



UNIVERSITY OF COPENHAGEN

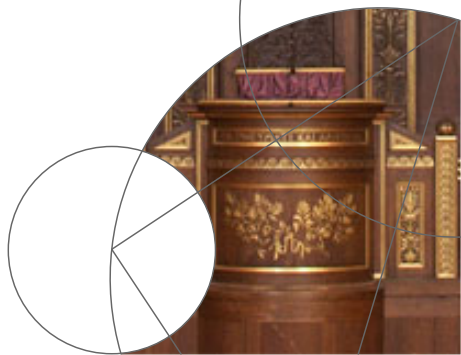
Extraction of Airways from Volumetric Data

PhD Thesis Defence

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Supervisors: Marleen de Bruijne, Jens Petersen

Department of Computer Science



Guess Who



<https://www.copdfoundation.org/>



Guess Who



Leonard Nimoy aka Spock
(1931-2015)

<https://www.copdfoundation.org/>



Guess Who



Leonard Nimoy aka Spock
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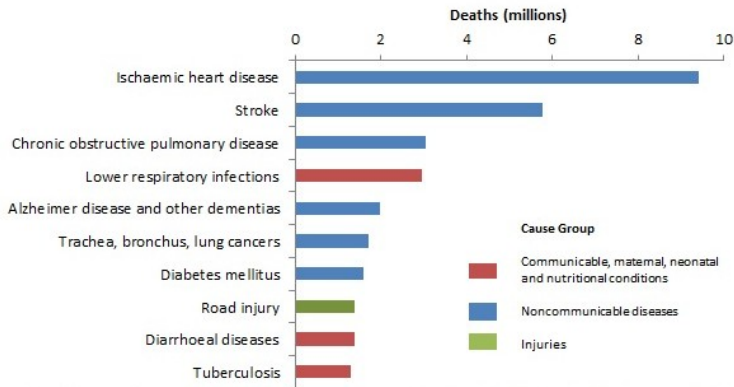
Chronic Obstructive Pulmonary Disease
(COPD)

<https://www.copdfoundation.org/>



Respiratory diseases: Major cause of morbidity & mortality

Top 10 global causes of deaths, 2016



Source: Global Health Estimates 2016, World Health Organization, 2018



Outline

- ① Airway diseases and diagnosis
- ② Objective of the study
- ③ Data
- ④ Contributions
 - Multiple Hypothesis Tracking
 - Bayesian Smoothing
 - Graph Refinement Models
- ⑤ Summary & Conclusions



Outline

- 1 Airway diseases and diagnosis
- 2 Objective of the study
- 3 Data
- 4 Contributions
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Respiratory diseases adversely affect airways

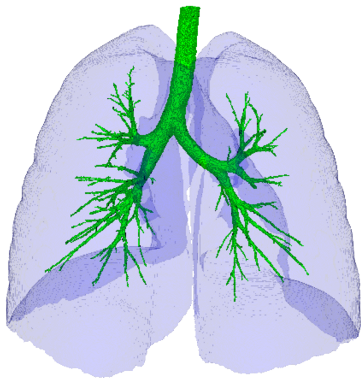


Image adapted from Wikimedia Commons



Respiratory diseases adversely affect airways

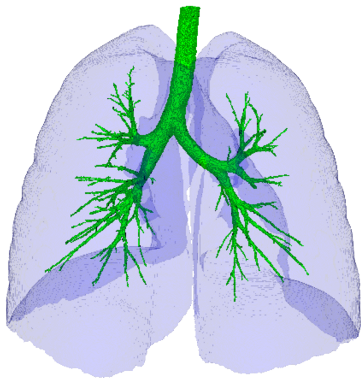
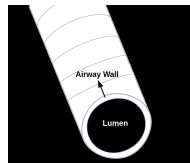


Image adapted from Wikimedia Commons

Particularly, airway morphology



Existing diagnostics are rudimentary



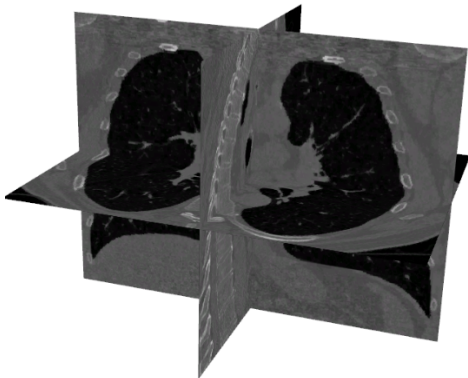
Image sourced from Wikimedia Commons

Lung Function Tests

- + Non-invasive
- + Inexpensive
- + Reliable, mostly
- Little or no insight on pathophysiology
- Patient dependent
- Low reproducibility
- Mild cases can go unnoticed



Imaging based Computer Aided Diagnosis



Computed Tomography (CT) chest scans

- High-resolution imaging
- Pathophysiology can be studied
- Possibility of automated analysis



Outline

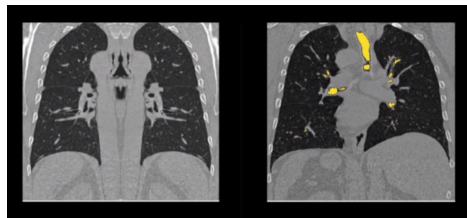
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Imaging based analysis of airways & challenges

Three primary steps:

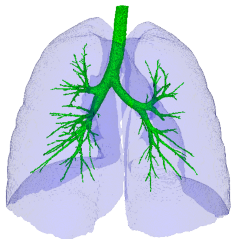
- 1 **Detection** of airways
- 2 Measurement of airway morphology
- 3 Deriving biomarkers



Coronal view of chest CT scan



Methods exist. Majority of them are sequential

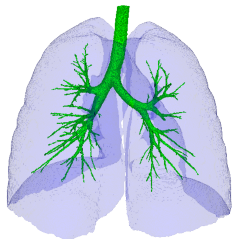


Sequential segmentation methods

Lo, P., et.al : Extraction of airways from CT (EXACT'09). IEEE Transactions on Medical Imaging, (2012)



Methods exist. Majority of them are sequential



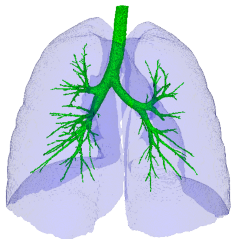
Sequential segmentation methods

- Susceptible to occlusions in data
- Small branches are challenging
- EXACT'09 Study
 - Airway extraction challenge
 - Compares 15 methods
 - 10 use region growing!

Lo, P., et.al : Extraction of airways from CT (EXACT'09). IEEE Transactions on Medical Imaging, (2012)



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Sequential segmentation methods

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Objective of this thesis

Extraction of airways from volumetric data

With automatic methods that:

- Are exploratory
- Use more global information in local decisions



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Data from Danish Lung Cancer Screening Trial (DLCST)

- > 10,000 Low-dose CT from 2052 subjects
- Smoker or former smoker (> 20 pack years)
- Voxels $\sim 0.75 \times 0.75 \times 1 \text{ mm}^3$

Pedersen, J. H., et.al : The Danish randomized lung cancer CT screening trial – Overall design and results of the prevalence round. *Journal of Thoracic Oncology*, (2009)



Outline

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Multiple Hypothesis Tracking (MHT)

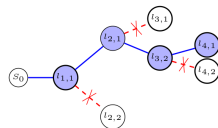
Work based on

- [1] Raghavendra Selvan, Jens Petersen, Jesper H. Pedersen, and Marleen de Bruijne. “Extracting Tree-structures in CT data by Tracking Multiple Statistically Ranked Hypotheses” (2018). (Under review)
- [2] Raghavendra Selvan, Jens Petersen, Jesper H. Pedersen, and Marleen de Bruijne. “Extraction of airway trees using multiple hypothesis tracking and template matching”. In The Sixth International Workshop on Pulmonary Image Analysis. MICCAI, 2016.



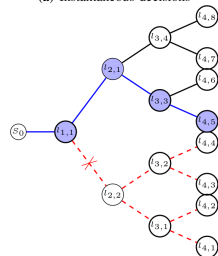
Improvements to an established method

- MHT is extensively used in object tracking
- *Interactive* vessel segmentation method (Friman et al. 2010)
- Modifications render it *automatic*; suitable for airway tree extraction
 - New scale-invariant statistic
 - Improved bifurcation handling
- Significant performance improvement



T_0 --- T_1 --- T_2 --- T_3 --- T_4

(a) Instantaneous decisions



T_0 --- T_1 --- T_2 --- T_3 --- T_4

(b) Deferred decisions

Friman, Ola, et al. "Multiple hypothesis template tracking of small 3D vessel structures." Medical image analysis 14.2 (2010): 160-171.



Bayesian Smoothing

Work based on

- [1] Raghavendra Selvan, Jens Petersen, Jesper H. Pedersen, and Marleen de Bruijne. “Extraction of airways with probabilistic state-space models and Bayesian smoothing.” In *Graphs in Biomedical Image Analysis, Computational Anatomy and Imaging Genetics, MICCAI, 2017*, pp. 53-63. Springer, Cham.



Airway extraction with Bayesian smoothing

Idea

- Track candidate branches from across the volume
- Use uncertainty measures to qualify branches



Airway extraction with Bayesian smoothing

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State-space models on sparse point cloud data

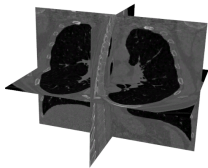


Airway extraction with Bayesian smoothing

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State-space models on sparse point cloud data



Dense Volume

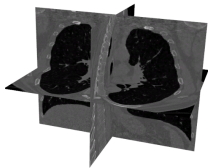


Airway extraction with Bayesian smoothing

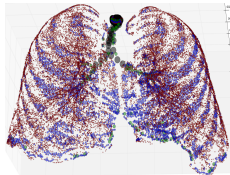
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Dense Volume



Sparse point cloud

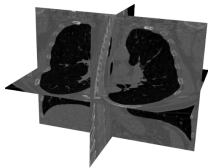


Airway extraction with Bayesian smoothing

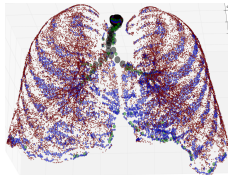
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State-space models on sparse point cloud data



Dense Volume



Sparse point cloud



Tracked branches

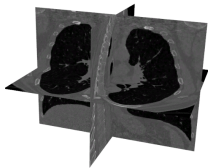


Airway extraction with Bayesian smoothing

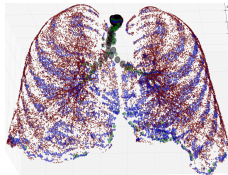
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Dense Volume



Sparse point cloud



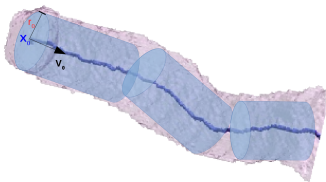
Tracked branches



Qualified branches



State-space model

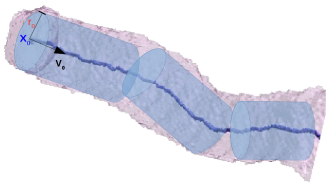


- Airway tree as a set of *independent* branches

$$\mathbf{X} = \{\mathbf{X}_1, \dots, \mathbf{X}_T\}$$



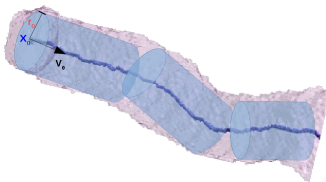
State-space model



- Airway tree as a set of *independent* branches
 $\mathbf{X} = \{\mathbf{X}_1, \dots, \mathbf{X}_T\}$
- Each branch as a sequence of state vectors
 $\mathbf{X}_i = [\mathbf{x}_0, \mathbf{x}_1, \dots, \mathbf{x}_{l_i}]$



State-space model



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$$\mathbf{X} = \{\mathbf{X}_1, \dots, \mathbf{X}_T\}$$

- Each branch as a sequence of state vectors

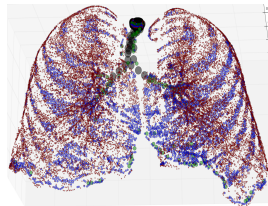
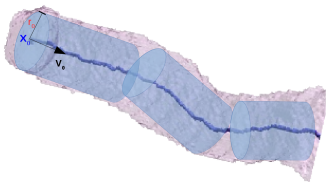
$$\mathbf{X}_i = [\mathbf{x}_0, \mathbf{x}_1, \dots, \mathbf{x}_{l_i}]$$

- State vector at each step

$$\mathbf{x}_k = [x, y, z, r, v_x, v_y, v_z]^T$$



State-space model



- Airway tree as a set of *independent* branches
 $\mathbf{X} = \{\mathbf{X}_1, \dots, \mathbf{X}_T\}$
- Each branch as a sequence of state vectors
 $\mathbf{X}_i = [\mathbf{x}_0, \mathbf{x}_1, \dots, \mathbf{x}_{l_i}]$
- State vector at each step
 $\mathbf{x}_k = [x, y, z, r, v_x, v_y, v_z]^T$

- Sparse, vectorised image data $\mathbf{Y} = [\mathbf{y}_0, \dots, \mathbf{y}_T]$;
 $\mathbf{y}_k = [x, y, z, r]^T$



Probabilistic state-space models



Probabilistic state-space models

Process model

$$p(\mathbf{x}_k | \mathbf{x}_{k-1}) \equiv \mathbf{x}_k = \mathbf{F}\mathbf{x}_{k-1} + \mathbf{q} \quad (1)$$

F: State transition function, $\mathbf{q} \sim N(\mathbf{0}, \mathbf{Q})$: Process noise



Probabilistic state-space models

Process model

$$p(\mathbf{x}_k | \mathbf{x}_{k-1}) \equiv \mathbf{x}_k = \mathbf{F}\mathbf{x}_{k-1} + \mathbf{q} \quad (1)$$

F: State transition function, $\mathbf{q} \sim N(\mathbf{0}, \mathbf{Q})$: Process noise

Measurement model

$$p(\mathbf{y}_k | \mathbf{x}_k) \equiv \mathbf{y}_k = \mathbf{H}\mathbf{x}_k + \mathbf{m} \quad (2)$$

H: Measurement function, $\mathbf{m} \sim N(\mathbf{0}, \mathbf{R})$: Measurement noise



Extraction of branches from posterior distribution

⁵Rauch-Tung-Striebel



Extraction of branches from posterior distribution

Estimation of $p(\mathbf{X}|\mathbf{Y})$

$$p(\mathbf{X}|\mathbf{Y}) \approx \prod_i^T p(\mathbf{X}_i|\mathbf{Y}) \quad (3)$$



Extraction of branches from posterior distribution

Estimation of $p(\mathbf{X}|\mathbf{Y})$

$$p(\mathbf{X}|\mathbf{Y}) \approx \prod_i^T p(\mathbf{X}_i|\mathbf{Y}) \quad (3)$$

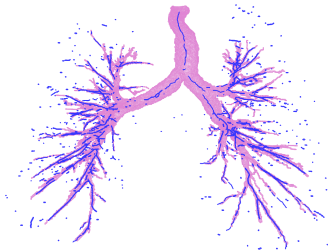
Recursive estimation of $p(\mathbf{X}_i|\mathbf{Y})$ using RTS⁵ smoother

- Off-the-shelf Bayesian smoother
- Closed form, simple-to-compute
- Gaussian density estimates at each step
- Inherent uncertainty measure

⁵Rauch-Tung-Striebel



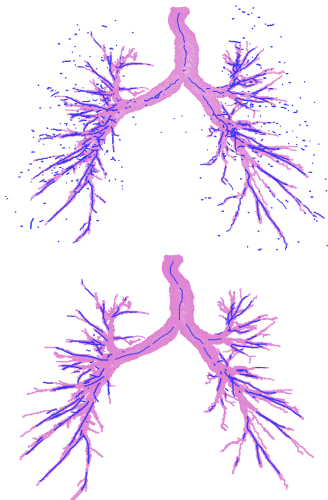
Qualification of tracked branches



- Exploratory nature → Several candidate branches
- Qualify branches based on posterior covariance
- Measures branch fitness to the model



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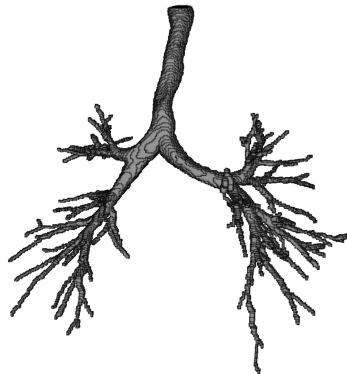
$$\mu_i = \frac{\sum_{k=1}^{l_i} \text{Tr}(\mathbf{P}_{k|k})}{l_i}. \quad (4)$$

$\mathbf{P}_{k|k}$ is posterior covariance matrix at step k .



Data

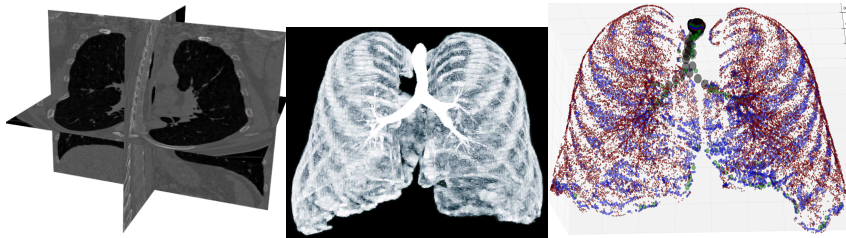
- Data from DLCST
- Reference dataset (32 scans)
- Additional 100 scans; automatic segmentations



Pedersen, J. H., et.al : The Danish randomized lung cancer CT screening trial overall design and results of the prevalence round. *Journal of Thoracic Oncology*, (2009)



Preprocessing of data



- Trained voxel classifier to obtain probability images (Lo et al.2010)
- Multi-scale Laplacian of Gaussians to obtain sparse point cloud

Lo, Pechin, et al. "Vessel-guided airway tree segmentation: A voxel classification approach." Medical image analysis 14.4 (2010): 527-538.



Experiments

- **Baseline:** Region growing on probability images
- Bayesian smoothing merged with region growing for evaluation
- Eight-fold cross validation



Experiments

- **Baseline:** Region growing on probability images
- Bayesian smoothing merged with region growing for evaluation
- Eight-fold cross validation
- **Error measures:**
 - Average centerline distance: $d_{err} = (d_{FP} + d_{FN})/2$
 - $d_{FP} \equiv$ Specificity
 - $d_{FN} \equiv$ Sensitivity
 - Percentage of tree length (TL)
 - False positive rate (FPR)



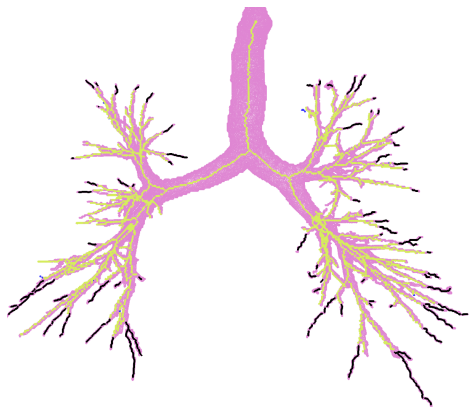
Performance comparison

	$d_{FP}(\text{mm})$	$d_{FN}(\text{mm})$	$d_{err}(\text{mm})$	TL.(%)	FPR(%)
Vox+RG	3.624 ± 0.776	5.155 ± 0.580	4.389 ± 0.441	79.6 ± 7.2	5.0 ± 3.9
BS+RG	3.921 ± 0.612	4.218 ± 0.334	4.069 ± 0.476	82.3 ± 6.1	8.7 ± 3.4

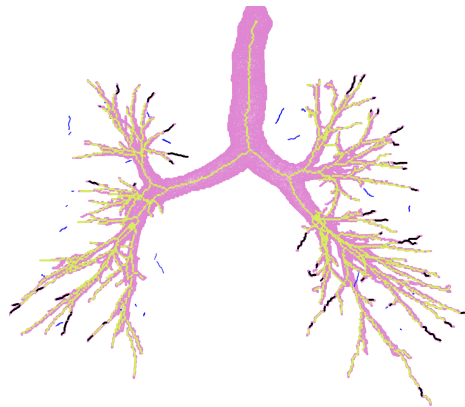
- $d_{FP} \equiv$ Specificity
- $d_{FN} \equiv$ Sensitivity
- Average centerline distance: d_{err}
- Percentage of tree length (TL)
- False positive rate (FPR)



Visualisation of extracted airways



Vox+RG



BS+RG

Legend: Reference (pink), True Positive (Yellow), False Negative (Black), False Positive (Blue)



Summary

- + Airway extraction in probabilistic state-space model setting
- + Bayesian smoothing method to track branches
- + Exploratory algorithm
- + Uncertainty estimates used to validate branches
- + Multivariate Gaussian density estimates /node/branch
- Increase in false positives
- Disconnected branches



Graph Refinement Models

Work based on

- [1] Raghavendra Selvan, Thomas Kipf, Max Welling, Jesper H. Pedersen, Jens Petersen, and Marleen de Bruijne. “Graph Refinement based Tree Extraction using Mean-Field Networks and Graph Neural Networks” (2018). (In progress)
- [2] Raghavendra Selvan, Max Welling, Jesper H. Pedersen, Jens Petersen, and Marleen de Bruijne. “Mean field network based graph refinement with application to airway tree extraction.” 21st Conference on Medical Image Computing & Computer Assisted Intervention (MICCAI 2018), pp. 750-758, Cham. Springer International Publishing.
- [3] Raghavendra Selvan, Thomas Kipf, Max Welling, Jesper H. Pedersen, Jens Petersen, and Marleen de Bruijne. “Extraction of Airways using Graph Neural Networks.” 1st Conference on Medical Imaging with Deep Learning (MIDL 2018), Amsterdam.



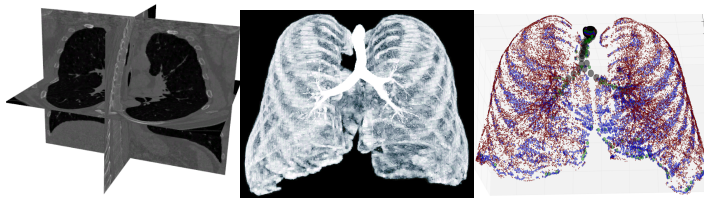
Graph Refinement Model for Airway Extraction

Motivation

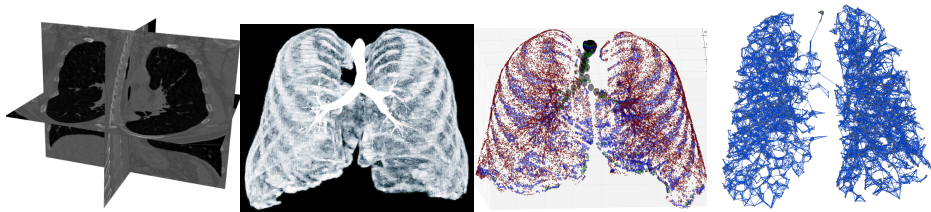
- Building on Bayesian smoothing method
- Graphs with features derived from Gaussian density
- Optimise global connectivity, instead of qualifying individual branches



Volumetric data to Graph data



Volumetric data to Graph data



- Overconnected input graph: $\mathcal{G}_{\text{in}} : \{\mathcal{V}, \mathcal{E}_{\text{in}}\}$, with $|\mathcal{V}| = N$
- Node features: $\mathbf{X} \in \mathbb{R}^{F \times N}$
- Input adjacency: $\mathbf{A}_{\text{in}} \in \{0, 1\}^{N \times N}$

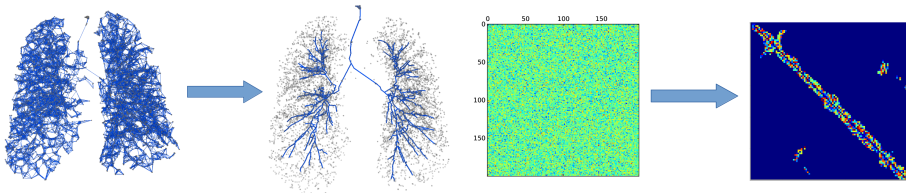


Airway extraction as Graph Refinement task

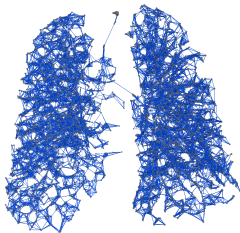
Graph Refinement Model

$$f : \mathcal{G}_{in} \rightarrow \mathcal{G}$$

Output subgraph \mathcal{G} with $\mathcal{E} \subset \mathcal{E}_{in}$; $\mathbf{A} \in \{0, 1\}^{N \times N}$



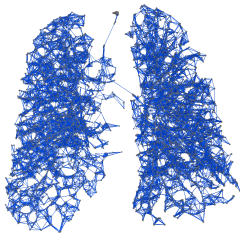
Probabilistic Graphical Model for MFN



- Binary random variable $s_{ij} \in \{0, 1\}$ with prob. $\alpha_{ij} \in [0, 1]$



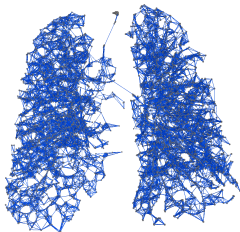
Probabilistic Graphical Model for MFN



- Binary random variable
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- For each node: $\mathbf{s}_i = \{s_{ij}\} : j = 1 \dots N$



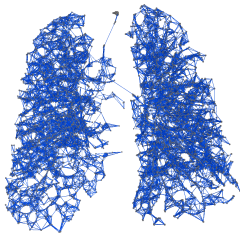
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- Instances of \mathbf{S} are $N \times N$ adjacency matrices



Probabilistic Graphical Model for MFN

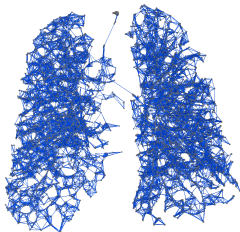


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Posterior density of interest: $p(\mathbf{S} | \mathbf{X}, \mathbf{A}_{in})$



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Posterior density of interest: $p(\mathbf{S} | \mathbf{X}, \mathbf{A}_{in})$

$$\begin{aligned} \ln p(\mathbf{S} | \mathbf{X}, \mathbf{A}_{in}) &\propto \ln p(\mathbf{S}, \mathbf{X}, \mathbf{A}_{in}) \\ &= \sum_{i \in \mathcal{N}} \phi_i(\mathbf{s}_i) + \sum_{(i,j) \in \mathcal{E}} \phi_{ij}(\mathbf{s}_i, \mathbf{s}_j) - \ln Z, \end{aligned}$$



Node and Pairwise Potentials for MFA

Node Potential: For each node $i \in \mathcal{V}$

$$\phi_i(\mathbf{s}_i) = \sum_{v=0}^D \beta_v \mathbb{I} \left[\sum_j s_{ij} = v \right] + \mathbf{a}^T \mathbf{x}_i \sum_j s_{ij}, \quad (5)$$

Pairwise Potential: For each edge, $(i, j) \in \mathcal{E}_{\text{in}}$

$$\phi_{ij}(\mathbf{s}_i, \mathbf{s}_j) = \lambda(1 - 2|s_{ij} - s_{ji}|) + (2s_{ij}s_{ji} - 1) \left[\eta^T |\mathbf{x}_i - \mathbf{x}_j| + \nu^T (\mathbf{x}_i \mathbf{x}_j) \right]. \quad (6)$$

Parameters = $[\cdot]$



Node and Pairwise Potentials for MFA

Node Potential: For each node $i \in \mathcal{V}$

$$\phi_i(\mathbf{s}_i) = \sum_{v=0}^D \beta_v \mathbb{I} \left[\sum_j s_{ij} = v \right] + \mathbf{a}^T \mathbf{x}_i \sum_j s_{ij}, \quad (5)$$

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Node and Pairwise Potentials for MFA

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Parameters = $[\boldsymbol{\beta}, \mathbf{a}, \lambda, \boldsymbol{\eta}, \boldsymbol{\nu}]$



Approximate posterior density with a simpler one



Approximate posterior density with a simpler one

Mean-Field Factorisation: $q(\mathbf{S}) \in \mathcal{Q}$

$$q(\mathbf{S}) = \prod_{i=1}^N \prod_{j=1}^N q_{ij}(s_{ij}), \quad (5)$$

Implication: Node connectivities are independent.



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Minimize KL Divergence \equiv Maximize Evidence Lower Bound (ELBO)

$$\text{ELBO}(q) = -\text{KLD}(q(\mathbf{S})||p(\mathbf{S}|\mathbf{X}, \mathbf{A}_{in})) + \ln Z \quad (7)$$



Maximising ELBO wrt $q_{ij}(s_{ij})$ yields MFA Iterations

MFA Iterations

$$\begin{aligned}\alpha_{kl}^{(t+1)} &= q_{kl}^{(t+1)}(s_{kl} == 1) \\ &= \frac{1}{1 + \exp^{-\gamma_{kl}}}\end{aligned}$$

$\forall k = \{1 \dots N\}, l \in \mathcal{N}_k$

α : Global connectivity prediction



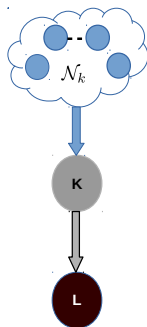
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$$\begin{aligned}\gamma_{kl} &= \prod_{j \in \mathcal{N}_k \setminus l} (1 - \alpha_{kj}^{(t)}) \left\{ \sum_{m \in \mathcal{N}_k \setminus l} \frac{\alpha_{km}^{(t)}}{(1 - \alpha_{km}^{(t)})} \left[(\beta_2 - \beta_1) \right. \right. \\ &\quad \left. \left. - \beta_2 \sum_{n \in \mathcal{N}_k \setminus l, m} \frac{\alpha_{kn}^{(t)}}{(1 - \alpha_{kn}^{(t)})} \right] + (\beta_1 - \beta_0) \right\} + \mathbf{a}^T \mathbf{x}_i \\ &\quad + (4\alpha_{lk}^{(t)} - 2)\lambda + 2\alpha_{lk}^{(t)} (\boldsymbol{\eta}^T |\mathbf{x}_i - \mathbf{x}_j| + \boldsymbol{\nu}^T (\mathbf{x}_i \mathbf{x}_j))\end{aligned}$$

↓

$$\alpha_{kl}^{(t+1)} = \sigma(\gamma_{kl}) = \frac{1}{1 + \exp^{-\gamma_{kl}}}$$

Note: MFA iterations resemble feed-forward operations in neural nets



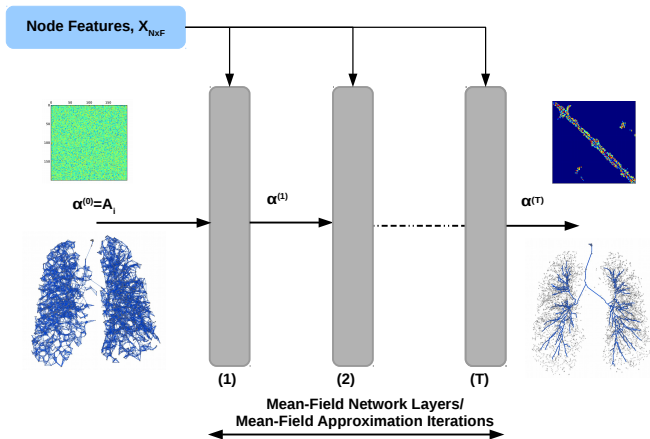
MFA as Mean-Field Networks

- T -iterations as a T -layered network



MFA as Mean-Field Networks

- T –iterations as a T –layered network
- Gradient descent to learn model parameters: $\mathcal{L}(\alpha, \mathbf{A}_r)$

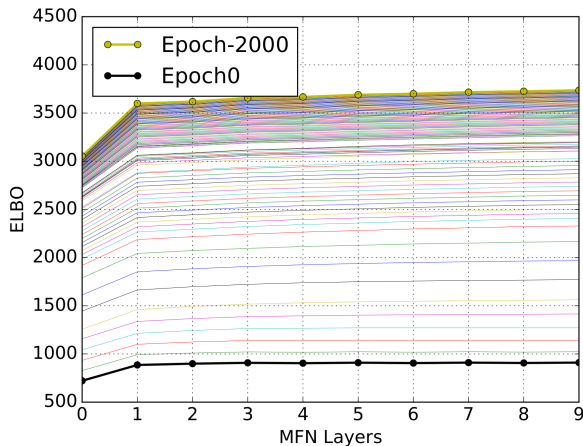


Experiments

- Same set-up as with Bayesian smoothing
- Pretraining dataset used to tune hyperparameters
- Eight fold cross validation



Increasing ELBO \implies Better approximation



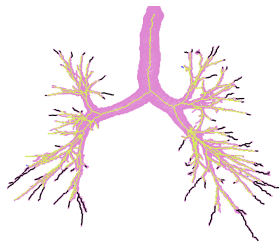
Performance comparison

	$d_{FP}(\text{mm})$	$d_{FN}(\text{mm})$	$d_{err}(\text{mm})$	TL(%)	FPR(%)
Vox+RG	3.624 ± 0.776	5.155 ± 0.580	4.389 ± 0.441	79.6 ± 7.2	5.0 ± 3.9
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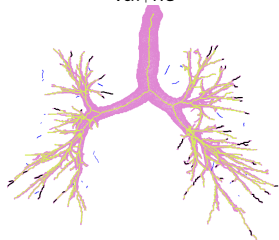
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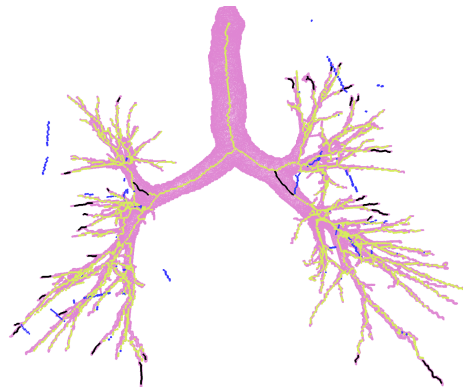
Visualisation of extracted airways



Vox+RG



BS+RG



MFN

Legend: Reference (pink), True Positive (Yellow), False Negative (Black), False Positive (Blue)



Summary

- Airway extraction as graph refinement
- Novel use of Mean-Field Approximation
- Proposed expressive node and pairwise potentials
- Mean-Field Network interpretation
- Few parameters (46 scalar weights)
- Easy to optimise using gradient descent
- Might not generalise across applications
- Hand-crafting potentials is cumbersome



Graph Neural Networks

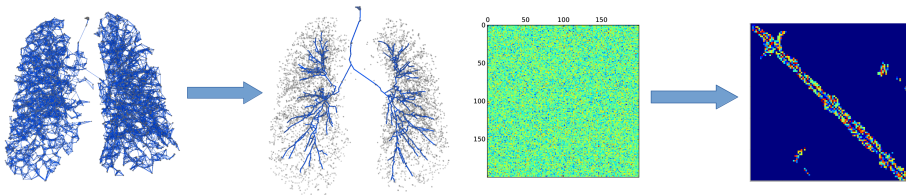


Graph Neural Networks

- Neural nets with graph input
- Step towards non-Euclidean (geometric) Deep Learning
- Generalisation of message passing algorithms
- Complex task-specific messages can be learnt
- End-to-end trainable inference systems



GNN based Graph Refinement



- Graph refinement task: $f : \mathcal{G}_{\text{in}} \rightarrow \mathcal{G}$
- GNN based encoder-decoder pair
- Encoder comprises stacks of GNNs; Message passing between nodes
- Joint training of encoder-decoder pair to learn useful embeddings
- Simple decoder predicts graph connectivity



GNN Model for Graph Refinement



GNN Model for Graph Refinement

Consider node j with neighbours \mathcal{N}_j ,

$$\text{Node Embedding: } \mathbf{h}_j^1 = g_n(\mathbf{x}_j) \quad (8)$$

$$\text{N2E mapping: } \mathbf{h}_{(i,j)}^1 = g_{n2e}([\mathbf{h}_i^1, \mathbf{h}_j^1]) \quad (9)$$

$$\text{E2E mapping: } \mathbf{h}_j^2 = g_{e2n}(\sum_{i \in \mathcal{N}_j} \mathbf{h}_{(i,j)}^1) \quad \forall i \in \mathcal{N}_j \quad (10)$$

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$g_{\dots}(\cdot)$ are MLPs, g_{dec} is MLP with 1 output channel



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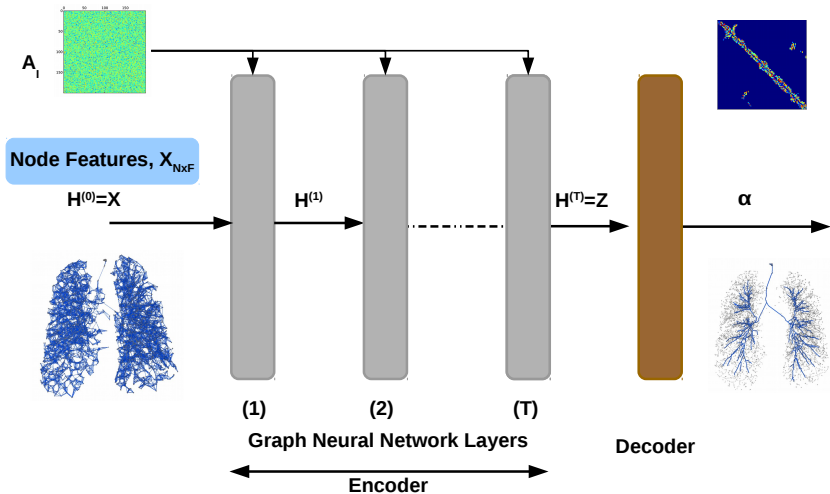
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Summarising GNN Model



Experiments

- Same set-up as with Bayesian smoothing, MFNs
- Pretraining dataset used to tune hyperparameters
- Eight fold cross validation



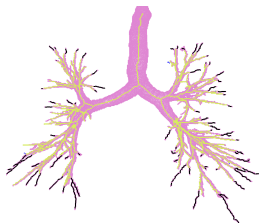
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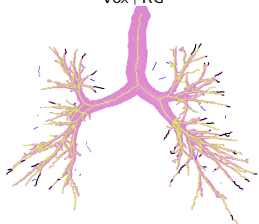
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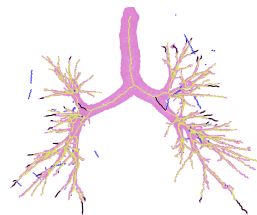
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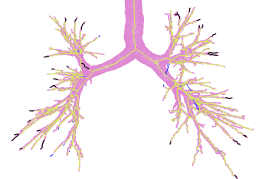
Vox+RG



BS+RG



MFN



GNN

Legend: Reference (pink), True Positive (Yellow), False Negative (Black), False Positive (Blue)



Summary

- GNN based supervised graph refinement
- Unique, inductive graph application of GNNs
- Edge embeddings used for prediction
- Competitive results with limited data
- Generalisations of MFNs
 - Disconnected trees
 - Relies on quality labelled training data



Outline

- ① Airway diseases and diagnosis
- ② Objective of the study
- ③ Data
- ④ Contributions
 - Multiple Hypothesis Tracking
 - Bayesian Smoothing
 - Graph Refinement Models
- ⑤ Summary & Conclusions



Summary of contributions

Addressed airway extraction from volumetric data with:

- Four exploratory methods
 - Modified MHT method
 - Bayesian smoothing
 - Mean-Field Networks
 - Graph Neural Networks
- Experimental validation on CT data
- Performance comparison with relevant baselines, mutual



Conclusions from the study

- Exploratory methods can extract more branches
- Graph based representations are less computationally intensive
- Using global information in local decisions is helpful
- Incorporating prior knowledge is valuable
- MFNs as structured neural networks
- GNNs as generalisations of message passing algorithms
- Bias-variance trade-off between MFNs and GNNs



Acknowledgements

- Max Welling
- Thomas Kipf
- BGR group, Erasmus MC



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Denmark (DFF)



Netherlands Organisation for
Scientific Research



And of course, The Image Section!



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