The assessment of retinal structure and neurodegeneration with optical coherence tomography

Doctoral theses

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1. Introduction

Optical coherence tomography (OCT) is one of the most commonly used imaging techniques in ophthalmology, playing an important role in the assessment of the anterior and posterior segments of the eye, influencing clinical decisions in various retinal pathologies. This non-invasive imaging method is based on low coherence interferometry and the measurement of reflectance differences of the retinal tissue. It provides a 2-3 μm depth resolution cross-sectional mapping (B-scan) of the retina. The segmentation of B-scans allows to examine retinal structure by layers, which could also be helpful in understanding the exchange of information between different cells and cellular layers that build up the retina. In addition to the objective measurement of the thickness of the retina and retinal layers, OCT allows B-scan based detection and calculation of changes in texture and optical properties. Such parameters are the reflectivity, contrast, and fractal dimension of the retinal layers. Previously in 2006, Bizheva et al. has shown that the OCT-derived optical properties of the retina may vary due to metabolic activity by light stimulation. Similarly, Huang et al. have described early changes in the reflection of the RNFL in a rat model of glaucoma. Thus, it seems logical that retinal thickness and optical parameters may provide an opportunity for the detection and differnatiation of pathological changes in the retina. Such an analysis could be a useful aid in both the diagnosis and follow-up of retinal diseases, supporting therapeutic decisions and the evaluation of their effectiveness.

Time-domain OCT (TD-OCT) had previously been extensively used in clinical practice and research as well; by now it has been replaced by spectral-domain OCT (SD-OCT) allowing faster and more precise imaging. The current commercially available devices are allowing the measurement of total thickness of the retina and also a limited segmentation of the inner retinal layers. However, automated measurements of the built-in software may be often be incorrect due to the presence of artifacts. These artifacts can be operator or software dependent, with some differences between the types of artifacts on TD- and SD-OCT. In addition, in pathological conditions such as diabetic macular edema, age-related macular degeneration, uveitis, or severe myopia, the automatic thickness measurements are failing quite often because of the false labeling of the retinal borders. An important adjustment of the OCT examination is the appropriate scanning distance of the examined eye, but its role in the presence of artifacts has not been studied yet.

In TD-OCT the built-in software is not suitable for the segmentation and separate measurement of retinal layers, while for SD-OCT the measured data are not accessible for external processing. For this reason, most groups are using manual segmentation which is still the gold standard for OCT image processing. The shortcoming of manual segmentation is that it is extremely time-consuming, inter- and intra-observer errors are common, and only small amounts of data can possibly be processed. Automated segmentation methods can get overcome these difficulties. Automated segmentation softwares for TD-OCT scans have been developed by several research teams, including DeBuc et al. In our studies, we used the custom-built OCT Retinal Image Analysis (OCTRIMA) software, developed by the Bascom Palmer Eye Institute of the University of Miami. This A-scan-based segmentation software is semi-automatic, after an automated segmentation offering manual refinement of any possible segmentation errors. Today, the wide clinical use of SD-OCT has lead to a new challenge for developers of segmentation algorithms due to the demand for a fast and efficient acquisition of large volume data. Noise, shadowing by retinal vessels and mostly retinal pathologies are the most challenges for recent automatic segmentation methods and algorithms that comply with these challenges are not currently available for either research or commercial use.

With the use of OCT image segmentation we can better understand not only the pathology of the retina but also the disorders of the central nervous system. Since the retina is part of the central nervous system, its structure could mirror the structure of the brain. Thus, retinal changes of the retina in neurological disorders would be much easier to measure and monitor, providing an opportunity to define disease-specific parameters that could be used as surrogate markers in clinical practice.

Multiple sclerosis is a chronic inflammatory disease of the central nervous system, associated with nerve fiber demyelination and axonal degeneration. It is the most common neurological disorder of young adults, which can lead to permanent disability and early retirement among the working-age population. In 20% of the cases the disease is first seen as acute inflammation of the optic nerve, although optic neuritis (ON) occurs in about 50% of the patients during the course of MS. Diagnosis and therapy of this disease is currently based on clinical, laboratory (liquor), radiological (MRI) and electrophysiological (visually evoked potential) examination results.

After the acute period of optic neuritis, the thinning of the nerve fiber layer (RNFL) and ganglion cell - inner plexiform layer complex (GCL+IPL) was observed within 5 weeks

to 3 months. Significant decrease was observed in the GCL+IPL not only in the affected but also in the fellow eyes, compared to healthy controls. In a post-mortem examination of Green et al., histological changes were found not only in the GCL but also in the INL, containing bipolar and amacrine cells. In multiple sclerosis the thinning of both inner and outer retinal layers were shown with spectral-domain OCT image segmentation. Correlation was seen between the structural changes of the retina and the central nervous system. Several studies found correlation between GCL+IPL thickness and visual acuityas well as between GCL+IPL thickness and EDSS values. In addition, there was a connection found between GCL+IPL thickness, electrophysiological and MRI parameters. All these findings suggest that changes in this layer can play an important role in the follow-up of neurodegeneration in the future.

Diabetes mellitus (DM) is a chronic metabolic disorder that is getting endemic not only in the developed Western world, but also in the developing world. By the continuos growth of its prevalence it becomes an increasing challenge in healthcare and economy, representing a significant social burden. Diabetic retinopathy (DRP) has now become a leading cause of adult vision loss in developed countries.

The complications of the posterior segment in diabetic retinopathy, most notably the presence and changing of diabetic retinal edema, can properly be detected by segmentation of OCT images, sometimes even when biomicroscopy and angiography do not show any deviation. Using OCT segmentation makes it possible to detect tissue level changes of the retina, especially in the early stages of macular diseases. Previous studies have described the thinning of the entire retina in patients with mild non-proliferative diabetic retinopathy (MDR) in both type 1 and type 2 diabetes mellitus compared to healthy controls. The thinning of the inner retinal layers have been shown to be behind this decrease. In addition, GCL thinning has been demonstrated in diabetic patients in the pericentral region of the macula that was also connected with decreased visual function. In a previous study of our workgroup with DRP and MDR patients, RNFL thickness was decreased in the pericentral and peripheral regions of the macula, while GCL+IPL thickness was reduced in the pericentral region of the macula in the MDR group. Another study has also shown thinning of the outer retinal layers compared to the macular thickness of age-matched healthy controls. These results indicate that neurodegenerative processes in the retina can be demonstrated early on, in the stage of mild DRP by the use of OCT examination.

2. Objectives

1. Investigation of thickness and optical property changes the retinal layers in type 1 diabetes

The purpose of our study was to evaluate the potential effects of suspected neurodegeneration in the retina in type 1 DM. In addition to the description of the macular thickness changes, we also planed to observe the changes by different optical parameters. The optical properties used in our study were layer index (the calculation of which was based on the reflectivity of the layers of the retina) and fractal dimension for the description of textural changes. We aimed to compare the structural differences of eyes with mild non-proliferative DRP with the eyes of non-DRP patients.

2. Investigations of changes in thickness and optical properties in retinal layers in multiple sclerosis.

Our aim was to evaluate the changes in thickness and optical properties of the retinal layers such as contrast, fractal dimension, layer index and total reflectivity in the macula in patients with multiple sclerosis. Our investigations were performed in eyes of MS patients with and without optic neuritis in their medical history.

3. The effect of incorrect scanning distance on boundary detection errors and macular thickness measurements by SD-OCT

The aim of our study was to investigate whether the scanning distance settings effect the quality of the captured SD-OCT image and the retinal boundary detection errors (RBDEs) of the RTVue built-in software. Our research was performed on healthy subjects and subjects with DME and wet AMD.

4. Testing of a new, automated segmentation software of macular SD-OCT images

The OCTRIMA 3D image analysis software was developed for processing SD-OCT volume scans. Our goal was to compare the automatic segmentation results of the new application with the results of the manual segmentation method as gold standard, and to examine the processing speed on the same sample, compared to other state-of-the-art software.

3. Methods

1. Investigation of changes in thickness and optical properties in the retinal layers in type 1 diabetes

In our prospective study we included 58 type 1 diabetic patients who had no or mild retinopathy (under ETDRS-level). Exclusion criteria were proliferative retinopathy, clinically significant diabetic macular edema (CSME), ocular disorders affecting macular structure, such as glaucoma, vitreo-retinal traction or epiretinal membrane. The examined eyes were divided into two groups based on the presence of mild retinopathy. The affected group (MDR) consisted of 43 eyes of 29 subjects (females: 49%, mean age: 43 ± 17 years), the non-affected group (DM) consisted of 38 eyes of 29 individuals (females: 53%, mean age: 35 ± 10 years). The control group (H) had 74 eyes of 41 healthy individuals (females: 70%, mean age: 34 ± 12 years) with a visual acuity greater than 0.8; without any ophthalmic or systemic disease, based on their history and with a clinically healthy macula on fundus biomicroscopy.

A comprehensive eye examination was performed in all subjects, including medical history, best corrected visual acuity, slit lamp examination, measurement of intraocular pressure (using Goldmann tonometer), fundus biomicroscopy and 2 standard field stereoscopic fundus photos (centered on the macula and the optic nerve head).

The fundus images were classified according to the criteria of international clinical DRP and DME severity scales. Macular OCT examination was performed by Stratus OCT (Carl Zeiss Meditec, Dublin, CA, USA) using the "Macular Thickness Map" protocol. Raw OCT images were processed using OCTRIMA software. The retinal thickness, layer index and fractal dimension parameters were measured for each eye for the total retina and RNFL, GCL+IPL, INL, outer plexiform layer (OPL), outer nuclear layer and photoreceptor internal segment complex (ONL+IS), photoreceptor outer segment (OS), retinal pigment epithelium (RPE) layers, using a custom-built software. The calculations were performed on the entire macula and three concentrically located macular regions (fovea, parafovea and perifovea).

One-way ANOVA was performed, followed by Newman-Keuls post-hoc analyses to test for differences of thickness, layer index and fractal dimension between groups; AUROC was calculated for each parameter to discriminate MDR patients from the other two groups. For the thickness, layer index and fractal dimension values ROC curves were generated. The level of statistical significance was set at $p < 0.001$. For the calculation of AUROC and statistical analyses SPSS versions 16 and 17 (SPSS Inc., Chicago, Illinois) were used.

2. Investigations of changes in thickness and optical properties in retinal layers in multiple sclerosis.

In our cross-sectional case-control study, we examined the eyes of patients with relapsing-remitting MS (RRMS) who met the McDonald diagnostic criteria, using healthy subjects as a control group. Patients' eyes were divided into two study groups based on the clinical diagnosis of optic neuritis in their history at least 6 months prior to enrollment. The MSON- group was composed of 31 eyes of 25 patients (female ratio: 56%, mean age: 34 ± 9 years, duration of illness: 71 ± 51 months) whose eyes were not affected by optic neuritis. The MSON + group contained 36 eyes of 26 patients (female ratio: 73%, mean age: 34 ± 9 years, disease duration: 72 ± 51 months) whose eyes were affected by optic neuritis. The control group consisted of 29 eyes (women ratio: 62.5%, mean age: 33 ± 9 years) of healthy, age and sex matched individuals whose best corrected visual acuity was 1.0 without any ophthalmic or systemic disease.

Each subject in the study underwent a detailed ophthalmic examination, which included ophthalmic medical history, best corrected visual acuity measurement, slit-lamp examination, applanation tonometry with Goldmann tonometer, fundus biomicroscopy and critical fusion frequency (CFF). Macular OCT examination was then performed with Stratus OCT (Carl Zeiss Meditec, Dublin, CA, USA) using the "Macular Thickness Map" protocol. Raw OCT images were further processed using OCTRIMA software. For each eye, the thickness of RNFL, GCL+IPL, ganglion cell complex (GCC, RNFL+GCL+IPL), INL, OPL, ONL+IS, OS, RPE and total retina was measured along with the contrast, fractal dimension and layer index parameters as applied in the previous study.

The thickness and optical property values were compared between the groups by "mixed model ANOVA" analysis to exclude defects due to the involvement of both eyes of SM patients. The level of significance was set at $p < 0.001$, due to the large number of comparisons. SPSS 16 was used for statistical analyses.

3. The effect of incorrect scanning distance on boundary detection errors and macular thickness measurements by SD-OCT

In our cross-sectional study, OCT images obtained with two scanning distence settings using the RTVue OCT-100 (Optovue, Fremont, CA, USA) SD-OCT device were compared in 30 eyes of 30 subjects. The study eyes were divided into three groups: the Normal group was made up of ten healthy individuals, while the DME group contained 10 eyes with diabetic

macula edema, and the AMD group consisted of 10 eyes with wet age-related macular degeneration. The study eye was selected randomly if both eyes were eligible for the study.

Each subject underwent routine ophthalmic examination comprising best corrected visual acuity measurement, macular OCT, slit-lamp examination, Goldmann applanation tonometry and fundus biomicroscopy. The tonometry was performed after the OCT exam.

The macula SD-OCT examination of each subject were performed using the MM5 scan protocol with two different scanning distance settings under non-mydriatic circumstances, before fundus biomicroscopy. For the first session with suboptimal settings, the device was set at 3.5 cm from the cornea in order to obtain detectable signal with low fundus image quality with peripheral obscuring of the fundus ont he image of the fundus camera. For the second session with optimal settings, the distance of the device was set at 2.5 cm from the cornea with a good quality fundus image. A minimum of 5 minutes elapsed between the two sessions. For both sessions the scan settings were optimized using the built-in „optimize" option of the RTVue OCT device before taking all scans.

The signal strength index (SSI) and regional thickness values were recorded for each eye. The score for inner and outer RBDE was calculated for five vertical and five horizontal selected scans of the MM5 grid protocol from each eye for both settings according to a grading system based on the scoring previously described by Sadda et al. and modified for the current study. RBDE scores were also recorded and calculated similarly for the peripheral regions 1.0 mm from the horizontal scan edge on both sides on all scans. The number of errors in the remaining central region was defined as the difference between the total number of errors found in the whole scan and the number of peripheral errors. The correlation between the SSI and the number of RBDEs was examined using linear correlation including all scans taken both with suboptimal and optimal scan distance settings. SSI values, RBDE scores and regional retinal thickness values were compared between the two sessions using Wilcoxon test. Intraclass correlation coefficients (ICC) with 95% confidence intervals were calculated for these variables, followed by the direct comparison of confidence intervals. The analyses were performed for all participating eyes (all-eyes group) and for the three subgroups (Normal, DME and AMD groups). The statistical analyses were performed with Statistica 8.0 (Statsoft Inc., Tulsa, OK, USA) and SPSS 19 (IBM Corp., Armonk, NY, USA) software. The level of significance was set at $p<0.05$.

4. Assessment of a novel automatic segmentation algorithm for macular SD-OCT images

We developed our novel SD-OCT sgemnetation algorithm, OCTRIMA 3D (OCT Retinal Image Analysis 3D) and tested its performance using manual segmentation as gold standard ground truth and four automatic segmentation algorithms for comparison.

Three performance metrics were defined to objectively measure the difference between the detection results and the ground truth: the signed error (SE), the mean of unsigned error (MUE), and 95% of the unsigned error (E95). The value of mean signed error (MSE) and standard deviation of signed error (SSE) indicate the bias and variablity of the detection results. The mean of the unsigned errors (MUE) measures the absolute difference between the automatic detection results and manual labeling. E95 indicates the highest value of the unsigned error after removing the top 5% of the biggest values. Comparisons were made by paired t-test. The level of significance was set at 0.001. Calculations were performed using SPSS 19 (IBM Corp., Armonk, NY, USA).

In the first part of the study, we processed the volume scans of 10 eyes of 10 healthy adult subjects. The selection criteria for healthy individuals were as follows: the best corrected visual acuity was at least 0.8, a history of no current ocular or systematic disease, and a normal appearance of the macula when examined with contact lens biomicroscopy.

Subjects were examined using Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany), the IR + OCT 30 ° scanning mode. We employed the TruTrack^{TM} Active Eye Tracking Technology (averaging 5 B-scan values per scan, ART = 5) in order to reduce background noise. To reduce the speckle noise, every B-scan was the average of five aligned images using the TruTrack active eye tracking technology (*ART* = 5).

A subset of 10 images were randomly selected from every volumetric data (61 B-scans) of a healthy patient for labeling and at least two of these frames contained the fovea. The segmented results from Observer 1 were taken as the ground truth, and the difference between manual segmentation of Observer 2 and Observer 1 along with the difference between OCTRIMA3D automatic segmentation and Observer 1 were calculated to evaluate the accuracy.

Manual segmentation was applied as a gold standard and compared with the segmentation of OCTRIMA3D, IOWA reference algorithm and Dufour's segmentation using the ILM, RNFLo, IPL-INL, OPLo, IS-OS and RPE-CH boundaries,. Differences were compared in the 9 ETDRS regions based on qualitative and quantitative values.

We also compared OCTRIMA 3D with a fourth algorithm by Chiu et al. using the segmentation of images from a Bioptigen device (Bioptigen Inc, Morrisville, North Carolina, USA). The manual labelings from their study were used as the ground truth for comparison. We also assessed the potential operational time needed for the analyses.

Finally, two B-scans from subjects with retinal pathologies were used to explore the potential of OCTRIMA 3D in pathological cases. For this purpose, we processed OCT scans from one subject with DME and another subject with wet-AMD using our algorithm. The OCTRIMA 3D segmentation was compared to the result of Spectralis 6.0 automatic segmentation software (DME) and Dufour's algorithm (wet-AMD).

4. Results

1. Investigation of changes in thickness and optical properties in the retinal layers in type 1 diabetes

1.1 Evaluation of the thickness changes of the retinal layers

The mean thicknesses of the GCL+IPL complex, OPL and OS were statistically significantly smaller in the MDR eyes compared to controls. In the foveal region, the GCL+IPL and INL layers showed thickening, while thinning of the OPL was seen in the same comparision. Significant changes were seen in the RNFL and GCL+IPL in the parafoveal region, and RNFL and OS layers in the perifoveal region in the MDR group compared to controls.

Moreover, the mean thicknesses of the OPL, OS and RPE were statistically significantly smaller in the MDR eyes compared to the DM eyes. Significant thinning of the RNFL and OS layers was seen in all regions and also in the case of the foveal OPL and the parafovela GCL+IPL, in the same comparision.

Based on the AUROC values, mean thickness of the OPL in all macular and foveal regions weas shown to be the best for discriminating between the MDR and healthy eyes. At the same time, mean thickness of the OS in all the regions but the fovea along with the RNFL were found to be the best for discriminating between MDR and DM eyes.

1.2. Evaluation of optical propery changes in the retinal layers using layer index parameter

Significantly smaller layer index values were observed in the RNFL, GCL+IPL complex, INL, OPL and OS layers in all regions, except the INL in the foveal region and in

the MDR eyes compared with healthy control eyes. Layer index was also smaller in the ONL+IS in the parafoveal region for the same comparison.

Moreover, when comparing MDR with DM eyes, the layer index values showed significant differences for the GCL+IPL, INL, OPL and OS layers in the all macular, foveal and parafoveal regions; for the RNFL in the para-and perifoveal regions, and the INL, OPL, OS in the perifoveal regions.

Based on AUROC values, layer index of the GCL+IPL in all but the perifoveal regions, the OPL in all macular and foveal regions were shown to be the best for discriminating between the MDR and healthy patients. Mean thickness of the OS in all the regions was found to be the best for discriminating between the MDR and DM patients.

1.3 Evaluation of optical propery changes in the retinal layers using fractal dimension

Significantly different fractal dimension values were found in the GCL+IPL, INL, OPL, OS layers in all macular and foveal regions and in the MDR eyes compared with healthy control eyes. The RNFL layer in all macular and parafoveal regions as well as OS in the parafoveal and perifoveal regions showed a significant increase between the same groups.

Moreover, when comparing MDR with DM eyes, the fractal dimension values showed significant differences for the RNFL, GCL+IPL, OPL and OS layers in the all macular and foveal regions; for the RPE in all macular regions along with the RNFL, GCL+IPL and OS in parafoveal, and OS and RPE in the perifoveal regions.

Based on AUROC values, fractal dimension of the GCL+IPL in all macular and foveal regions was shown to be the best for discriminating between the MDR and healthy patients. Mean thickness of the INL in all the regions was found to be the best for discriminating between the MDR and DM patients.

2. Investigations of changes in thickness and optical properties of retinal layers in multiple sclerosis.

The thinning of the RNFL, GCL+IPL and also GCC was significant in all comparisons in each macular region except the foveal region. In the foveal region a significant difference was observed in the GCL+IPL and the GCC between MSON+ and the other groups, and in the RNFL between H and MSON.

Significantly higher contrast values were observed in the MSON+ group compared to the H and MSON- groups in the RNFL, GCL+IPL, INL, OPL and GCC layers in the whole macular region. A significant difference was found in the foveal region between the MSON+

and the two other groups in the GCL+IPL and GCC, similarly to the INL in the MSON+ versus the healthy group. The GCL+IPL was significantly different between the three groups in the parafoveal region, and so was the RNFL and GCC in the MSON+ vs. H comparison. The perifoveal region showed a significant difference between the three groups in the RNFL, GCL+IPL and GCC layers.

Fractal dimension was significantly higher in the MSON+ group compared to the H group in the GCL+IPL and INL in the whole macular region, in the INL in the foveal and in the GCL+IPL in the perifoveal regions. Also, a significant difference was found in the OPL between the H and MSON- groups in the parafoveal region. There were no significant differences found in any other layers in other comparisons.

The layer index values were significantly lower in the MSON- and MSON+ groups compared to the healthy controls, and also in the MSON+ versus MSON- comparisons in the RNFL, GCL+IPL and GCC in the whole macular, parafoveal and perifoveal regions. In the foveal region the GCL+IPL was significantly thinner in MSON+ compared to the other two groups, and the same was observed for the GCC in the MSON+ and H groups.

3. The effect of incorrect scanning distance on boundary detection errors and macular thickness measurements by SD-OCT

The SSI was significantly lower with suboptimal scan distance settings compared to optimal scan distance settings (63.9 ± 12.0 vs. 68.3 ± 12.2, respectively, $p = 0.001$). The number of RBDEs was significantly lower with optimal scan distance settings, for the entire scan in the “all-eyes”, Normal and DME groups and also for the peripheral part in the „all eyes” and DME groups.

The ICC of the RBDE scores of the two settings showed a mild difference in all regions in the Normal and DME groups (Entrire scan, central and peripherial 0.337, 0.476, 0.206 and 0,218, 0.432, 0.253, respectively) while in the peripheral region and total scan it was low (0.591, 0.718, respectively).

The number of RBDEs negatively correlated with the SSI value in the „all-eyes”, Normal and DME groups, in the entire and central 3 mm part of the scan.

In the AMD group, the number of RBDEs was higher compared to all other groups and there was no difference in RBDEs between optimal and suboptimal settings, with the errors being independent of the SSI. The ICC showed the highest difference in SSI values between the two scanning sessions in eyes with AMD.

Regional retinal thickness measurements (RTMs) between the two scan distance settings were significantly different only in the inner and outer-superior region (R2 and R6, respectively) in the case of DME eyes and in the R6 region in the "all-eyes" group. There was a high correlation between the RTM values of the two sessions in each region.

4. Testing of a new automatic segmentation software of macular SD-OCT images

The difference between the two manual segmentations and OCTRIMA 3D vs. manual segmentation was found small in all retinal layers. The automatic segmentation results were less than 1 pixel (~4μm) for all the boundaries, compared to the manual segmentation. The ILM, IS-OS and RPE-Ch labelings showed the least errors between segmentations. MUE was almost 1 pixel for all layers, compared to the manual labeling.

The processing time for the volume using OCTRIMA was 26.15 seconds while the processing time for Dufour's software and the Iowa Reference Algorithm was about 60 seconds and 75 seconds, respectively. The UE for OCTRIMA 3D in all the surfaces was significantly smaller than that of the Dufour Software and of the IOWA Reference Algorithm ($p < 0.001$ for both comparisons). The ILM, IS-OS and RPE-CH surfaces were more reliably delineated than the other three surfaces.

For the comparison of the results of OCTRIMA 3D and the algorithm by Chiu et al., every OCT B-scan was processed independently, and the average processing time was 1.15 seconds with our algoirthm. Our implementation showed a significant improvement compared to the 9.74 seconds that Chiu et al reported in their paper. The results of both algorithms agreed well, the main discrepancy was in the vessel shadow regions. Compared to manual labelings provided by Chiu et al., OCTRIMA 3D showed a slight increase in errors, as our application delineated the small bumps of the boundary more than the manual segmentation

In case of the eye with DME and vitreoretinal traction, OCTRIMA 3D outperformed the built-in algorithm in detecting the ILM and RPE-CH boundaries. The built-in software of Spectralis had obvious detection errors, while our algorithm was able to label all layers accurately.

In the case of wet AMD eye, the IS-OS boundary detection of Dufour's software failed in two areas of the B-scan.

In comparison, the OCTRIMA 3D was able to segment the layer correctly except for the drusen area, where the fine tuning of the algorithm was required for the precise detection of IS-OS and OS-RPE boundaries.

5. Conclusions

1. In mild non-proliferative DRP, significant thinning of the GCL + IPL, OPL and OS layers were observed, which draw attention to the initial alterations caused by the disease. We found that the GCL + IPL is the best layer for differentiating the affected eyes from healthy.

2. In mild non-proliferative DRP, the fractal dimension and the layer index optical parameters were significantly different from healthy eyes, in the inner retinal layers, the OPL and OS layers. The GCL + IPL layer seemed to be appropriate parameter to differentiate the affected eyes from healthy.

3. In diabetes, the changes of the OS layer were found to be appropriate to differentiate eyes with mild non-proliferative DRP from non-affected eyes.

4. In multiple sclerosis, we found significant change of thickness and optical properties of the inner retinal layers in eyes affected by optic neuritis compared to healthy and fellow eyes. We also revealed a significant change in layer index and total reflectance between healthy and fellow eyes, the latter suggesting that optical properties may also be useful for detecting early neurodegeneration in multiple sclerosis.

5. The importance of correct scanning distance was demonstrated using RTVue SD-OCT for reducing peripheral artifacts. The most boundary detection errors were found in neovascular AMD, independently of the scanning distance; in DME a significant number of errors were seen, mostly in case of suboptimal setting.

6. We could show that our custom-built, SD-OCT B-scan based segmentation algorithm, OCTRIMA3D using the shortest path graphing model is faster and more accurate than state-of-art segmentation softwares.

6. Publications

1. Publications related to the thesis

1. DeBuc, D., Tatrai, E., Laurik, L., Varga, B.E., Olvedy, V., Somogyi, A., Smiddy, W. E., Somfai, G.M. (2013) Identifying Local Structural and Optical Derangement in the Neural Retina of Individuals with Type 1 Diabetes. J Clin Exp Ophthalmol 4: 289. IF: 0.65
2. Somfai, G. M., Tátrai, E., Laurik, L., Varga, B. E., Ölvedy, V., Smiddy, W. E., DeBuc, D. C. (2014). Fractal-based analysis of optical coherence tomography data to quantify retinal tissue damage. BMC bioinformatics, 15(1), 295. IF: 2.576
3. Varga, B., Tátrai, E., DeBuc, D. C., Somfai, G. M.(2014): The effect of incorrect scanning distance on boundary detection errors and macular thickness measurements by spectral domain optical coherence tomography: a cross sectional study. BMC Ophthalmology, 14(1), 148 IF: 1.02
4. Tian, J., Varga, B., Somfai, G. M., Lee, W. H., Smiddy, W. E., DeBuc, D. C. (2015). Real-time automatic segmentation of optical coherence tomography volume data of the macular region. PloS one, 10(8), e0133908 IF: 3.057
5. Varga, B. E., Gao, W., Laurik, K. L., Tátrai, E., Simó, M., Somfai, G. M., DeBuc, D. C. (2015). Investigating tissue optical properties and texture descriptors of the retina in patients with multiple sclerosis. PloS one, 10(11), e0143711. IF:3.057

2. Publications not related to the thesis

1. Gao, W., Tátrai, E., Ölvedy, V., Varga, B., Laurik, L., Somogyi, A., Somfai, G. M., DeBuc, D. C. (2011). Investigation of changes in thickness and reflectivity from layered retinal structures of healthy and diabetic eyes with optical coherence tomography. Journal of Biomedical Science and Engineering, 4(10), 657.
2. Somfai, G. M., Tátrai, E., Laurik, L., Varga, B., Ölvedy, V., Jiang, H, DeBuc, D. C. (2014). Automated classifiers for early detection and diagnosis of retinopathy in diabetic eyes. BMC Bioinformatics, 15(1), 106. IF: 2.576
3. Szigeti, A., Tátrai, E., Varga, B. E., Szamosi, A., DeBuc, D. C., Nagy, Z. Zs, Németh, J., Somfai, G. M. (2015). The effect of axial length on the thickness of intraretinal layers of the macula. PloS one, 10(11), e0142383. IF: 3.057
4. Tian, J., Varga, B., Tatrai, E., Fanni, P., Somfai, G.M., Smiddy, W.E., Debuc, D.C. (2016) Performance evaluation of automated segmentation software on optical coherence tomography volume data. Journal of Biophotonics 9:(5) pp. 478-489.
(IF of the journal is 4.328, but it is not shown because of the review type of the publication)