Statistical Methodology for Computed Tomography Scans of the Lungs

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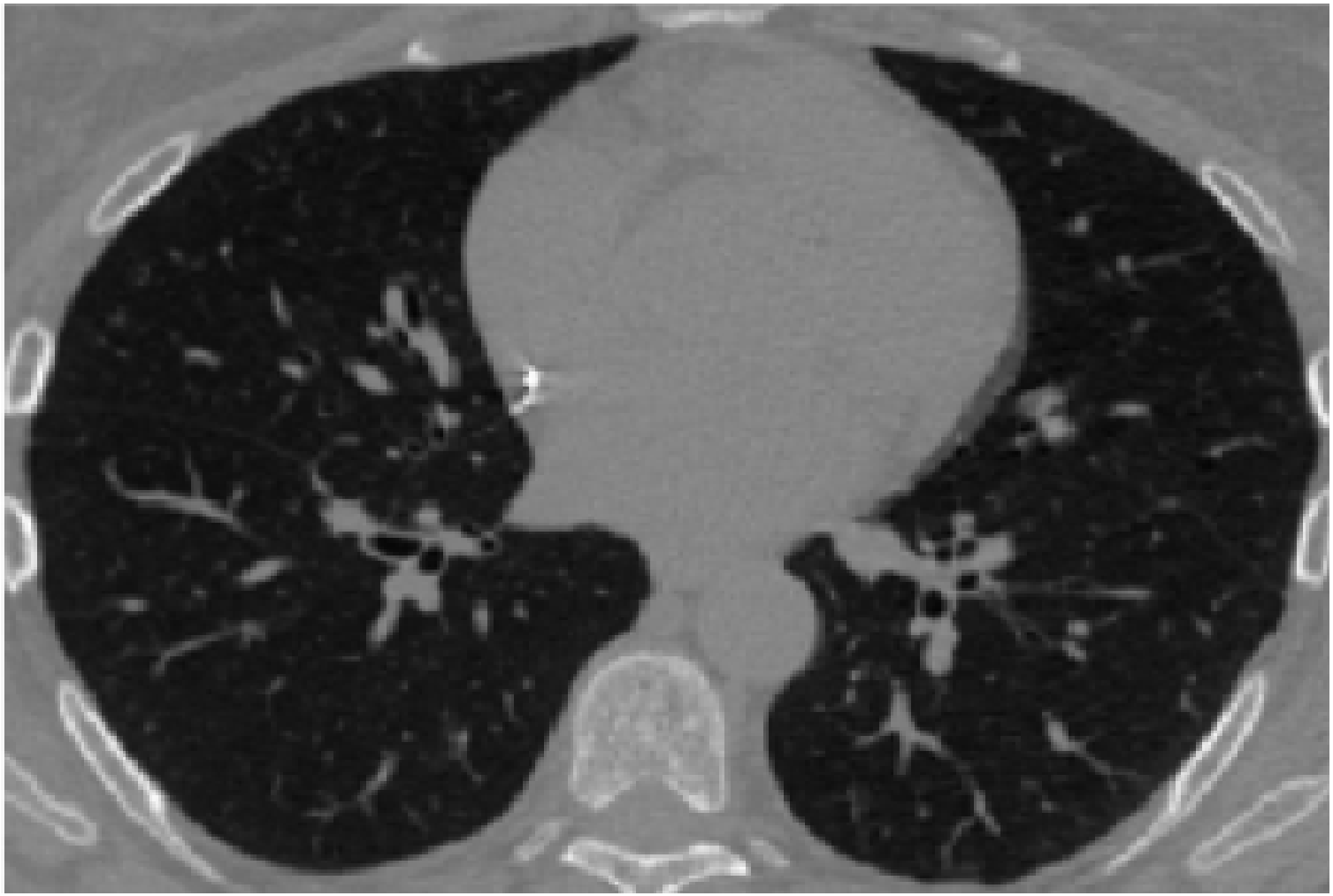
January 27, 2020

Computed Tomography (CT)

A computerized x-ray imaging procedure which generates cross-sectional images of the body that can be combined to form three-dimensional images

CT Scans of the Lung

Healthy Lung

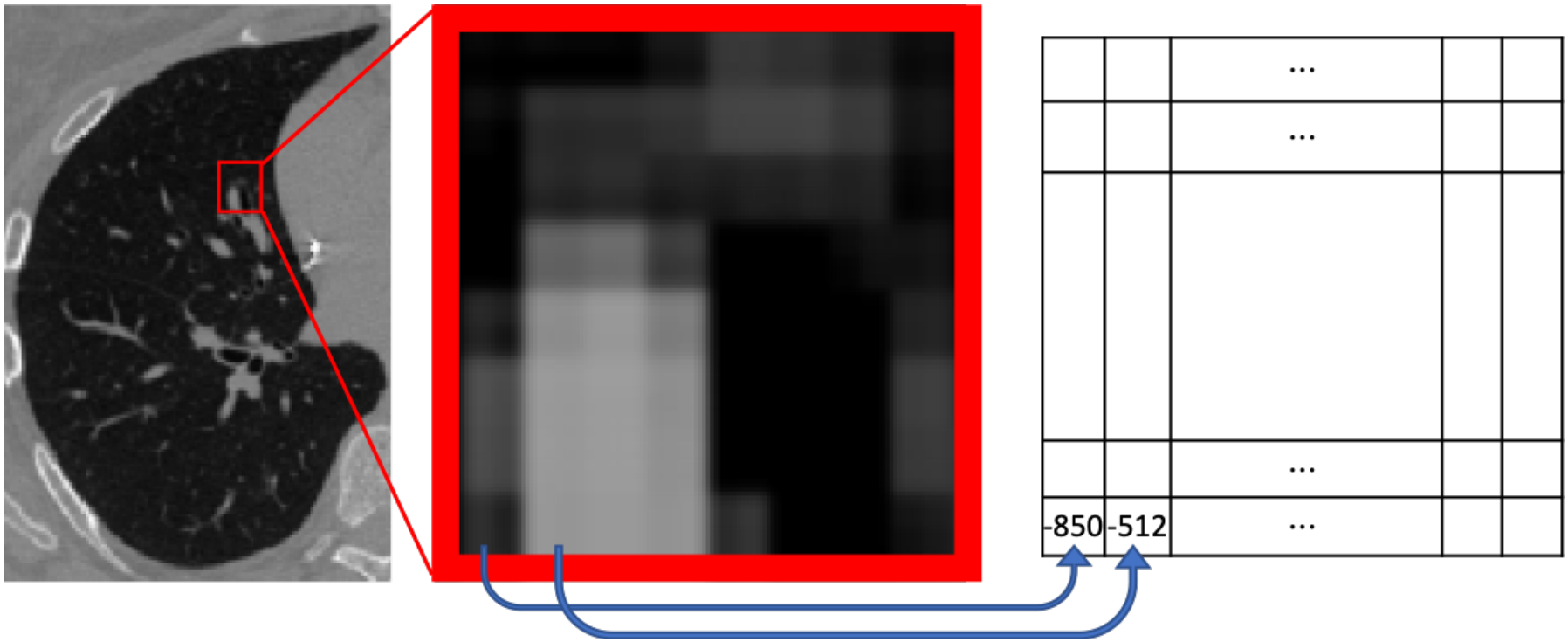


CT Scans of the Lung

Fibrotic Lung

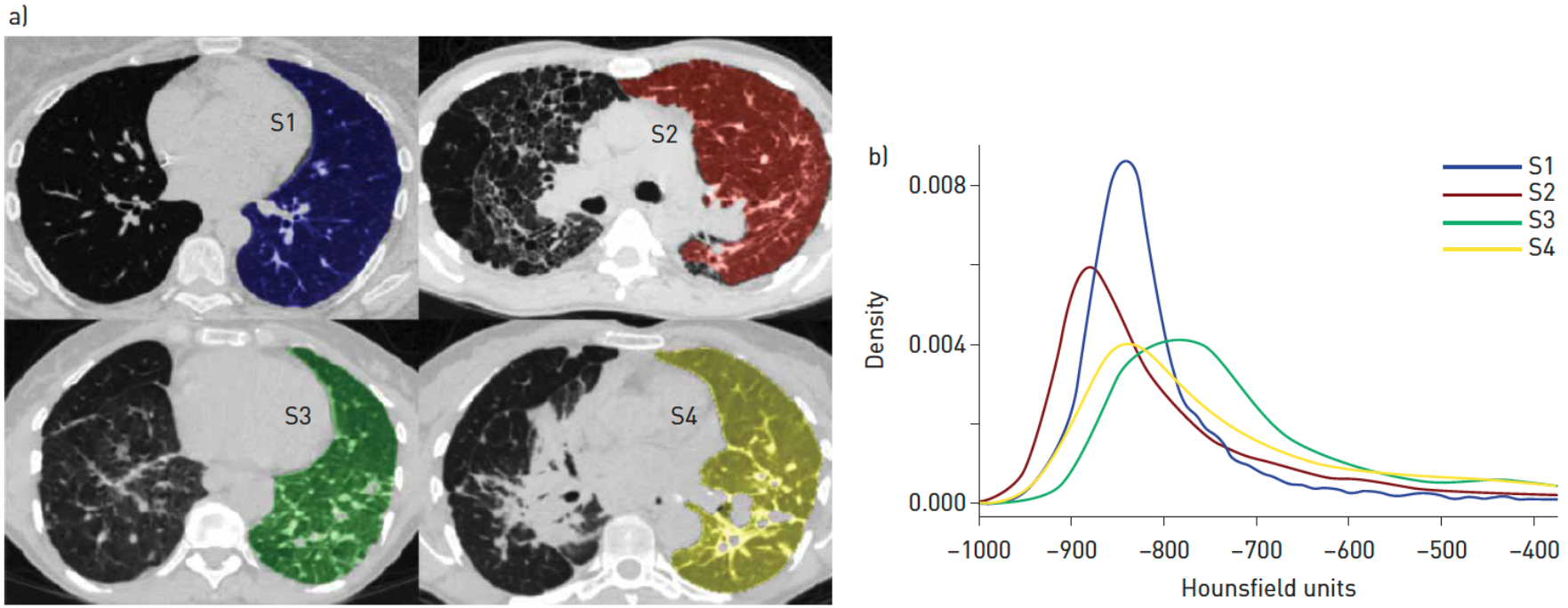
CT Scans are Data

Hounsfield Unit (HU): A measure of the radiodensity of a pixel from a CT scan



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]



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Clinical Question:

Where is disease commonly found in the lung?

Methodological Questions:

1. **How do we align spatial coordinates across scans when scans are different sizes and shapes?**
2. **After aligning spatial coordinates across scans, how do we identify significant areas of disease?**

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   - **Create a lung template**

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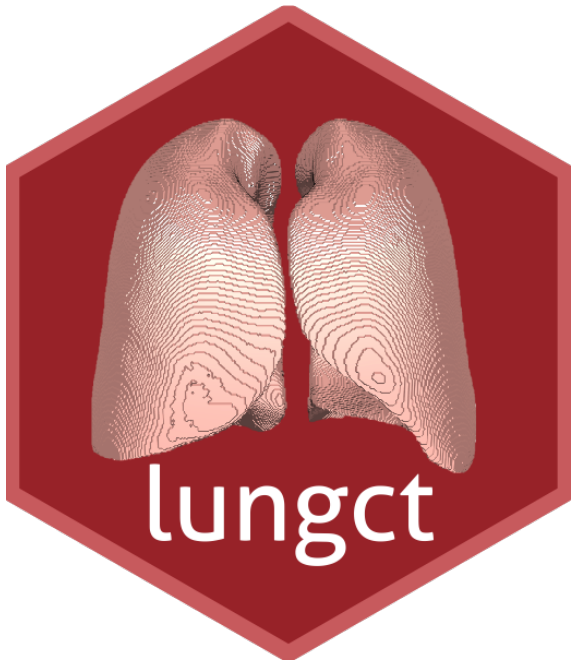
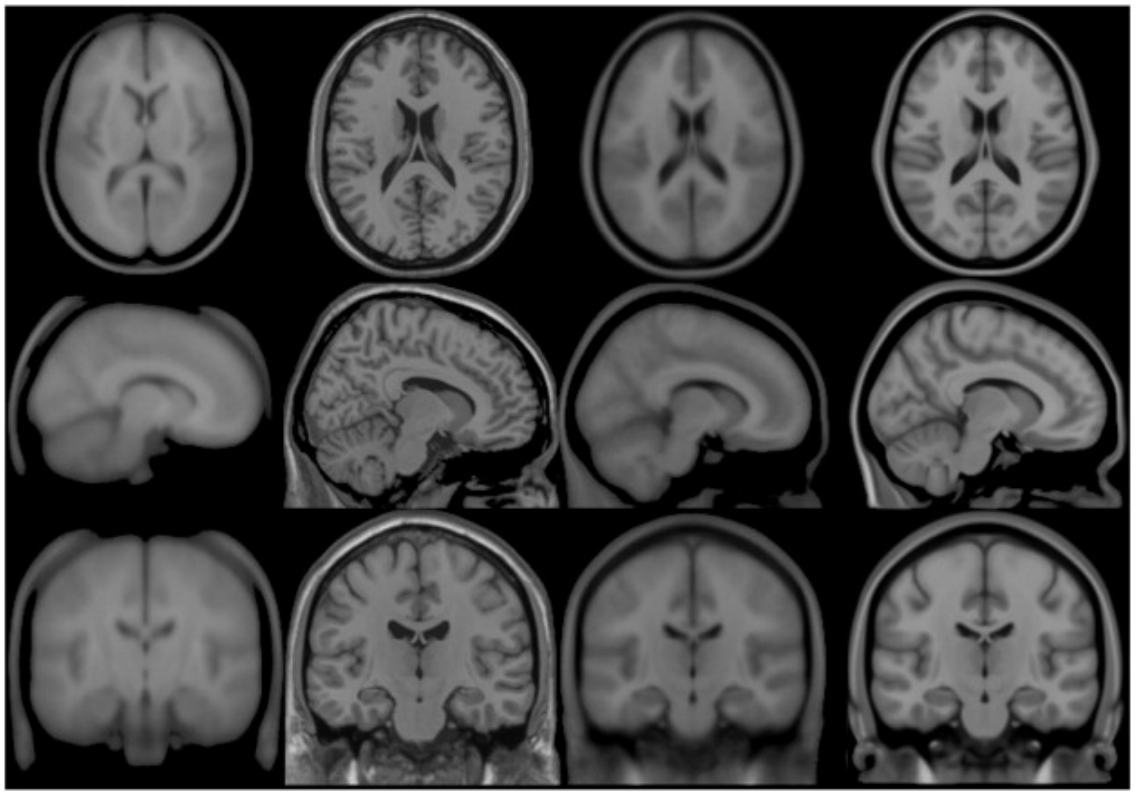
   - **Develop a spatial model for whole-lung population-level inference**

Create a Lung Template *(with R!)*

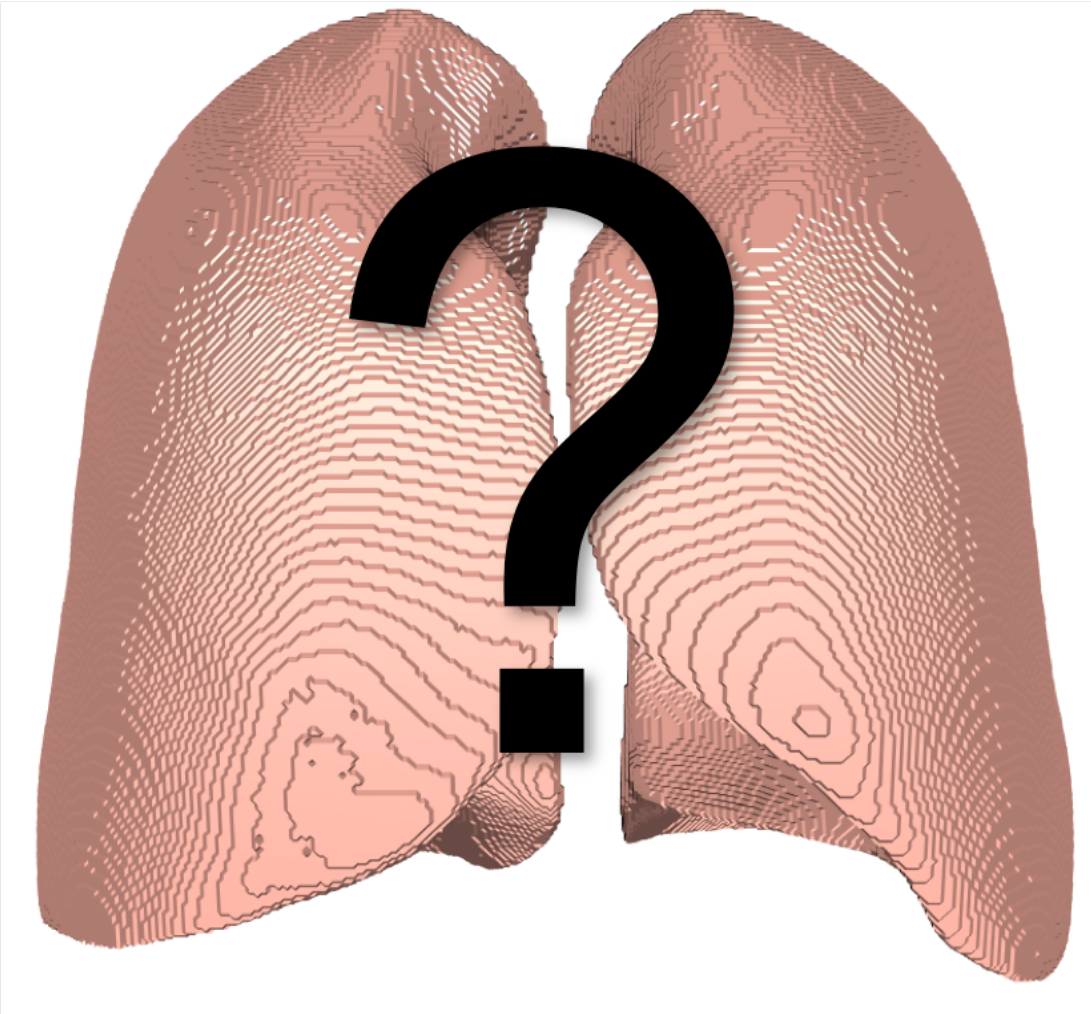


Templates

A **template** is a standardized 3D coordinate frame which allows researchers to combine data across subjects and/or studies [Evans et al., 2012].



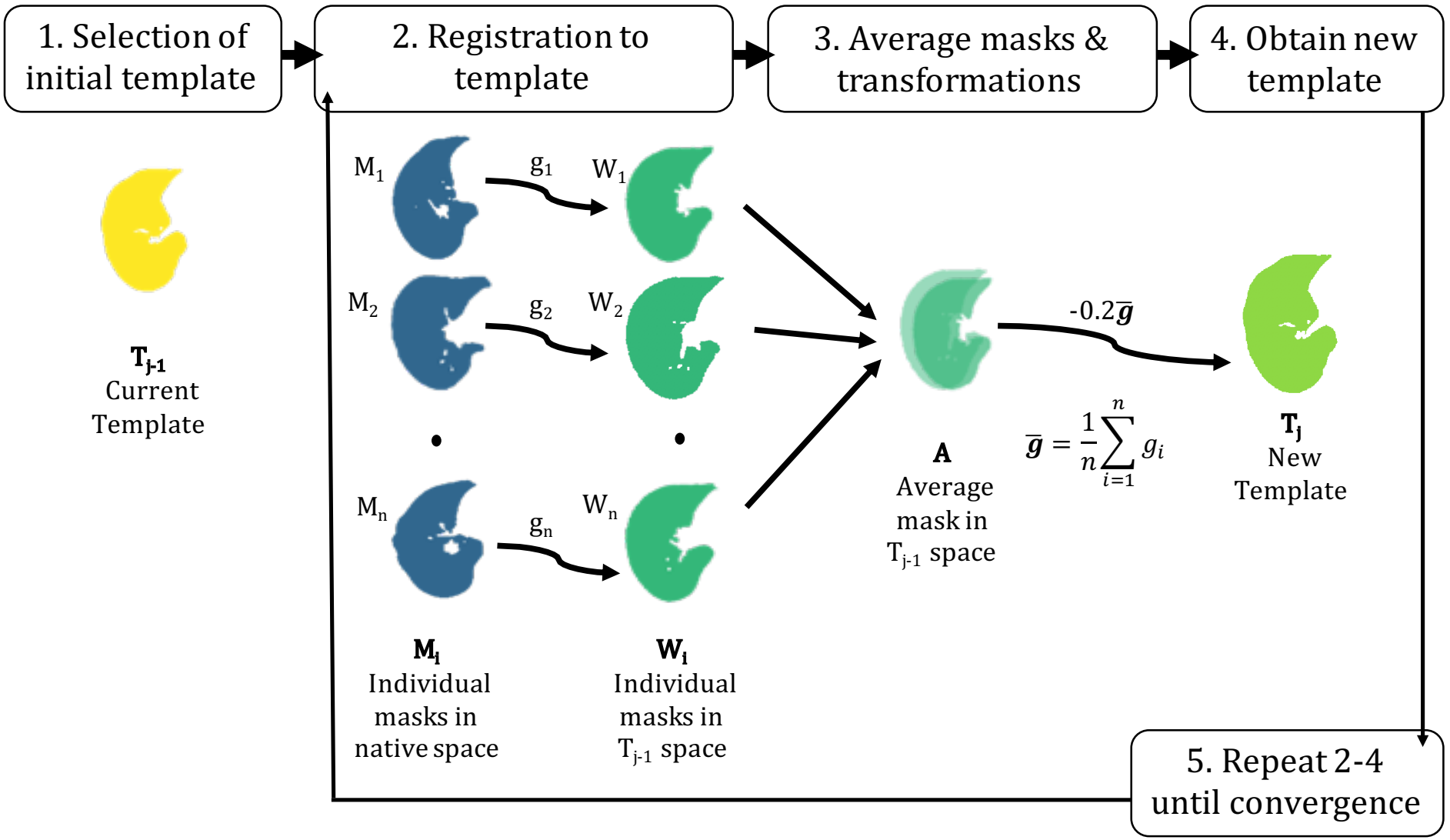
There is no standard lung!



Healthy Population

- **COPDGene** is a cross sectional prospective cohort of smokers with and without COPD, with a goal to perform epidemiological and genetic studies [Regan et al., 2011]
- A small (100) group of similar aged non-smokers without COPD were enrolled to provide a comparison point for CT scans in the aging lung
- We used $\mathbf{N = 62}$ adult subjects, with equal proportions of males/females, age range: 51-72 years.

Template Creation

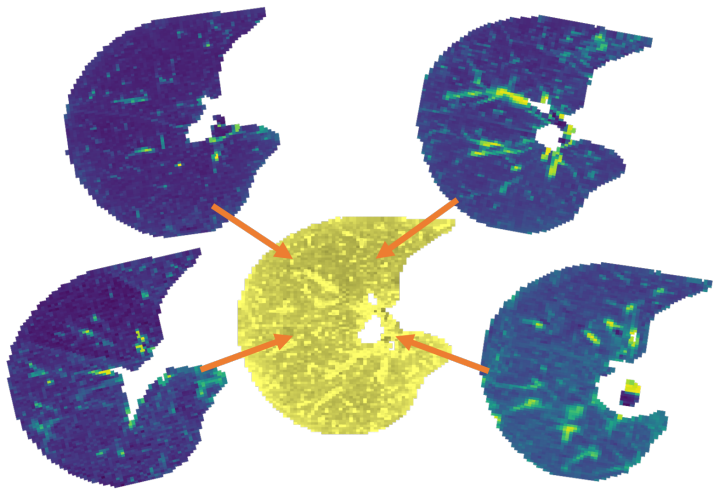


[Ryan et al., 2019b]

Notes on Registration

Registration is the procedure of transforming voxels from their original space into a common space

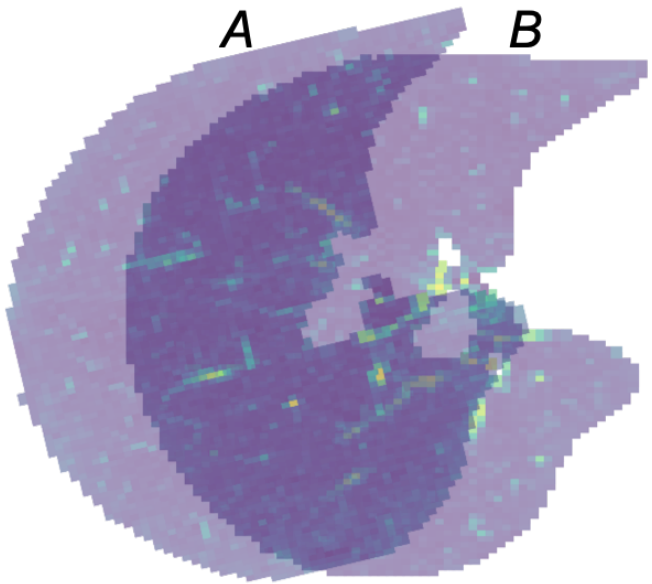
- Left and right lungs were registered separately to account for differences in lung shape and size
- Symmetric Normalization (SyN) non-linear registration was used due to its flexibility and success in EMPIRE10 Challenge [Avants et al., 2008]

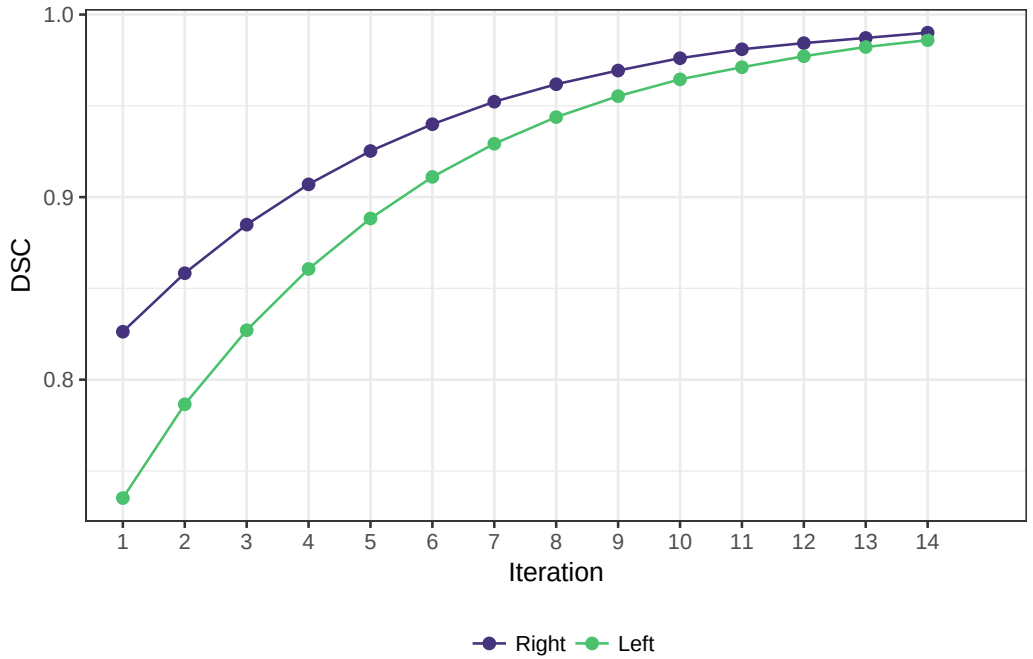


Convergence Criteria

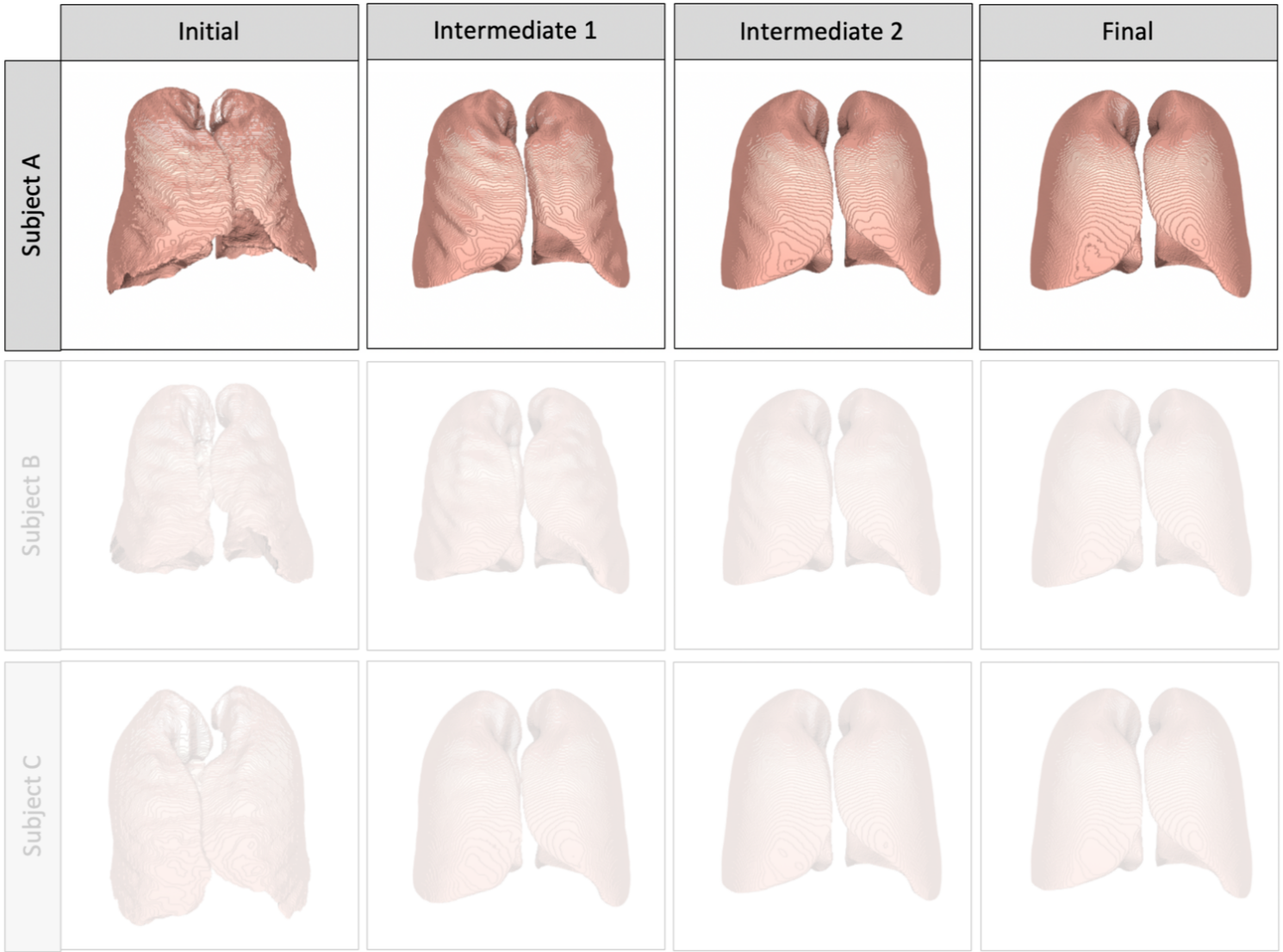
We define convergence using a dice similarity coefficient (DSC) between successive iterations of at least 0.99

$$DSC(A, B) = \frac{2|A \cap B|}{|A| + |B|}$$

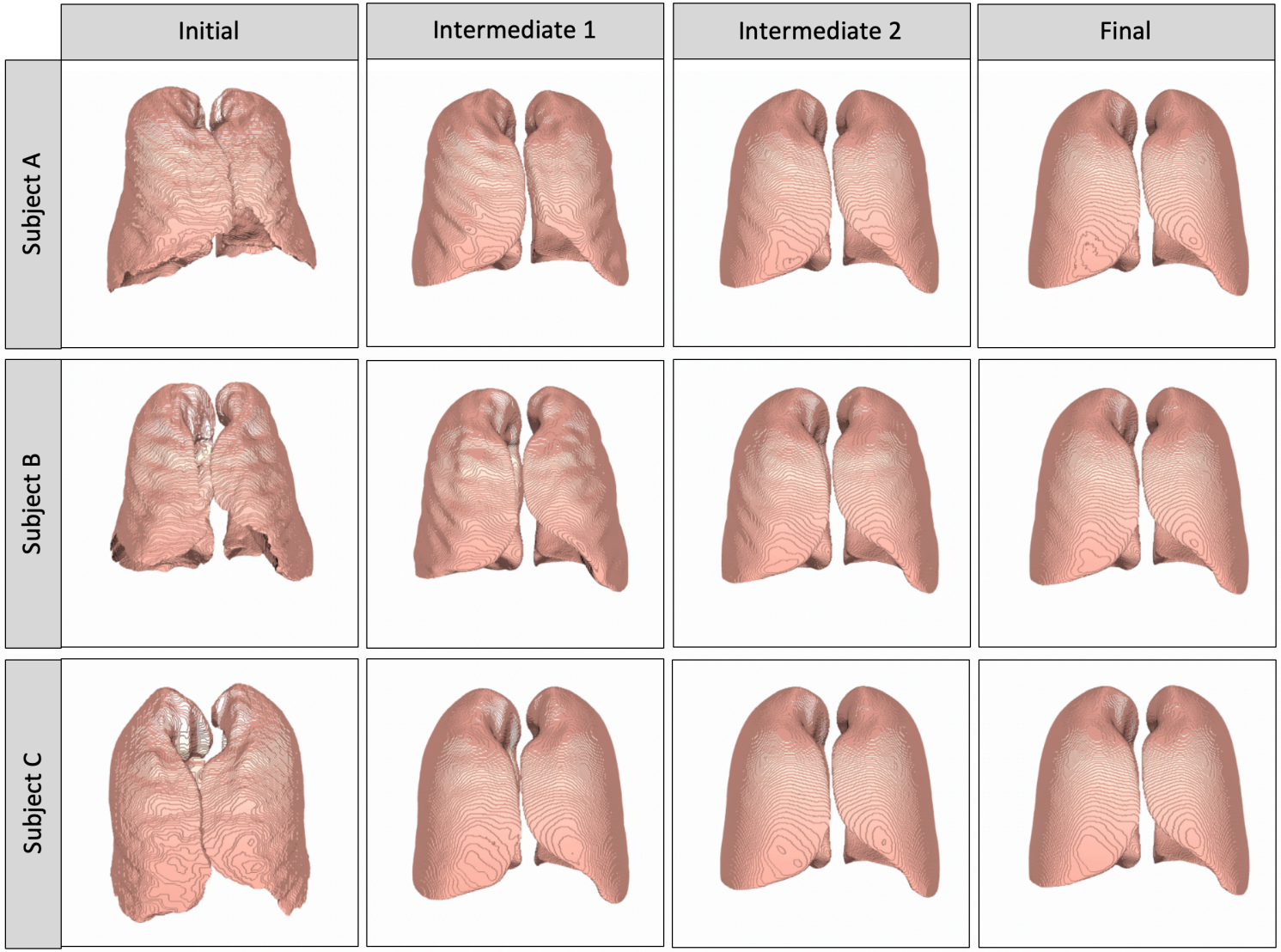




Convergence



Sensitivity to Initial Template Choice



Healthy Lung Template Characteristics

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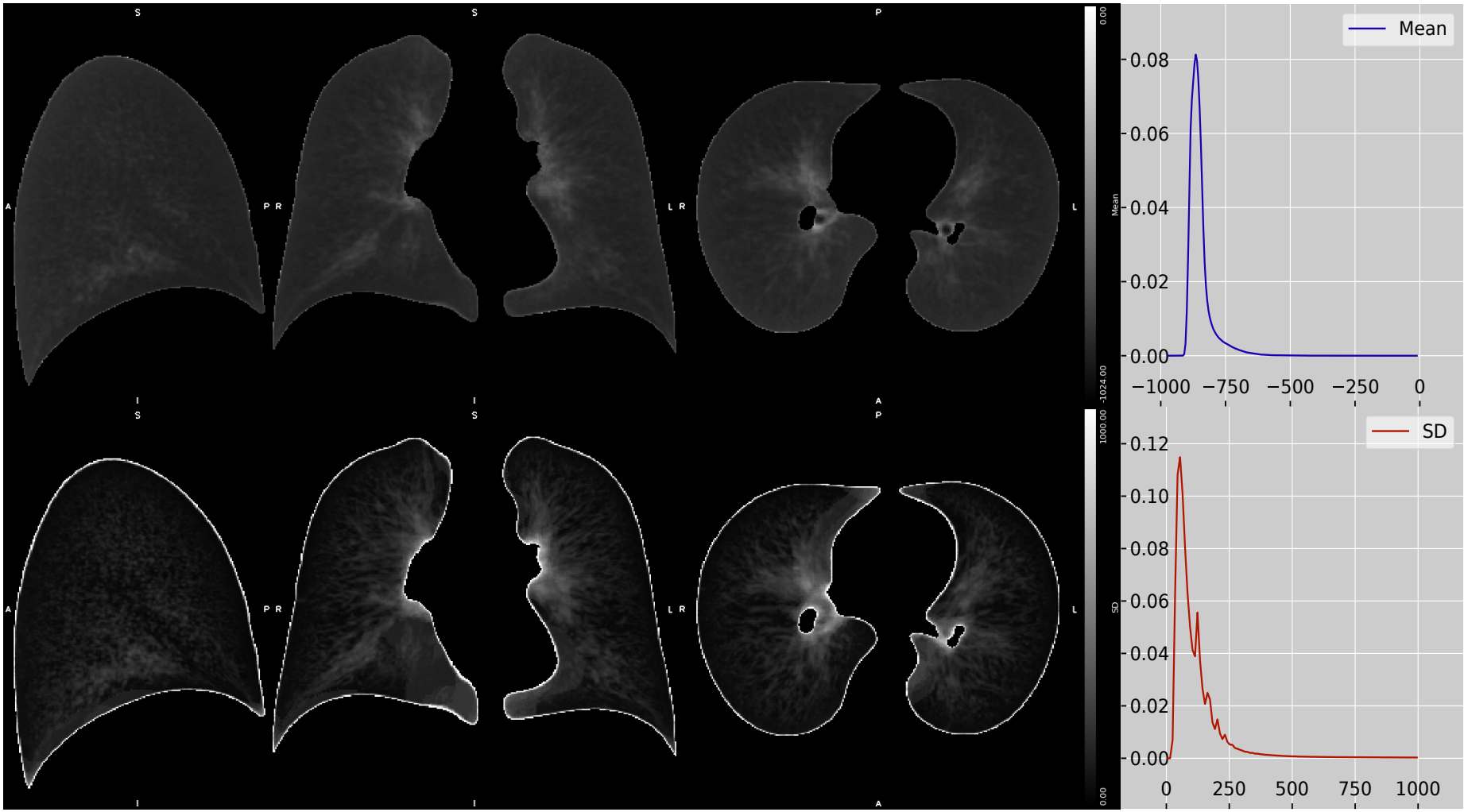
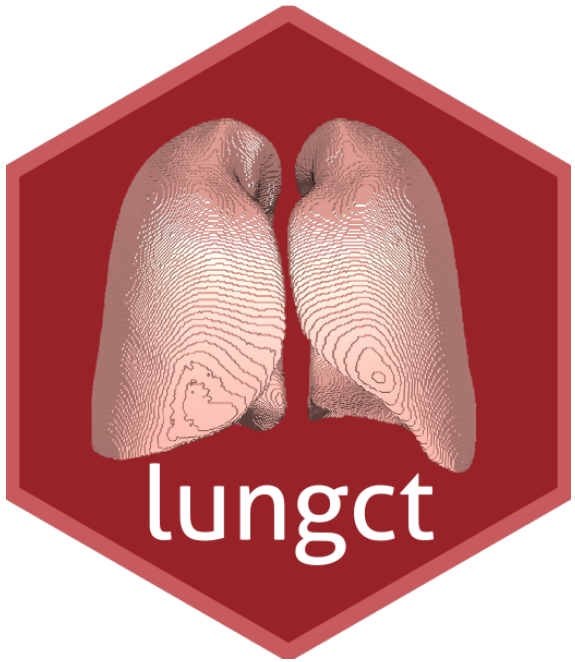
Number of iterations: 14



Conclusions

1. We created 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



Where is disease commonly found in the lung?

Methodological Questions:

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   - ~~**Create a lung template**~~
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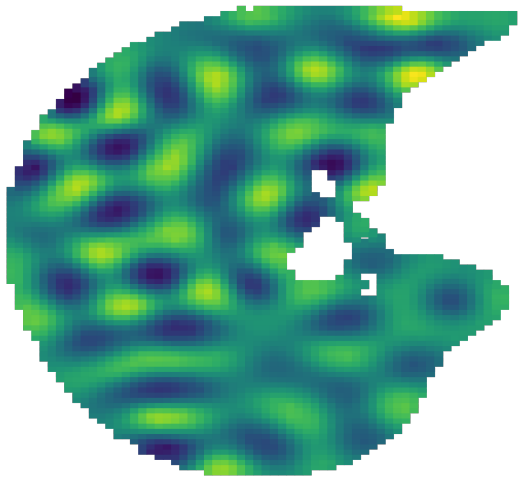
   - **Develop a spatial model for whole-lung population-level inference**

Develop a Model for Whole-Lung Population-Level Inference



Classical Method for Imaging Data

Voxel-based morphometry (VBM) - A mass univariate statistical test where separate statistical models are fit on every voxel

- Fails to account for spatial correlation between voxels
- Arbitrary, post-hoc smoothing of data
- High false positive rate and low power depending on multiple comparison correction

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A spatial model for high-dimensional data is desired.

Spatial Models for High-Dimensional Data

- **Integrated Nested Laplace Approximation (INLA)**
  - Type of Gaussian Markov random field-based approximation
  - Provides computationally efficient estimation and inference for latent Gaussian models
  - Extended to neuroimaging fMRI data [Mejia et al., 2019]
  - Problem: Its memory consumption depends on N.
- **Eigenvector Spatial Filtering (ESF)**
  - A type of low rank approximation
  - Describes spatial variation using a linear combination of L basis functions where $L << N$
  - Related to Moran's I, a common spatial summary measure
  - A computationally-efficient and memory-free approach has been developed [Murakami and Griffith, 2019a]

Note: Not an extensive list of spatial modeling approaches for high-dimensional data

Eigenvector Spatial Filtering

ESF models spatial maps using eigenvectors associated with the Moran coefficient (MC) [Moran, 1950]:

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

- $\mathbf{y}$ is a spatial response
- $\mathbf{C}$ is a spatial correlation matrix, such as the exponential
- $\mathbf{M}$ is a centering matrix, ensuring eigenvectors are orthogonal and uncorrelated
- $\mathbf{MCM}$ is decomposed into spatially orthogonal variables, or eigenvectors
- A subset of L eigenvectors, $\mathbf{E}$, where $L << N$, are selected

Murakami's ESF Model

The resulting eigenvector matrix, $\mathbf{E}$, can be used to construct spatially-varying coefficients (SVC) in a mixed-effects model [Murakami et al., 2017]:

$$\begin{aligned} \mathbf{y} &= \sum_{k=1}^{K} \mathbf{x}_k \circ \boldsymbol{\beta}_k^{SVC} + \boldsymbol{\varepsilon}, \quad \boldsymbol{\varepsilon} \sim N\left(\mathbf{0}, \sigma^2 \mathbf{I}\right) \\ \boldsymbol{\beta}_k^{SVC} &= \beta_k \mathbf{1} + \mathbf{E}\boldsymbol{\gamma}_k, \quad \boldsymbol{\gamma}_k \sim N\left(\mathbf{0}_L, \sigma_{k(\gamma)}^2 \boldsymbol{\Lambda}\left(\alpha_k\right)\right) \end{aligned} \tag{2}$$

- Parameters are estimated using restricted maximum likelihood (REML)
- Fits high-dimensional spatial data efficiently
- Shown to have less bias in the SVC estimates as compared to geographically-weighted regression [Murakami and Griffith, 2019a]

Our ESF Model for Imaging Data

Our spatial voxel-based morphometry, or **spVBM**, model extends the Murakami's ESF based SVC model by incorporating non-spatial random effects **Zb**. For a single subject, the model is:

$$\mathbf{y_i} = \sum_{k=1}^{K} x_{k,i} \circ \beta_{k,i}^{SVC} + \mathbf{Z_i b_i} + \boldsymbol{\varepsilon_i} \tag{3}$$

$$\beta_{k,i}^{SVC} = \beta_k \mathbf{1} + \mathbf{E_i} \gamma_k \tag{4}$$

$$\mathbf{b_i} \sim N(\mathbf{0}, D), \quad \boldsymbol{\varepsilon_i} \sim N(\mathbf{0}, \Sigma_i), \quad \boldsymbol{\gamma_k} \sim N\left(\mathbf{0}, \sigma_k^2 \boldsymbol{\Lambda}(\alpha_k)\right) \tag{5}$$

where $\mathbf{y_i}$ is the response vector, $x_{k,i}$ is the k^{th} covariate, $\beta_{k,i}^{SVC}$ is a vector comprised of the k^{th} spatially-varying coefficient, $\mathbf{Z_i}$ is a matrix of covariates for the random effects, $\mathbf{b_i}$ is the vector containing the random effects, and $\boldsymbol{\varepsilon_i}$ are the residuals. See [Murakami and Griffith, 2019b].

The spVBM Model: Estimation and Inference

The parameters are estimated in the following steps:

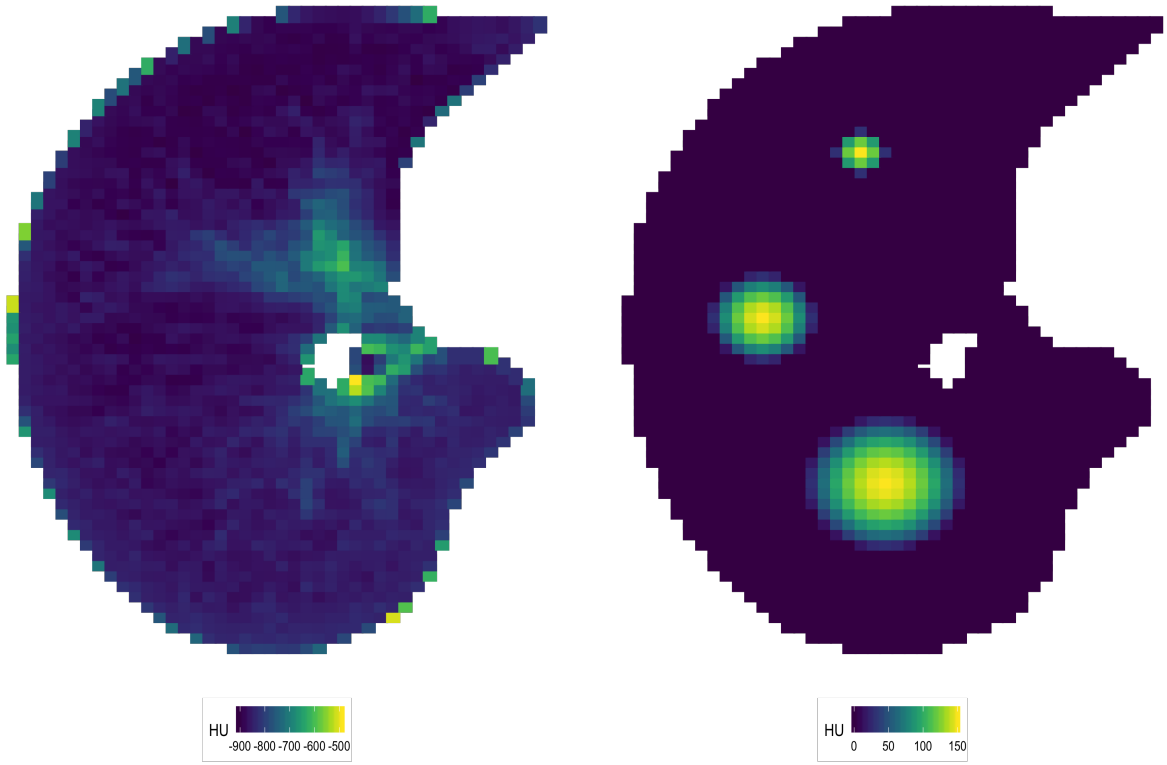
1. β are estimated using maximum likelihood and the normal equations
2. The variance parameters are sequentially estimated by maximizing the restricted log-likelihood

Inference:

- Interested in β_k^{SVC}
- Voxel-level null hypothesis that β_k^{SVC} at voxel j is equal to 0.
- Wald statistic: $W = \frac{(\beta_{k,j}^{SVC} - 0)^2}{Var(\beta_{k,j}^{SVC})}$

Simulation Study

- Simulate local regions of disease with a binary covariate to represent a case-control study
- Local regions based on small, medium and large disease regions using an Epanechnikov kernel
- Compare spVBM to VBM



Eigenvectors in the Lung

- Distance matrix: (N_u x N_u) dimension
- Eigenvector design matrix: (N_u x L) dimension

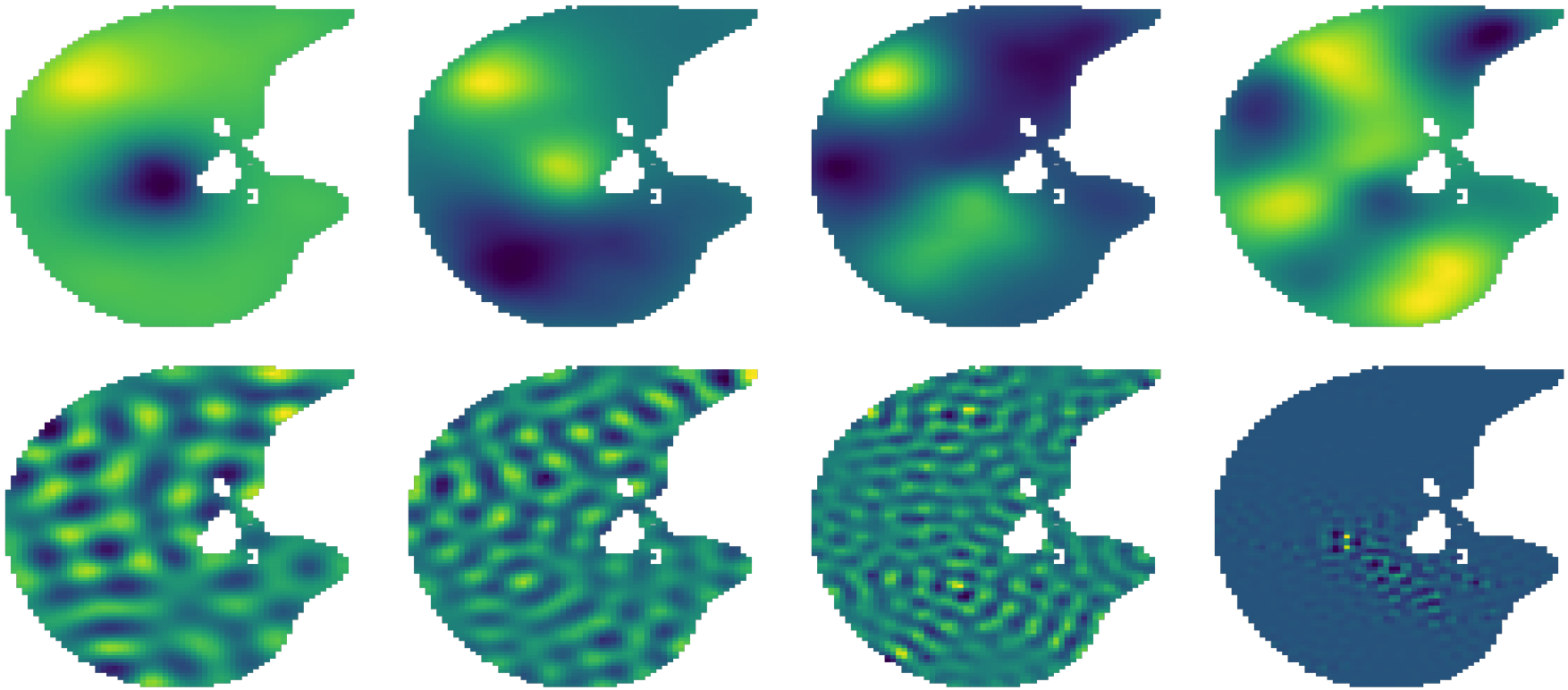
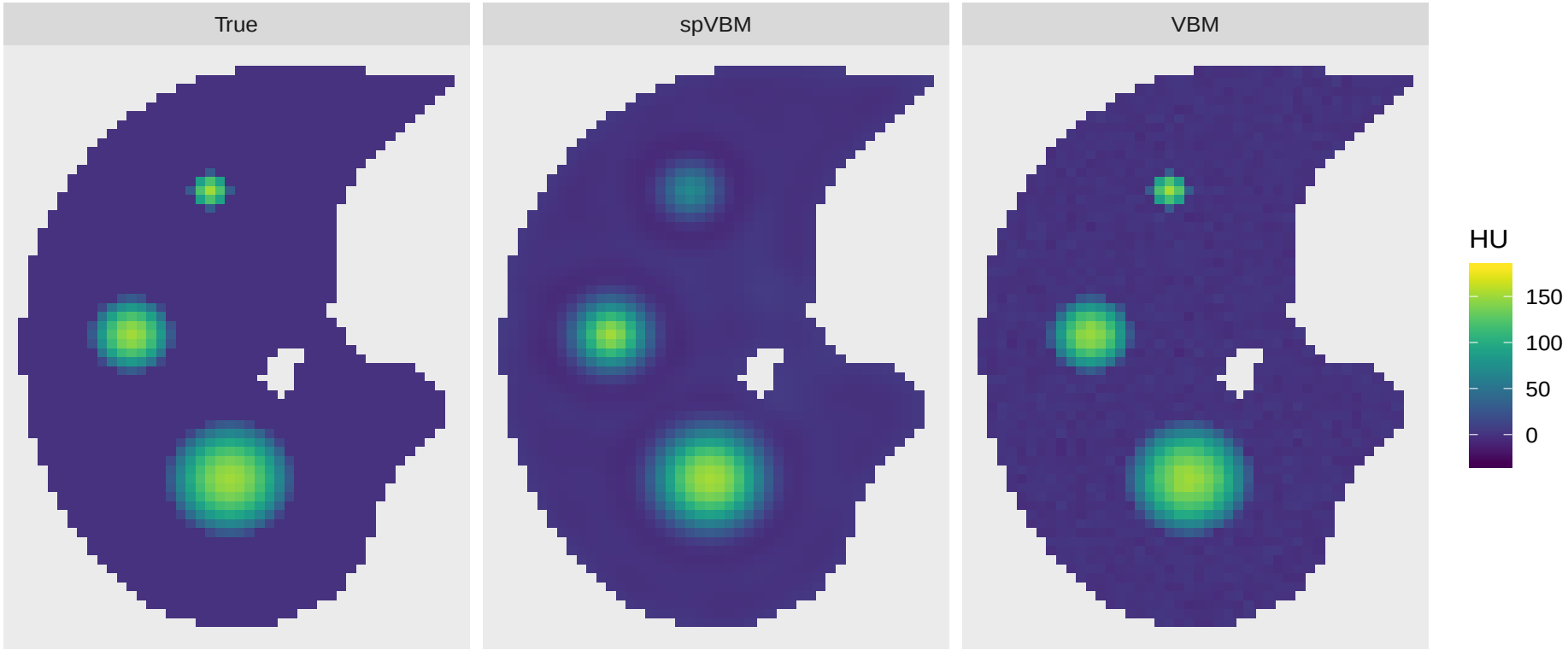
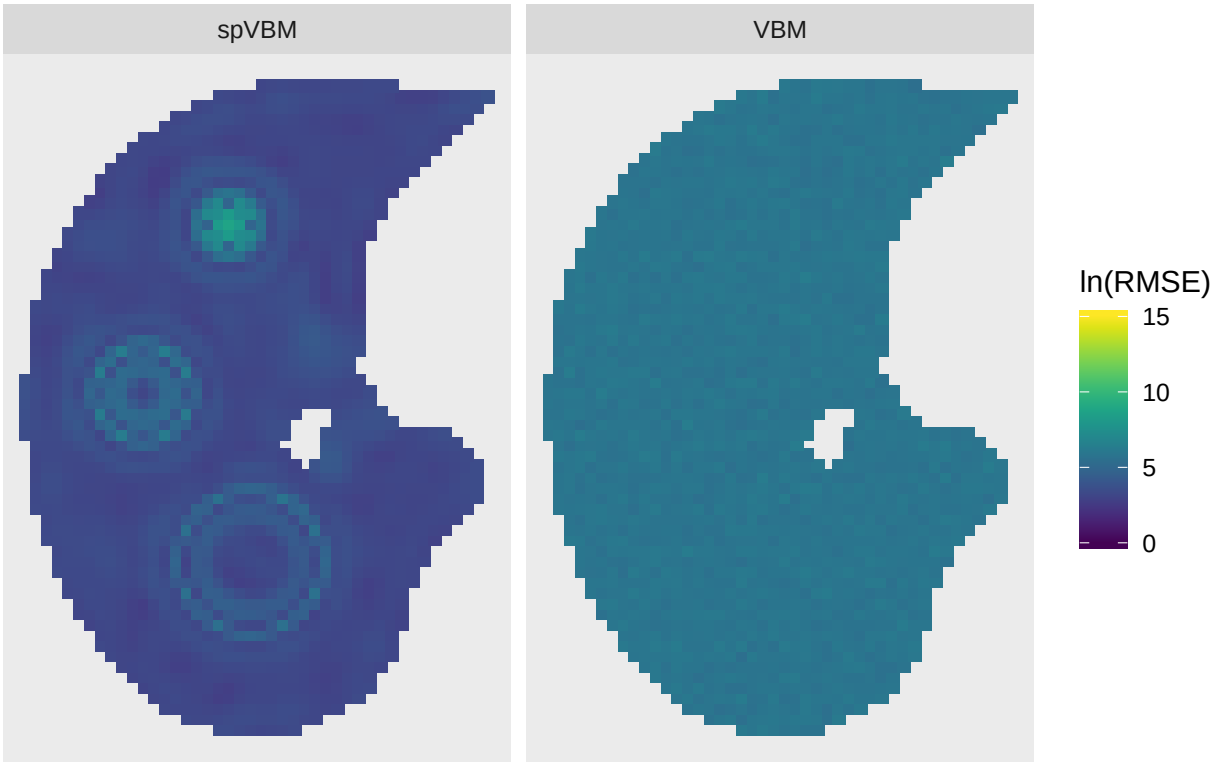


Figure: Moran eigenvectors (1, 2, 4, 8, 100, 200, 400, 800) based on the spatial correlation matrix from a 2D axial slice of the lung.


True
spVBM
VBM
HU
150
100
50
0

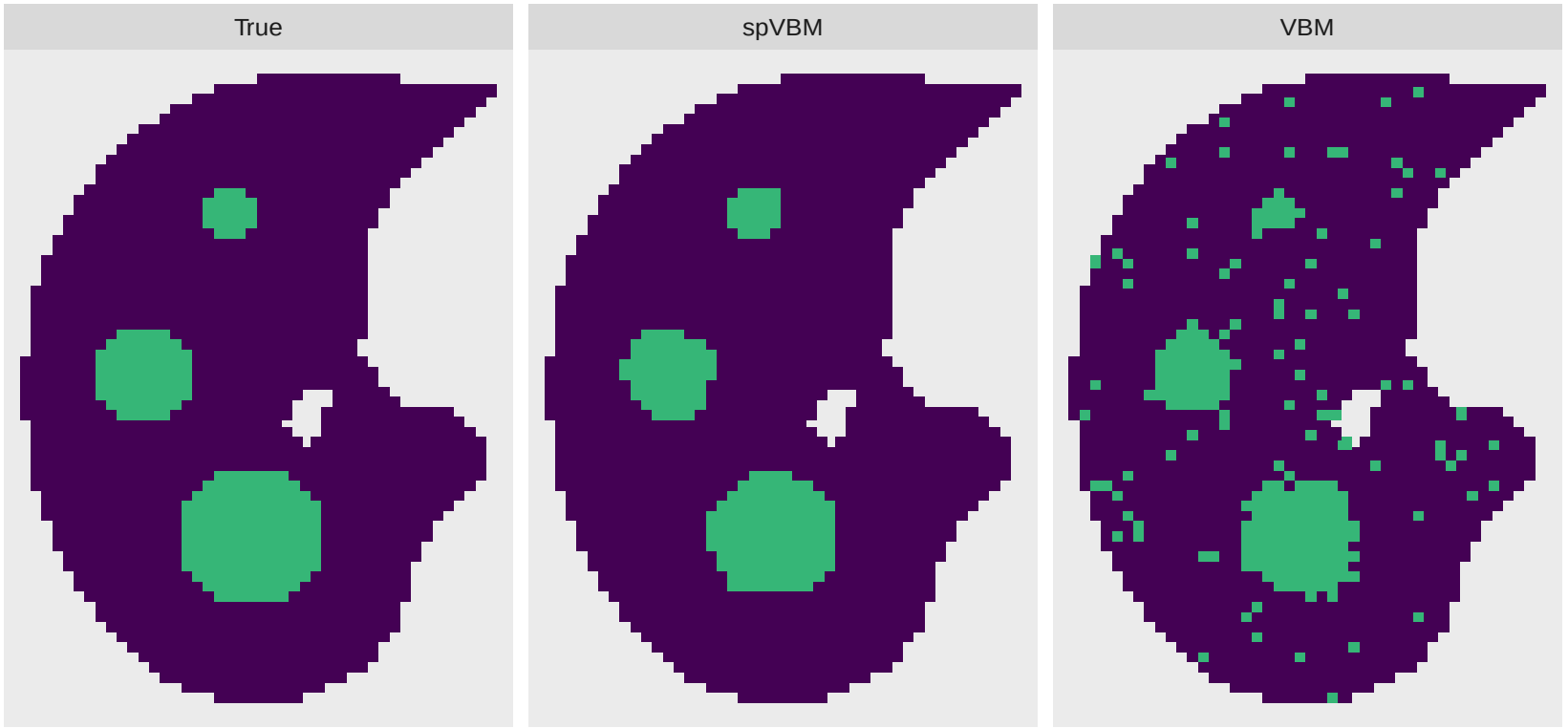
RMSE in $\hat{\beta}_1^{SVC}$



Inference for $\hat{\beta}_1^{SVC}$

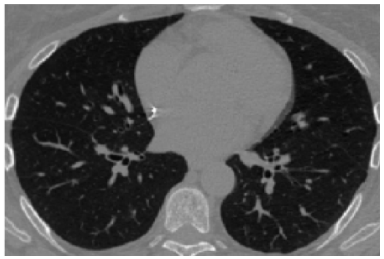
spVBM : FPR = 0.007, FNR = 0.105

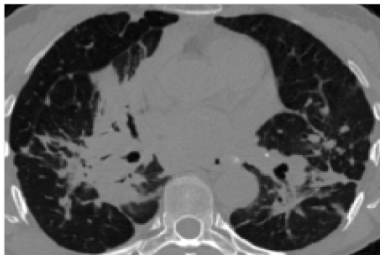
VBM : FPR = 0.050, FNR = 0.315



Application to Diseased Population

GRADS
GENOMIC RESEARCH IN ALPHA-1 ANTITRYPSIN DEFICIENCY AND SARCOIDOSIS



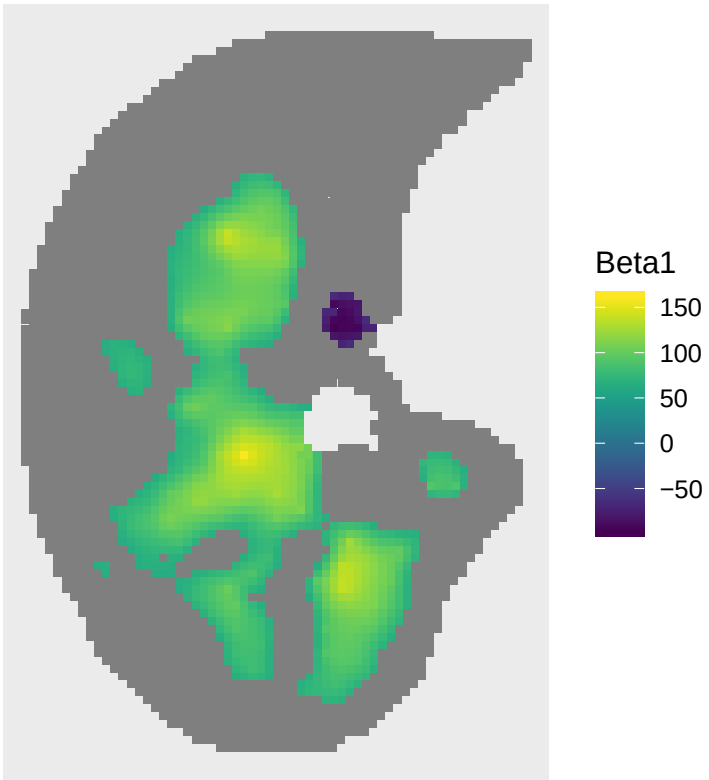


	Healthy	Fibrotic	P-value
Sample Size	13	29	
Male (%)	6 (46.2)	13 (44.8)	1.000
White (%)	11 (84.6)	17 (58.6)	0.194
Hispanic (%)	3 (23.1)	1 (3.4)	0.151
Age (mean (SD))	56.29 (8.87)	55.03 (7.69)	0.641
BMI (mean (SD))	33.09 (4.18)	28.83 (5.38)	0.016

Application to Diseased Population

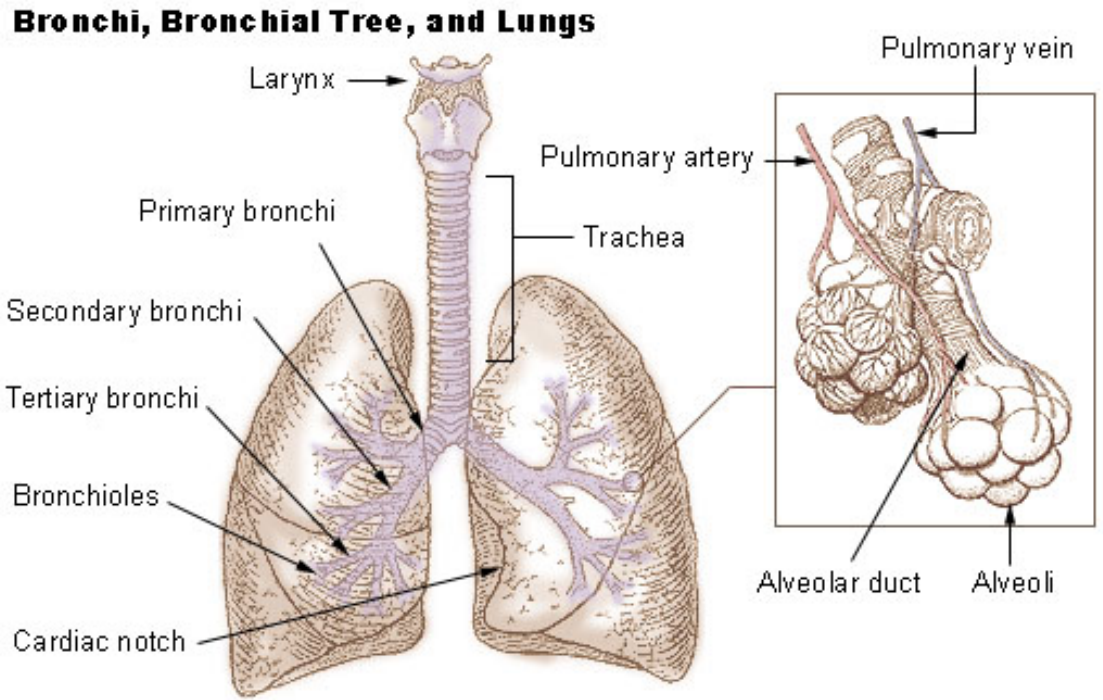
$$\mathbf{HU_i} = \beta_{0,i}^{SVC} + \beta_{1,i}^{SVC} * X_{fibrosis} + \beta_{2,i}^{SVC} * X_{BMI} + \mathbf{b_i} + \boldsymbol{\varepsilon_i}$$

$$\mathbf{b_i} \sim N\left(\mathbf{0}, \sigma_b^2 \mathbf{I}\right), \quad \boldsymbol{\varepsilon_i} \sim N\left(\mathbf{0}, \sigma_e^2 \mathbf{I}\right), \quad \boldsymbol{\gamma_k} \sim N\left(\mathbf{0}, \sigma_k^2 \boldsymbol{\Lambda}\left(\alpha_k\right)\right)$$



Compared to healthy patients, patients with fibrosis have areas of significantly higher intensity near the bronchi.

Application to Diseased Population



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Future Directions

- Develop a spectrum of lung templates
  - Age-specific
  - Disease-specific
- Extend spVBM
  - To 3D data
  - To non-normal data
  - To different spatial correlations
  - Compare to Mejia's INLA method for imaging data
- Explore other imaging modalities and anatomical areas
  - fMRI
  - Animal studies

Collaborators

- Nichole Carlson, PhD, Colorado School of Public Health
- Tasha Fingerlin, PhD, National Jewish Health
- Debashis Ghosh, PhD, Colorado School of Public Health
- Lisa Maier, MD, MSPH, National Jewish Health
- John Muschelli, PhD, Johns Hopkins Bloomberg School of Public Health

Funding Sources

- National Institutes of Health (R01 HL114587; R01 HL142049; U01 HL112695)
- GRADS study (NIH grant U01 HL112707, U01 HL112707, U01 HL112694, U01 HL112695, U01 HL112696, U01 HL112702, U01 HL112708, U01 HL112711, U01 HL112712)
- COPDGene study (NIH grants U01 HL089856 and U01 HL089897, COPD Foundation)

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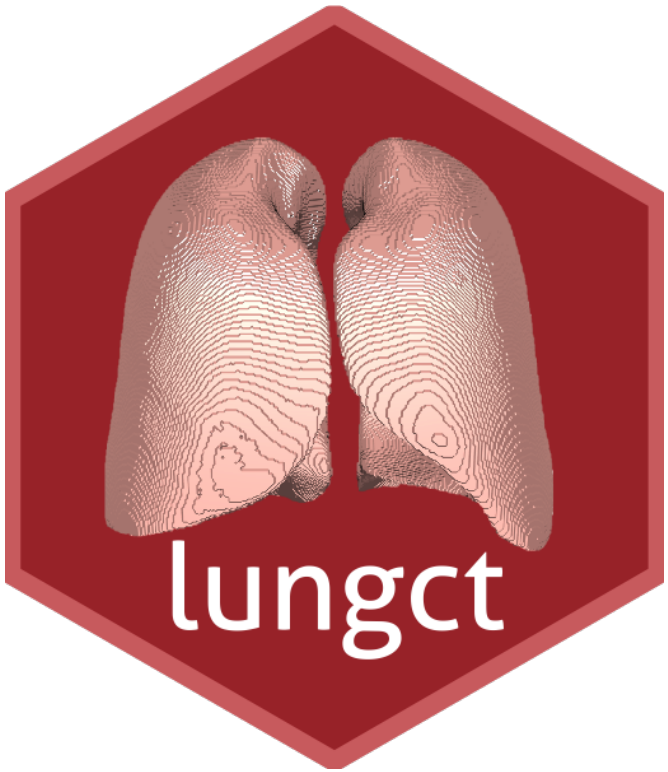

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The spVBM Model: Multi-subject model

$$\mathbf{Y} = \sum_{k=1}^{K} X_k \circ \beta_k^{SVC} + \mathbf{Zb} + \varepsilon \tag{6}$$

$$\beta_k^{SVC} = \beta_k \mathbf{1} + \mathbf{E}\gamma_k \tag{7}$$

where $\mathbf{Y} = [\mathbf{y_1} \ldots \mathbf{y_N}]^T$, $X_k = [x_{k,1} \ldots x_{k,N}]^T$, $\mathbf{b} = [\mathbf{b_1} \ldots \mathbf{b_N}]^T$, $\varepsilon = [\varepsilon_1 \ldots \varepsilon_N]^T$ and $\mathbf{E} = [\mathbf{E_1} \ldots \mathbf{E_N}]^T$, and where $\mathbf{Z}$, is the block diagonal matrix with blocks $\mathbf{Z_i}$ on the diagonals and zeros elsewhere. The dimension of $\mathbf{Y}$ is equal to $n = \sum_{i=1}^{N} n_i$.

The spVBM Model: Reparameterizatior

Separating the global $\mathbf{X}\beta$ and spatial terms $\tilde{\mathbf{E}}\tilde{\gamma}$:

$$\begin{aligned} \mathbf{Y} &= \mathbf{X}\beta + \tilde{\mathbf{E}}\tilde{\gamma} + \mathbf{Z}\mathbf{b} + \varepsilon, \quad \varepsilon \sim N\left(\mathbf{0}, \sigma^2\mathbf{I}\right) \\ \tilde{\mathbf{E}} &= [\mathbf{X}_1 \circ \mathbf{E} \cdots \mathbf{X}_K \circ \mathbf{E}] \end{aligned} \tag{8}$$

Obtaining common variance terms as in [Bates et al., 2014]:

$$\mathbf{Y} = \mathbf{X}\beta + \tilde{\mathbf{E}}\tilde{\mathbf{V}}(\Theta)\tilde{\mathbf{u}} + \mathbf{Z}\Omega(\Phi)\mathbf{w} + \varepsilon, \quad \tilde{\mathbf{u}}, \mathbf{w}, \varepsilon \sim N\left(\mathbf{0}, \sigma^2\mathbf{I}\right)$$

$$\tilde{\mathbf{V}}(\Theta) = \begin{bmatrix} \mathbf{V}\left(\theta_1\right) & & \\ & \ddots & \\ & & \mathbf{V}\left(\theta_K\right) \end{bmatrix}, \quad \Omega(\Phi) = \begin{bmatrix} \Omega\left(\phi_1\right) & & \\ & \ddots & \\ & & \Omega\left(\phi_H\right) \end{bmatrix} \tag{9}$$

The spVBM Model: Estimation

1. $\boldsymbol{\beta}, \tilde{\mathbf{u}}, \mathbf{w}$ are estimated using maximum likelihood and the normal equations;

$$\begin{bmatrix} \hat{\boldsymbol{\beta}} \\ \hat{\tilde{\mathbf{u}}} \\ \hat{\mathbf{w}} \end{bmatrix} = \mathbf{P}^{-1} \begin{bmatrix} \mathbf{X}'\mathbf{y} \\ \tilde{\mathbf{V}}(\boldsymbol{\Theta})\tilde{\mathbf{E}}'\mathbf{y} \\ \boldsymbol{\Omega}(\boldsymbol{\Phi})\mathbf{Z}'\mathbf{y} \end{bmatrix} \tag{10}$$

$$\mathbf{P} = \begin{bmatrix} \mathbf{X}'\mathbf{X} & \mathbf{X}'\tilde{\mathbf{E}}\tilde{\mathbf{V}}(\boldsymbol{\Theta}) & \mathbf{X}'\mathbf{Z}\boldsymbol{\Omega}(\boldsymbol{\Phi}) \\ \tilde{\mathbf{V}}(\boldsymbol{\Theta})\tilde{\mathbf{E}}'\mathbf{X} & \tilde{\mathbf{V}}(\boldsymbol{\Theta})\tilde{\mathbf{E}}'\tilde{\mathbf{E}}\tilde{\mathbf{V}}(\boldsymbol{\Theta}) + \mathbf{I} & \tilde{\mathbf{V}}(\boldsymbol{\Theta})\tilde{\mathbf{E}}'\mathbf{Z}\boldsymbol{\Omega}(\boldsymbol{\Phi}) \\ \boldsymbol{\Omega}(\boldsymbol{\Phi})\mathbf{Z}'\mathbf{X} & \boldsymbol{\Omega}(\boldsymbol{\Phi})\mathbf{Z}'\tilde{\mathbf{E}}\tilde{\mathbf{V}}(\boldsymbol{\Theta}) & \boldsymbol{\Omega}(\boldsymbol{\Phi})\mathbf{Z}'\mathbf{Z}\boldsymbol{\Omega}(\boldsymbol{\Phi}) + \mathbf{I} \end{bmatrix} \tag{11}$$

The spVBM Model: Estimation

2. The variance parameters are estimated by maximizing the restricted log-likelihood

$$\text{loglik}_R(\boldsymbol{\Theta}, \boldsymbol{\Phi}) = -\frac{1}{2}\log|\mathbf{P}| - \frac{N-K}{2}\left(1 + \log\left(\frac{2\pi\tilde{d}(\boldsymbol{\Theta})}{N-K}\right)\right) \quad (12)$$

$$\tilde{d}(\boldsymbol{\Theta}, \boldsymbol{\Phi}) = \min_{\beta, \tilde{\mathbf{u}}, \mathbf{w}} \|\mathbf{Y} - \mathbf{X}\beta - \tilde{\mathbf{E}}\tilde{\mathbf{V}}(\boldsymbol{\Theta})\tilde{\mathbf{u}} - \mathbf{Z}\boldsymbol{\Omega}(\boldsymbol{\Phi})\mathbf{w}\|^2 + \|\tilde{\mathbf{u}}\|^2 + \|\mathbf{w}\|^2 \quad (13)$$

The spVBM Model: Estimation

3. The residual variance is estimated below, where n is the dimension of Y and K is the number of fixed effects:

$$\hat{\sigma}^2 = \frac{\|\mathbf{Y} - \mathbf{X}\boldsymbol{\beta} - \tilde{\mathbf{E}}\mathbf{V}(\boldsymbol{\Theta})\tilde{\mathbf{u}} - \mathbf{Z}\boldsymbol{\Omega}(\boldsymbol{\Phi})\mathbf{w}\|^2}{n - K} \tag{14}$$

To perform statistical inference on the β_k^{SVC}, we obtain the covariance matrix of β_k^{SVC} following [Murakami and Griffith, 2019c], where $\hat{\mathbf{P}}_k^*$ is a subset of $\mathbf{P}^{-1}$, only including rows and columns associated with x_k:

$$Var(\hat{\beta}_k^{SVC}) = \hat{\sigma}^2 \begin{bmatrix} 1 & \mathbf{E}\mathbf{V}(\hat{\theta}_k) \end{bmatrix} \hat{\mathbf{P}}_k^* \begin{bmatrix} \mathbf{1}^T \\ \mathbf{V}(\hat{\theta}_k)\mathbf{E}^T \end{bmatrix} \tag{15}$$