Population-wide Disease Modeling to Predict Macular Thickness and Treatment Response in Longitudinal OCT Data

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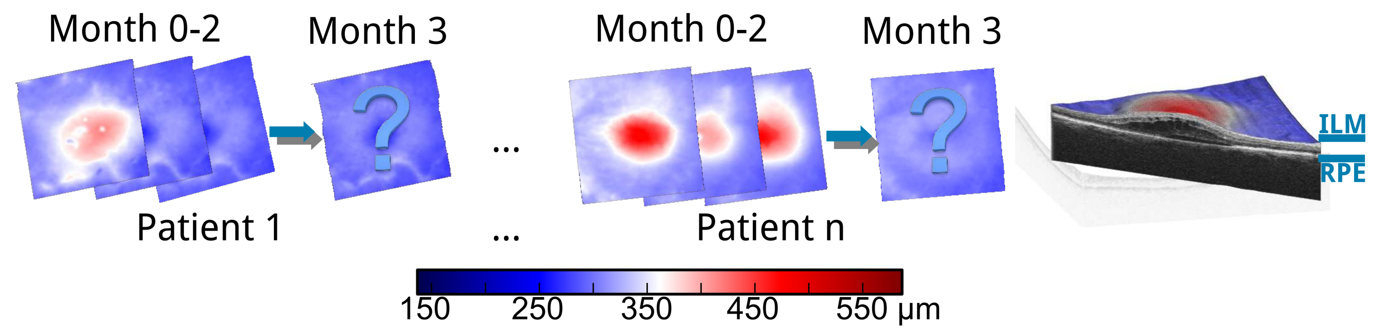
Introduction

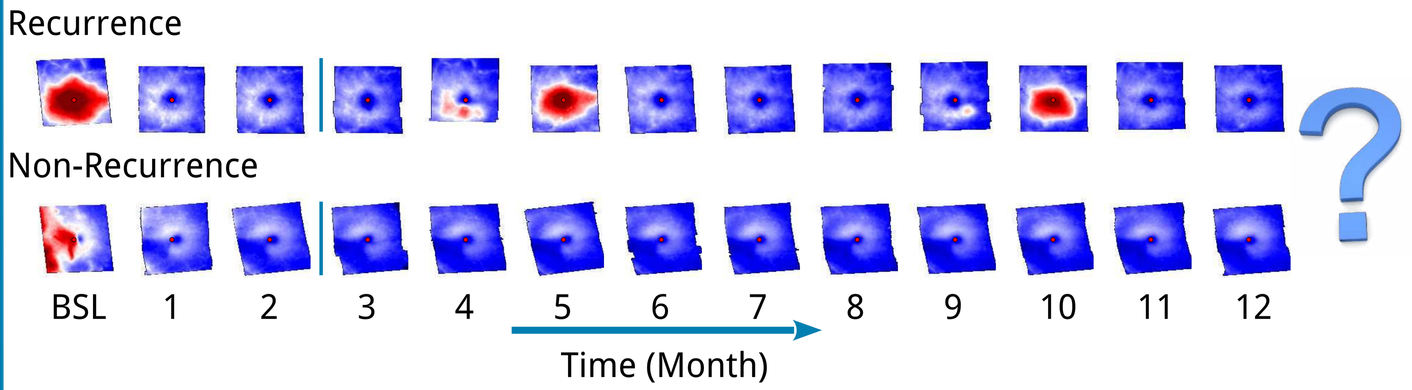
Motivation:
The ability to predict the future development of a disease is an extremely important goal both in clinical and scientific practice, as well as in the general health care setting.

Aim:
Predict **future** treatment response and disease path from longitudinal spectral domain optical coherence tomography (SD-OCT) images.

(1) Predict the total retinal thickness at month four from initial three month induction phase.



(2) Predict from retinal images of the first three month if macular edema will recur within a 12 month follow-up period.

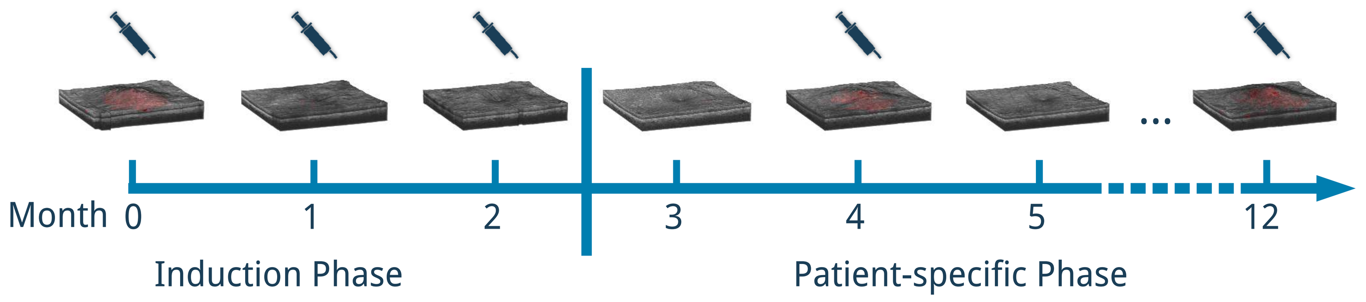


Idea:
- Learn disease progression patterns from a large cohort of longitudinal SD-OCT images using sparse machine learning methods.
- Use total retinal thickness maps as feature describing the development of the underlying retinal structure and pathology.
- Normalize scans to compensate for anatomical and scan position variations.

Data

Training and Validation Set:
- 155 patients with macular edema secondary to central retinal vein occlusion.
- Retinal SD-OCT baseline scan + 12 monthly follow-up scans from two vendors (Heidelberg Spectralis, Zeiss Cirrus). 2,015 scans overall.
- 28 patients showed no recurring edema within 12 month (= 18%).

Treatment:
- Three month induction phase with monthly ranibizumab injections, followed by a PRN (pro re nata = per need) regimen.



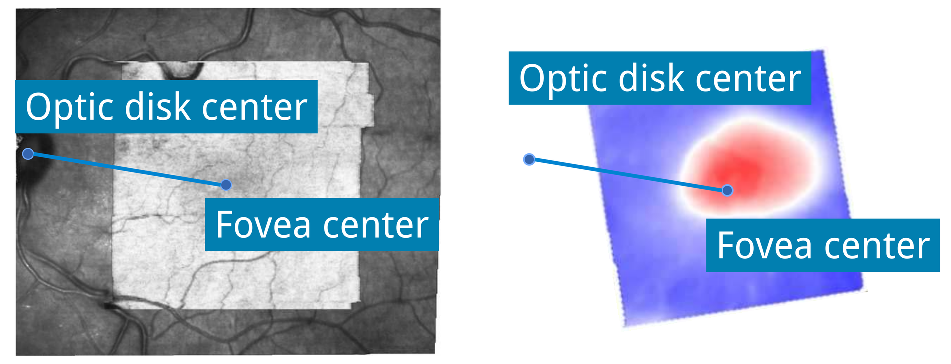
Methods

1. Total Retinal Thickness Maps
- Total retinal thickness maps are computed as distance between ILM and RPE layer. Layers are automatically segmented using Iowa reference algorithm[1].

2. Spatio-temporal Features in a Joint Reference Space
- Transformation of scans and thickness maps into a joint reference space via:

(1) Intra-patient registration by aligning the vessel structures[2]
(2) Inter-patient registration by aligning fovea center and optic disk center landmarks

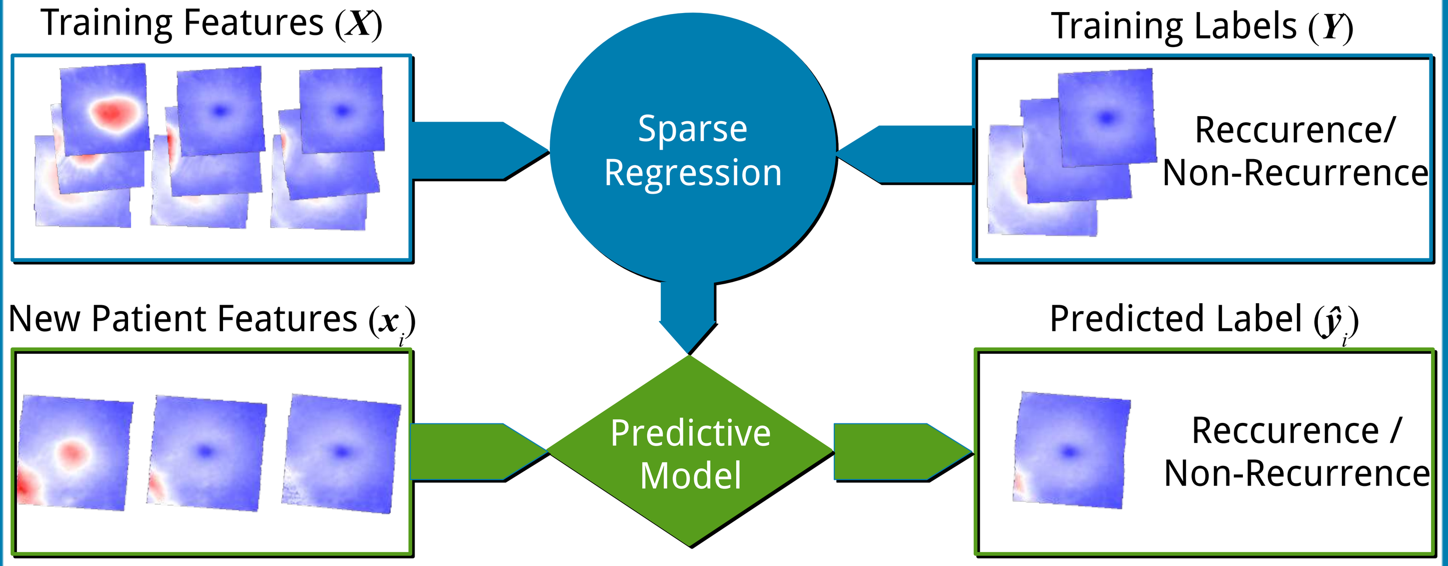
(1) Intra-patient registration of follow-up scans via vessel structures.



(2) Inter-patient registration via optic nerve head center and fovea center. Transformation of the thickness map into the joint reference space.

- Concatenate transformed thickness maps into a feature vector, forming a spatio-temporal disease signature for each individual.
- Pool feature vectors in a design matrix X for training the disease model.

3. Prediction



- Multivariate regression in a high-dimension-low-sample-size setting (p>>n).
- Generalized linear model (GLM) with elastic net regularization[3] to get sparse coefficients w.
- Non-zero coefficients reveals anatomically important locations for prediction.
- Logistic regression GLM is used for prediction of recurrence / non-recurrence of edema.

Linear regression with elastic net regularization:

$$\arg\min_{\mathbf{w}} \frac{1}{2n_{samples}} * ||\mathbf{y} - \mathbf{X}\mathbf{w}||_2^2 + \lambda * l1_{ratio} * ||\mathbf{w}||_1 + \frac{\lambda}{2} * (1 - l1_{ratio}) * ||\mathbf{w}||_2^2$$

Logistic regression with elastic net regularization:

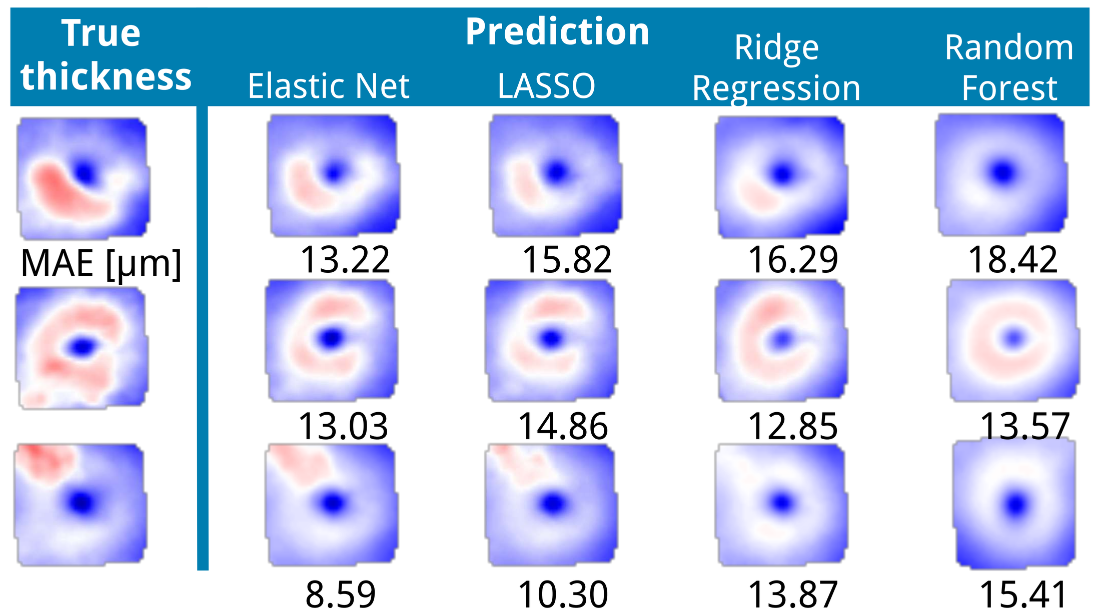
$$\arg\min_{\mathbf{w}} \sum_{i}^{n} \log(1 + \exp(-y_i \mathbf{w}^T \mathbf{x}_i)) + \lambda * l1_{ratio} * ||\mathbf{w}||_1 + \frac{\lambda}{2} * (1 - l1_{ratio}) * ||\mathbf{w}||_2^2$$

Results

Validation
- 5-fold cross validation setup.
- Compare elastic net regression and logistic regression with other regression methods (Random forest, LASSO, Cox...).
- Performance measures:
  - Mean absolute error (MAE) in µm for thickness prediction.
  - Sensitivity / specificity, and ROC Area under curve (AuC) for recurrence prediction.

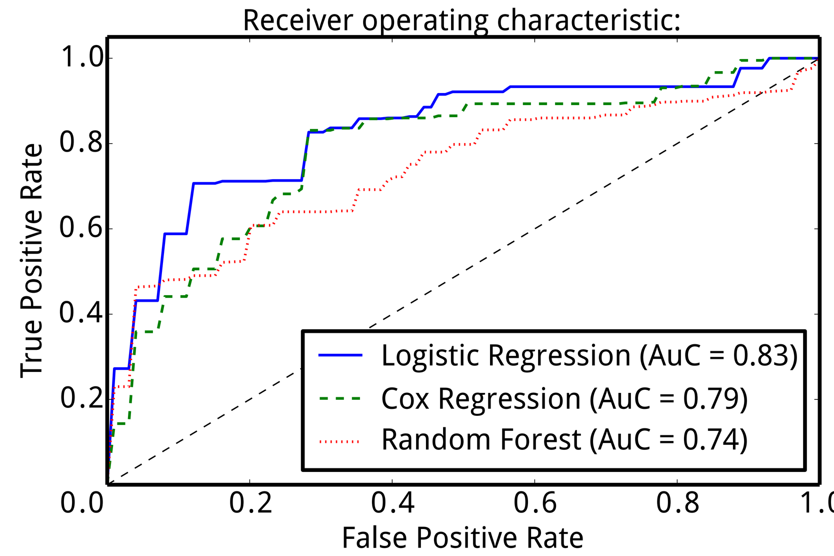
Prediction of Total Retinal Thickness

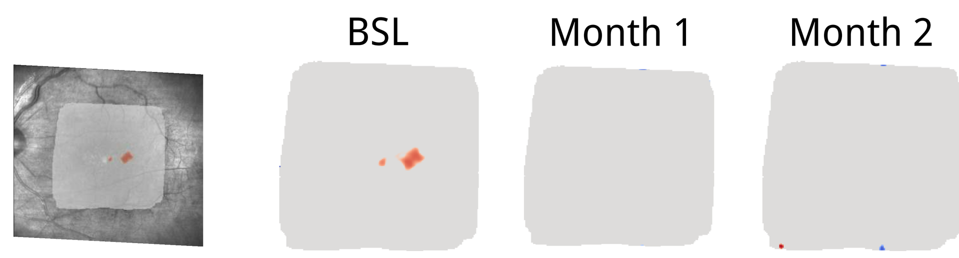
Method	Parameter	Median MAE [µm]	Mean (Std) MAE [µm]	R^2
Elastic Net	λ = 500, l1 = 0.5	**13.64**	**20.26** (20.86)	**0.45**
LASSO	λ = 100	14.71	20.88 (21.50)	0.40
Ridge Regression	λ = 1.4 x 10^7	14.83	21.47 (20.97)	0.43
Random Forest	trees = 100	16.03	21.91 (19.48)	0.43



Prediction of Recurring / Non-recurring Edema

Method	Sensitivity	Specificity	ROC AuC
Logistic Regression	**70**	75	**83**
Cox Regression	**70**	73	79
Random Forest	32	**93**	74





Sparse coefficients of logistic regression. Note that mainly baseline thicknesses in fovea and parafovea temporal areas are selected.

Conclusion

- We propose a method for prediction of **future** development of disease under treatment using sparse machine learning models based on longitudinal SD-OCT imaging data.
- The method predicts the outcome of two variables: (1) total retinal thickness after induction phase, (2) non-recurrence vs. recurrence of edema within twelve month follow-up.
- Sparse feature selection via elastic net in a multivariate generalized linear model setting yields accurate predictions and interpretable results.

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