Predicting Future Visual Acuity Outcomes From Early Morphologic and Functional Response in Anti-VEGF Treated Retinal Vein Occlusion

Wolf-Dieter Vogl[1,2] , **Sebastian M. Waldstein**[2] , **Bianca S. Gerendas**[2] , **Thomas Schlegl**[1,2], **Jing Wu**[2] , **Dominika Podkowinski**[2] , **Ursula Schmidt-Erfurth**[2] **and Georg Langs**[1]

[1]Computational Imaging Research Lab (CIR), Department of Biomedical Imaging and Image-guided Therapy [2]Vienna Reading Center, Department of Ophthalmology and Optometry

Christian Doppler Laboratory for Ophthalmic Image Analysis (OPTIMA), Medical University of Vienna, Austria

3397 - D0334

Financial disclosures: Waldstein: Bayer Healthcare AG; Novartis Pharma AG (Consultant)
Osborne: Genentech, Inc (Employment)
Schmidt-Erfurth: Alcon Laboratories, Inc.; Bayer Healthcare AG;Boehringer Ingelheim GmbH; Novartis Pharma AG (Consultant)

Introduction

Motivation:
Predicting the subject-specific future outcome of a disease under treatment is essential in precision medicine.

Aim:
Predict **future** visual acuity outcomes of patients under treatment from early time-points combining longitudinal spectral domain optical coherence tomography (SD-OCT) images and ETDRS Best-Corrected Visual Acuity (BCVA) scores.

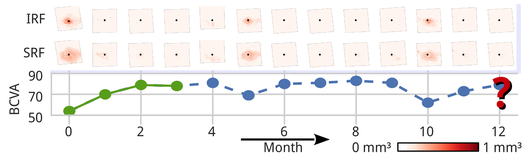

Fig.1: Visits of a patient over one year. Top rows show en-face projection of intraretinal (IRF) and subretinal (SRF) fluid. Bottom row shows the corresponding measured BCVA score. We predict the visual acuity outcome at month 12 based on fluid volume and BCVA from initial time-points (illustrated as green dots).

Methodology

• Assumption: visual acuity and its development is affected by three major factors: (1) amount of fluid in retina, (2) reversible damage and (3) irreversible damage.
• Population-wide BCVA trajectories are modeled as a function of time and fluid volume using Mixed-effects regression [1]. Using random slope and intercept per subject allows to model deviation from population-wide BCVA trajectory accounting for variance in reversible and irreversible damage (random intercept) and speed of recovery (random slope) (Fig.3).
• IRF and SRF volume in central millimeter are obtained from automatic segmentations in fovea aligned OCT volumes [2] (Fig.4).
• BCVA trajectories for an unobserved subject are predicted from population-wide model and initial subject observations by estimating random intercept/slope and BCVA trajectory for the subject using Best Linear Unbiased Predictor (BLUP) [1].

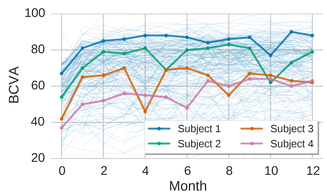

Fig. 2: BCVA trajectories of analyzed dataset (thin blue lines). Trajectories for 4 subjects are highlighted, illustrating the variance in initial BCVA and maximum gain in BCVA, as well as spiky deviations due to recurrence of edema.

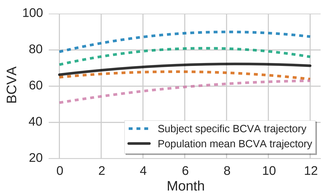

Fig. 3: Mean BCVA trajectory obtained from the mixed-effects model and subject specific deviations modeled by random effects.

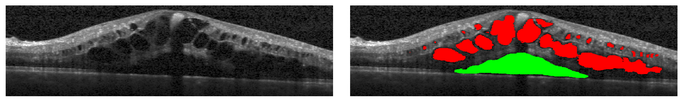

Fig. 4: Example of an automatic segmentation of IRF (red) and SRF(green).

Results - Model fit

Training and Validation Set:
• 194 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). 2,433 scans overall.
• ETDRS BCVA acquired at each visit.
• Treatment: three month induction phase with monthly ranibizumab injections, followed by a PRN (pro re nata = per need) regimen.

Models:
• Two models were fitted to BCVA scores, one incorporating IRF and SRF volume, as well as a quadratic time term ($\mathcal{P}_{bcva+oct}$), and a baseline model assuming linear trajectories based on BCVA only ($\mathcal{P}_{bcva}$).

Results:
Morphology:
• IRF and SRF volume factors were significant (p<0.0001).
• An increase of IRF / SRF volume by 1000 µm³ cause a mean decrease (SD) in BCVA of 0.0409 (0.00021) / 0.0258 (0.0033) letters.
• Median IRF volume at baseline is 188 x 10³ µm³, resulting in median reduction of BCVA by 7.6.

Goodness-of-fit:
• Marginal R^2 (variance explained by fixed factors): 0.108 ($\mathcal{P}_{bcva+oct}$), 0.021 ($\mathcal{P}_{bcva}$)
• Conditional R^2 (fixed and random factors): 0.900 ($\mathcal{P}_{bcva+oct}$), 0.826 ($\mathcal{P}_{bcva}$)
• $\mathcal{P}_{bcva+oct}$ is significantly better than $\mathcal{P}_{bcva}$ in a likelihood ratio test (p<0.0001) and has a lower Akaike Information Criterion (AIC) score.

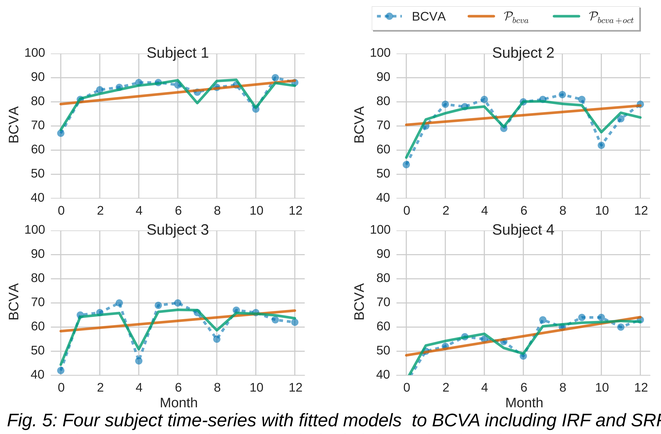

Fig. 5: Four subject time-series with fitted models to BCVA including IRF and SRF volume ($P_{bcva+oct}$),resp. without morphologic information (P_{bcva}).

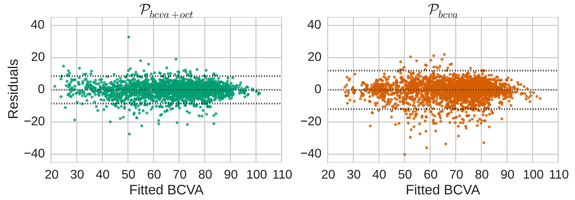

Fig. 6: Residual plots for the two models. Dotted lines are mean and ±1.96 SD of residuals. Residual SD in $\mathcal{P}_{bcva+oct}$ model is lower than in $\mathcal{P}_{bcva}$.

Results - Prediction

Validation
• 5-fold cross validation setup.

• Population models $\mathcal{P}_{bcva+oct}$ and $\mathcal{P}_{bcva}$ are computed from training fold.

• For each subject in test fold random factors and BCVA trajectories are predicted for an increasing amount of time-points. (Fig. 7)

• Target variable: median BCVA month 10 to 12

• Performance measures:
  • Mean absolute error (MAE) in letters.
  • Predicted R^2

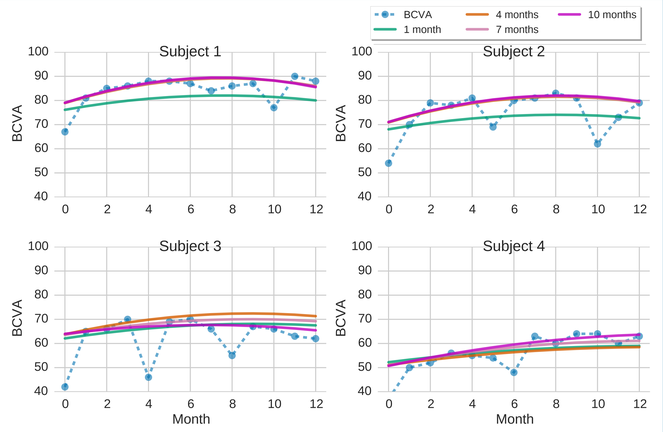

Fig. 7: Predicted BCVA trajectories for four subjects using 1,4,7 resp. 10 months. Note the refinement of trajectories with increasing number of time-points available for prediction.

Table 1: BCVA outcome prediction performance with increasing numbers of time-points used for prediction (#months). $\mathcal{P}_{bcva+oct}$ yield a significant better performance than $\mathcal{P}_{bcva}$. P-values are from a Diebold-Mariano (DM) test.

	MAE (SD) [letters]		Predicted R^2	
	$\mathcal{P}_{bcva+oct}$	$\mathcal{P}_{bcva}$	$\mathcal{P}_{bcva+oct}$	$\mathcal{P}_{bcva}$
BSL	**8.78** (8.16)	9.91 (7.92)***	**0.36**	0.29
4 months	**5.84** (6.13)	6.46 (6.48)**	**0.64**	0.63
7 months	**4.70** (5.02)	5.79 (5.33)***	**0.79**	0.73
10 months	**4.05** (4.50)	4.49 (4.58)	**0.84**	0.81

*** p < 0.001, ** p < 0.01, * p < 0.05

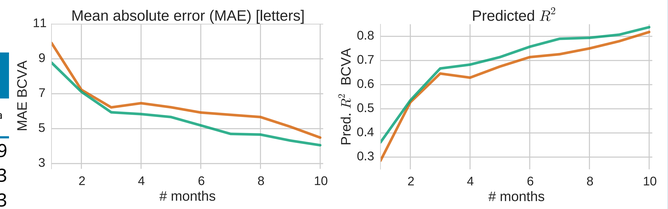

Fig. 8: Performance in terms of MAE and predicted R^2 when using increasing numbers of time-points for prediction (#months).

Conclusion

• We propose a method to predict **future** visual acuity development and outcome under treatment combining knowledge from a population-wide model and patient specific information from initial visits.
• Longitudinal mixed-effects-model allow to model the population-wide trend of BCVA development, and the patient-wise deviation from the general trend accounting for the various disease progression stages at first visit and differing response to treatment. Furthermore, the model allows to estimate the influence of intraretinal and subretinal fluid on BCVA.
• Incorporating intraretinal and subretinal fluid into the model from automatic segmentations in SD-OCT images improve model accuracy and prediction performance.

References

[1] Laird, N.M., Ware, J.H.: Random-effects models for longitudinal data. Biometrics (1982) 963-974
[2] Schlegel, T. et al.: Predicting Semantic Descriptions from Medical Images with Convolutional Neural Networks. Information Processing in Medical Imaging, 24th International Conference, IPMI 2015 (2015)

Department of Ophthalmology | http://optima.meduniwien.ac.at

wolf-dieter.vogl@meduniwien.ac.at

Financially supported by the Austrian Federal Ministry of Science, Research and Economy and the national Foundation for Research, Technology and Development