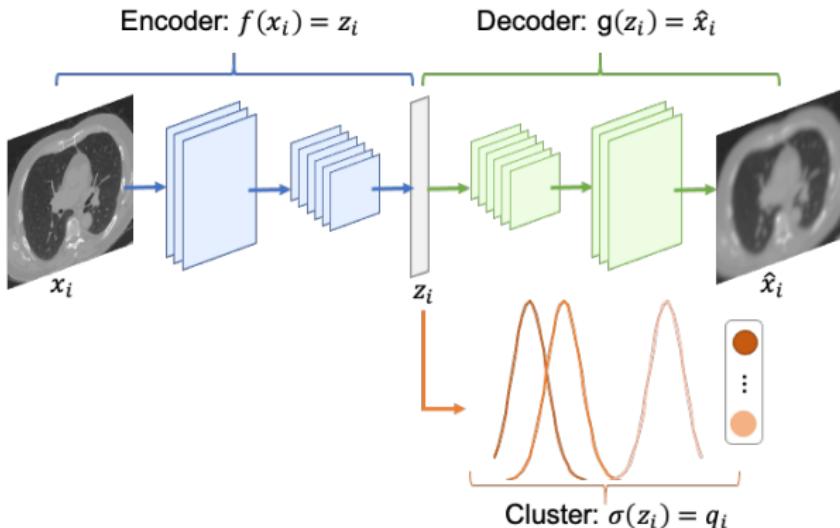


1. Training



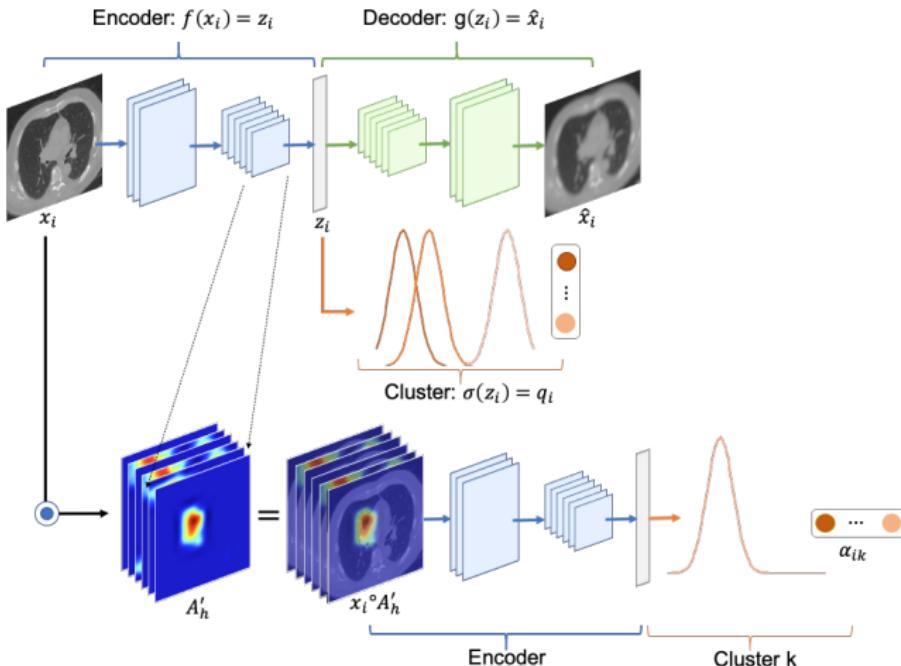
- Layers: Convolutional
- Loss function: $L_r = \sum_{i=1}^N \sum_{s=1}^S [x_i(s) - \hat{x}_i(s)]^2$
- Optimization function: Adaptive moment (Adam)

2. Clustering



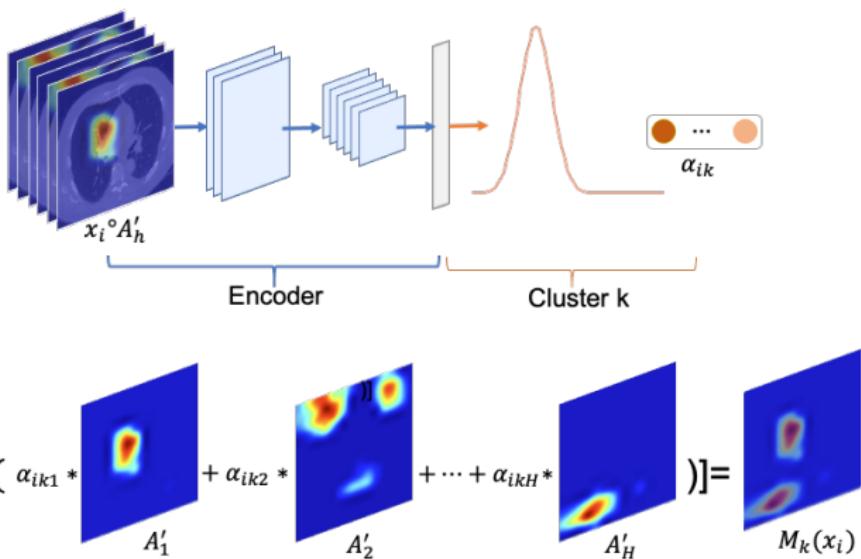
- Clustering layer: $q_{ik} = \frac{\left[1 + \sum_{j=1}^J (z_{i,j} - \mu_{k,j})^2\right]^{-1}}{\sum_{k=1}^K \left[1 + \sum_{j=1}^J (z_{i,j} - \mu_{k,j})^2\right]^{-1}}$
- Clustering loss: $L_c = KL(P||Q)$
- Total loss: $L = L_r + \gamma L_c$

3. Weighting



- Last convolutional layer used to create the activation map
- CLAM created for the cluster with the highest probability

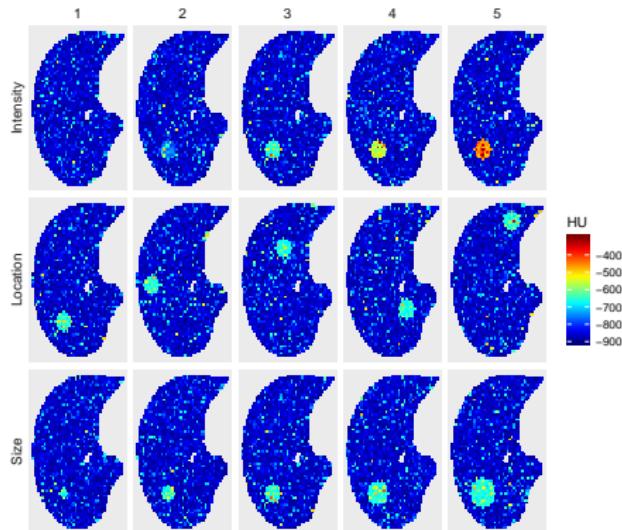
4. Linear Combination



- ReLU used to only keep sections with positive influence
- Normalized between [0, 1], so the most discriminative region is 1
- *Importance* - unit of measurement for the CLAMs

Simulation Study

- Simulated lung slices, varying either the intensity, location or size of the abnormalities
- $N=300$ scans, $k = 3, 4, 5$ clusters
- Ran for 200 epochs in training, then 500 epochs for clustering



Simulation Study

- All simulations resulted in 100% accuracy for cluster assignment, when the number of clusters is set at the true value
- CLAM successfully identified the region of the simulated abnormality in all cases.

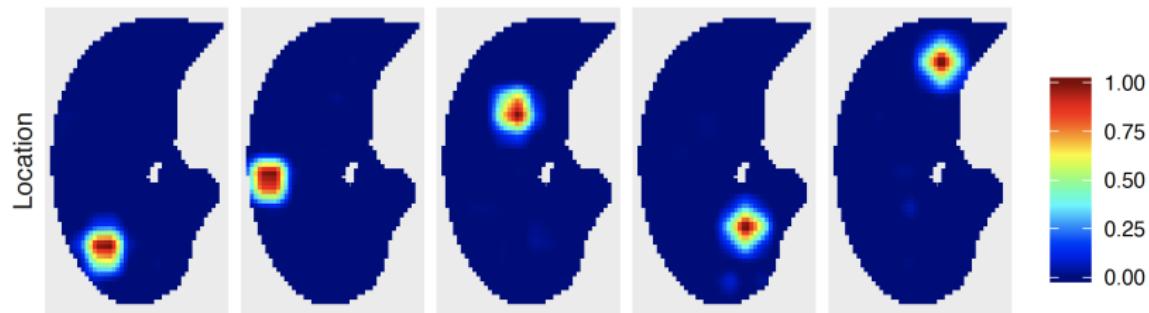


Figure: CLAMs from the simulation when $K = 5$ and location is varied

- **Data:** GRADS
- **Methods:**

- ▶ Pre-processing: Segmentation, Registration
- ▶ Resampling: $3mm^3$ voxel spacing
- ▶ CAE structure: $3D \ conv_{32}^2 \rightarrow conv_{64}^2 \rightarrow conv_{128}^2 \rightarrow FC_{60}$, with stride length of 2
- ▶ Ran for 200 epochs in training, then 500 epochs for clustering
- ▶ Estimated the optimal number of clusters using the average silhouette method after training [Rousseeuw, 1987]

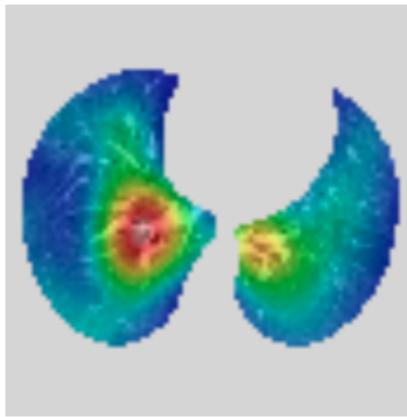
Results

Table: Demographic features from sarcoidosis population by cluster assignment

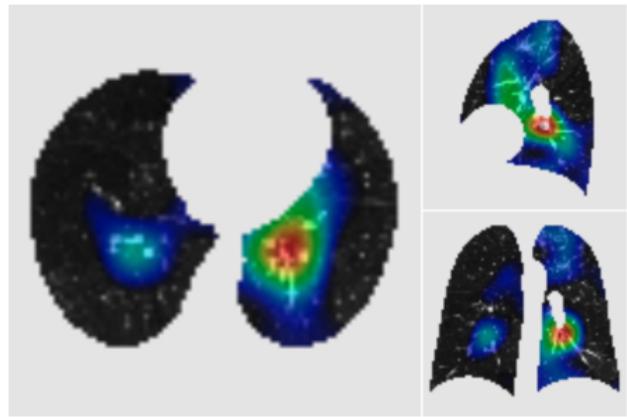
	Cluster 1	Cluster 2	P-value
Sample Size	126	175	
Male (%)	51 (40.5)	91 (52.0)	0.063
White (%)	77 (61.1)	141 (80.6)	<0.001
Hispanic (%)	8 (6.4)	6 (3.4)	0.355
Age (mean (sd))	53.58 (9.32)	52.36 (10.04)	0.287
BMI (mean (sd)))	31.05 (7.05)	30.20 (6.16)	0.267
Height (mean (sd))	66.52 (3.96)	67.49 (4.24)	0.045
Scadding (%)			<0.001
0	7 (5.6)	33 (18.9)	
1	17 (13.5)	42 (24.0)	
2	32 (25.4)	55 (31.4)	
3	16 (12.7)	27 (15.4)	
4	54 (42.9)	18 (10.3)	

CLAM superimposed on Images

Cluster 1



Cluster 2



See in 3D

Clinical Importance

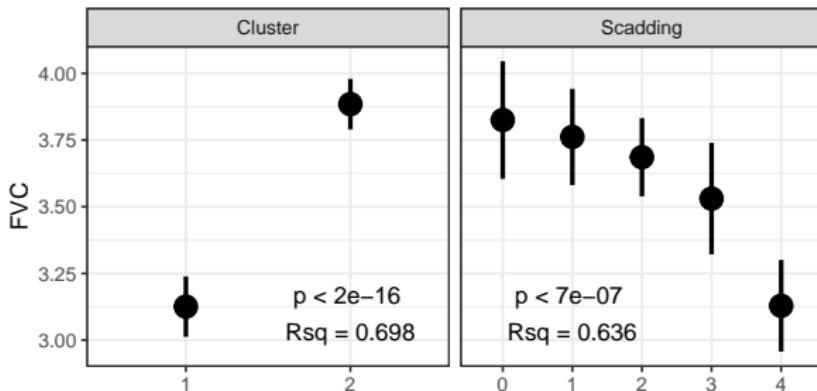


Figure: Associations between forced vital capacity (FVC) with our new clusters and Scadding stage. Results are presented mean (95% CI), adjusted for age, sex, race, BMI, height.

- FEV1, DLCO, SOBQ and SF-12 Physical scores also showed a significant association with our clusters, and explained more variation in these outcomes than Scadding stage.

Chapter 5:

Conclusion

We have developed three novel statistical methodologies for lung CT:



We created a publicly available standard lung template, along with an R software package called lungct.



We developed a population-level spatial modeling approach for lung CT scans, called spVBM.



We developed methodology to cluster lung CTs and to identify the cluster-specific discriminative regions from the images, which we call CLAM.

Together, these methodologies advance the field of lung imaging by providing novel methodologies and publicly available software to perform population-level inference and clustering for lung CT scans

Improved Clinical Understanding



We identified the average size and shape of the lungs from a healthy adult population in the U.S., enabled spatial comparisons across lung scans, and improved existing methodologies by removing biases related to differences in size and shape of the lung.



In pulmonary sarcoidosis, patients with Stage 4 (fibrosis) see increased HU near the hilar compared to patients with Stage 0 (no pulmonary involvement). HU is also significantly associated with lung function at a global level.



Applied to GRADS, we identified two clusters of patients with pulmonary sarcoidosis using just the CT scans, which are better predictors of PFTs and PROs than Scadding stage, the current classification

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