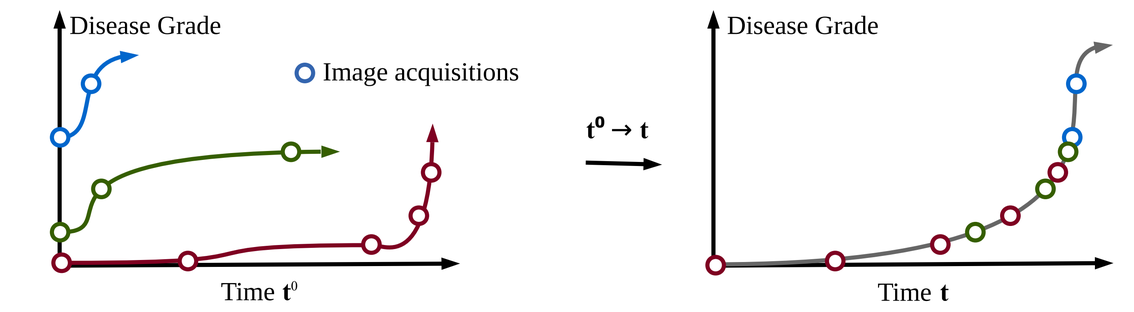
LONGITUDINAL ALIGNMENT OF DISEASE PROGRESSION IN FIBROSING INTERSTITIAL LUNG DISEASE

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Abstract

Generating disease progression models from longitudinal medical imaging data is a challenging task, due to the varying and often unknown state and speed of disease progression at the time of data acquisition. We propose an appearance driven method for aligning follow-up series of multiple patients *in time*, resulting in a cross-sectional spatio-temporal disease distribution model. We demonstrate the benefit by classifying instances of different fibrosing interstitial lung diseases.



Unaligned follow-up acquisitions of subjects. *Population-wide temporal alignment.*

Method

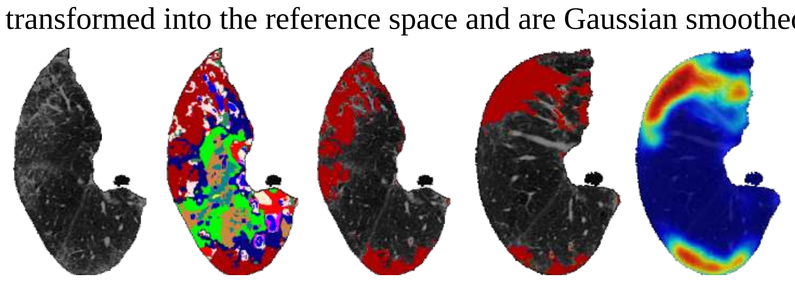
Idea

We assume that diseases at similar stage have a similar appearance. After identifying the disease appearance we perform an optimization process driven by a dissimilarity measure, where the acquisition time-points are shifted so that images with similar appearance are positioned close in time. From the aligned images we create a spatio-temporal disease progression model.

1. Identifying appearance classes in a joint reference space

Tissue classification. We perform unsupervised texture classification using Gray-Level Co-occurence matrices and Haralick features, followed by PCA and k-Means clustering with 15 clusters on the feature vector across the entire population. Two clusters forming reticular and honeycombing pathologic patterns are selected for further computation.

Atlas building. A mean shape, mean intensity atlas is build by group-wise LDDMM registration. Cluster labels are transformed into the reference space and are Gaussian smoothed, resulting in $\mathbf{G}_i$



From left to right: Lung CT with fibrosis, k-Means cluster labels, label forming reticular and honeycombing patterns, atlas transformed disease label, Gaussian smoothed label G_i.

2. Longitudinal Alignment

Dissimilarity Matrix. Compute Bray-Curtis dissimilarity matrix **D** from acquisitions **G**.

$$\mathbf{D}_{i,j} = \frac{\sum_x |\mathbf{G}_i(x) - \mathbf{G}_j(x)|}{\sum_x |\mathbf{G}_i(x) + \mathbf{G}_j(x)|}$$

Objective Function. Perform longitudinal alignment by minimizing $C(\mathbf{t})$ to obtain mapping of initial timepoints $\mathbf{t}^0$ to final timepoints **t**.
$C(\mathbf{t})$ contains three terms, (1) a tissue distribution similarity term S, (2) a temporal rigidity term R, (3) a disease volume regularization term V.
$c_{i,j}$ is 1 if acquisitions i and j are from the same subject, 0 otherwise. Second constraint keeps order of acquisitions within a subject. λ and μ are weighting factors for the second and third term.

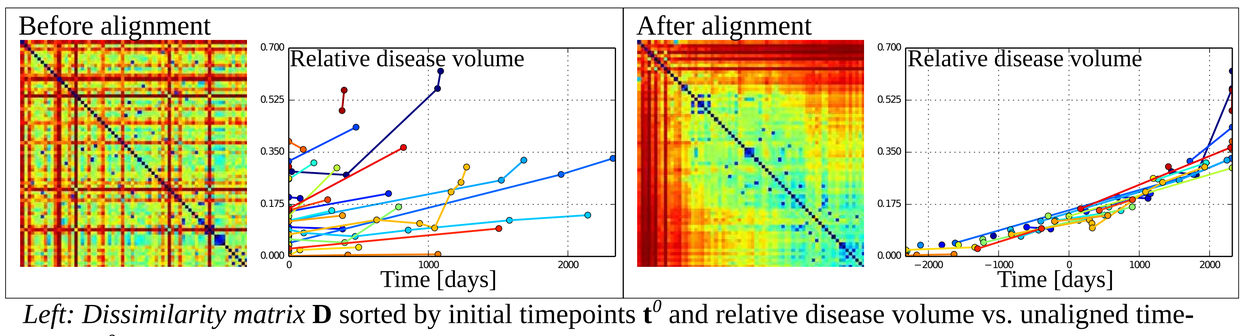
$$\begin{aligned}\mathbf{t} &= \underset{\mathbf{t}}{\operatorname{argmin}}(C(\mathbf{t})) = \\ &= \underset{\mathbf{t}}{\operatorname{argmin}}(S(\mathbf{t}) + \lambda R(\mathbf{t}) + \mu V(\mathbf{t})) \\ &\text{subject to } \; t_{\min} < t_i < t_{\max}, \quad t_i \in \mathbf{t} \\ &t_i < t_j \Leftrightarrow t_i^0 < t_j^0, \quad c_{i,j} = 1, \; t_i, t_j \in \mathbf{t}\end{aligned}$$

Similarity term. Penalizes dissimilarities of pairs of acquisitions within a short temporal distance.
w weights the dissimilarity costs according to the temporal distance.

$$S(\mathbf{t}) = \sum_i \sum_j w(t_i, t_j)\mathbf{D}_{i,j}$$
$$w(t_i, t_j) = \exp\left(-\frac{(t_i - t_j)^2}{h^2}\right)$$

Temporal rigidity term. Penalizes temporal distance deviations of acquisition within a subject. We can assume temporal rigidity if disease progression speed is the same over the whole population.

Disease volume regularization term. Enforces acquisitions with a higher disease volume to be sorted after acquisitions with a lower disease volume



Left: Dissimilarity matrix **D** sorted by initial timepoints $\mathbf{t}^0$ and relative disease volume vs. unaligned time-points $\mathbf{t}^0$ per patient. Right: **D** sorted by aligned timepoints **t** and relative disease volume vs. aligned timepoints **t**.

3. Disease progression model building

From the aligned acquisitions we generate a cross-sectional spatial distribution **G** at an arbitrary timepoint t, by computing a weighted sum of the label distributions **G:**

$$\bar{\mathbf{G}}(\mathbf{t}, \mathbf{t}) = \frac{1}{Z} \sum_i w(\mathbf{t}, t_i) \cdot \mathbf{G}_i$$

Label distributions close to specified timepoint t gets an higher weight than volumes farther away. A time-parameterized spatio-temporal disease progression model **M**(t) is obtained by computing $\bar{\mathbf{G}}$ at any timepoint.

4. Fitting a new subject to the disease progression model

Atlas-transformed smoothed label acquisitions $\mathbf{G}^s$ of a new subject are fitted to the model **M** by finding the optimal timepoints $\mathbf{t}^s$ in an optimization process, so that the Kullback-Leibler distance of the subject label distributions and the model label distribution is minimized.

$$\mathbf{t}^s = \underset{\mathbf{t}^s}{\operatorname{argmin}} \sum_i \left(D_{\mathrm{KL-Sym}}(\mathbf{M}(t_i^s) || \mathbf{G}_i^s) \right) + \lambda R(\mathbf{t}^s)$$

Experimental Results

Data

70 HRCT thorax acquisitions from 31 patients with instances of fibrosing interstitial lung diseases, with 29 Usual Interstitial Pneumonia (UIP), 15 Nonspecific Interstitial Pneumonia (NSIP), 21 chronic Extrinsic Allergic Alveolitis (EAA), and 3 other.

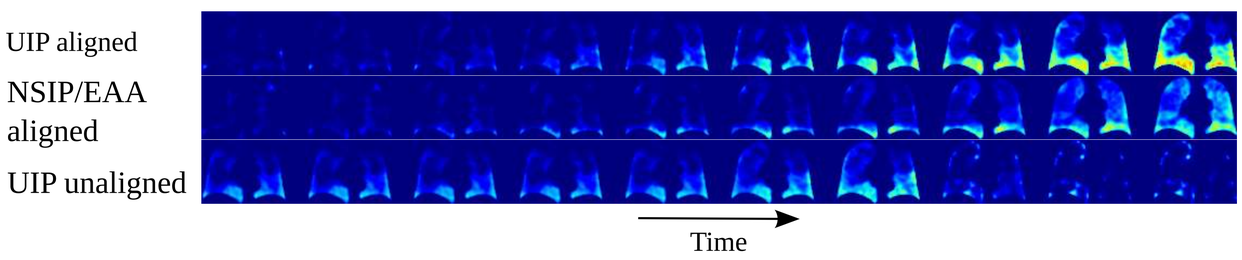
Questions

- Does longitudinal alignment improve classification UIP vs. non-UIP, resp. UIP vs. EAA?
- Influence of temporal rigidity regularization term.

Experiment

Evaluation has been performed in a leave-one-out cross validation setting per subject. A spatio-temporal model is built for UIP, EAA and non-UIP from the training cases, once with the temporal rigidity term (rigid) and once without this term (non-rigid). The test case is fitted to the models. The disease label is determined by the model which fits better to the test case, indicated by a lower Kulback-Leibler divergence.

Model building results





3D reconstruction of the UIP model at four timepoints.

Classification Results

Temporal alignment improves classification results. Non-rigid temporal alignment performs better than rigid in the case of UIP vs. EAA.

Alignment	UIP vs non-UIP AuC	UIP vs EAA AuC
Non-rigid	0.771	0.875
Rigid	0.775	0.812
Un-aligned	0.710	0.781

Conclusion

We propose to align disease progression across patients based on imaging data. The alignment establishes temporal correspondence across patients, and enables building progression models that reflect observations made across multiple patients. The alignment is based on appearance patterns that are identified by unsupervised learning in a study population. It allows fitting a new subject to an existing model, and thereby allows for evaluating the similarity between an individual and a population whose imaging data spans different disease stages.
We evaluated the longitudinal alignment in terms of classification performance, by differentiating between UIP and non-UIP, resp. UIP and EAA. Results show that temporal alignment of longitudinal data improves the classification performance in this case.

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