Quantitative retinal imaging with optical coherence tomography

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2020

document version
Publisher's PDF, also known as Version of record

Chapter 8 |

Summary

Methods and devices for medical imaging are developed for multiple purposes. They should aid clinicians and medical researchers in the determination of the health of their patients, deliver feedback about treatments and help studying the progression of diseases. In this thesis applications for two aspects for diagnostic devices are addressed:

- Early diagnosis: for the treatment of a disease it is best to diagnose it as early as possible allowing physicians to use countermeasures against unhealthy developments. This is especially the case for retinal diseases.
- Follow-up monitoring: studying a disease progression and the effectiveness of a treatment can be important for its improvement and decision-making for example if multiple treatment options exist.

For both purposes it is important that small changes in the tissue and its functionality are quantified in order to follow the progression of diseases in detail. On the one hand, regular checkups and screening of healthy patients are needed. On the other hand, if a diagnosis is available already, a patient must be checked frequently to monitor any changes of their condition. Therefore, it is not just beneficial but partially even necessary to work with (ideally) non-invasive devices which minimize the risk of harm and discomfort to the patient.

Optical coherence tomography (OCT) is by now already an established investigation method in ophthalmology and a good candidate for such purposes. It is non-invasive and commercial devices are already being used in many standard clinical routines. Features like the visualization of the retinal structure blood vessels (angiography) are available.

OCT is based on interferometry which categorizes several methods that can, for example, be used to measure the speed of light or the optical path traveled by photons in a certain time with very high precision. In case of OCT the interferometer is used to record tomograms of tissue by measuring how long the light has traveled when it is scattered from different depths in the tissue. The device illuminates it from one direction and in first approximation the optical path encodes the depth from which photons are scattered back towards the device.

In the most common configurations, near infrared light is used for OCT in ophthalmology. This exploits the fact, that the human eye is naturally designed to be transparent for visible and (partially) for infrared light. Additionally, the use of infrared light poses only a very low risk for causing harm as only thermal energy is deposited in a well-controlled manner and therefore patients cannot be blinded. Measurements often take only seconds and reach resolutions of typically a few micrometers. All these benefits make OCT well suited as screening tool and for frequent checkups.

In many fields of medicine quantitative devices and different contrast methods are of great interest to allow more accurate diagnoses. The scope of this thesis was to further develop quantitative methods which can be applied with OCT. Those were applied in two fields.

The larger part covers the development and experiments for the validation of a new theory for velocimetry – the estimation of flow velocities. A potential application of it is the evaluation of blood flow. The intended use for it is the detection of unhealthy changes in the blood supply of the tissue and therefore to use it for early diagnoses of diseases. This is expected to contain high value for the field of medical imaging and so a significant effort has already been made by the scientific community to approach this topic. However, despite a high interest from researchers, as well as manufacturers of commercial products, applications for blood flow quantification have not made it into standard clinical procedures, so far. One of the main obstacles which still makes velocimetry difficult to be applied in ophthalmology is the amount of the required measurement data for each velocity estimation. While structural measurements and OCT angiography only need a low number of measurements of each point in the three-dimensional volume, demonstrations of OCT velocimetry often needed hundreds of measurements. Requiring a large number of measurements for each point would increase the time to record a whole volume by at least the same factor and makes this method rather impractical for ophthalmic applications.

The above mentioned considerations triggered the work in this thesis regarding OCT velocimetry. A reduction of the required measurements per velocity estimation was the main goal of **chapters 4** and **5**. To achieve this, the statistical error of possible estimation methods was analyzed and optimized. A low statistical error means that a low number of measurements are needed for an estimated velocity to lie within a specific tolerance. Considering one individual point in a volume, an OCT measurement delivers the backscattered electrical field which contains an amplitude and phase. Both quantities can be used individually for velocity estimations or in combination with each other. In **chapter 4** the statistical error for a purely phase-based analysis was evaluated for an established and newly proposed algorithms. It was found that the new algorithms can achieve an improvement of a factor of 8.9 less measurements compared to the previously established algorithm. In **chapter 5**, the theory for the phase-based analysis was extended to cover an amplitude-based analysis and the combination of both which is the analysis of complex-valued fields. This made it possible to compare all analysis bases both theoretically and experimentally with respect to the best achievable precision and the information they contain regarding velocity estimations. The most significant result in this study was that the phase of the OCT-measurement contains a much larger part of the information about the velocity and can be better analyzed over a large range of velocities in contrast to amplitude-based methods. As an example, when switching the analysis method from amplitude-based to an analysis of complex valued fields, the number of measurements can be reduced by approximately an order of magnitude. This could bring OCT-velocimetry closer to ophthalmic applications.

The second part of the thesis covers an application to detect subretinal fibrosis (SRFib) in the human retina with polarization-sensitive (PS) OCT. This part is aiming at the quantification of the progression of a disease. SRFib is a form of scar tissue. It can arise during the late stage of some retinal diseases and the development often results in severe loss of vision. Thus, it is of interest to study in detail the process of SRFib development and how it might depend on the treatment history of a patient. In this context, PS-OCT represents a useful tool due to its sensitivity to birefringence and fibrous structures such as SRFib which exhibits birefringent properties. In **chapter 6**, a study is presented in which the detection of SRFib with PS-OCT is compared to an established method which consists of a combination of examinations of best corrected visual acuity, standard OCT and fundus photography which had to be evaluated by retinal specialists for a final decision on the presence of SRFib. Twenty-nine eyes were measured. In cases when a clear decision was found by the retinal specialist (positive as well as negative) the results could be confirmed, except for one positive case in which a very thin retina made an evaluation difficult and it was deemed inconclusive. In cases for which the retinal specialists were in doubt or in disagreement on the presence of SRFib, PS-OCT could deliver better insight for a decision, except for one for which the signal-to-noise ratio was too low. Several analysis methods for PS-OCT data were evaluated on aspects how to localize birefringent material laterally and axially, the possibility to quantify it and on a metric for improved sensitivity of PS-OCT to birefringent media. The metric optic axis uniformity (OAxU) compares the optical axis of pixels to pixels in its neighborhood and can localize colinearly aligned fiber structures, well. It has a high sensitivity to birefringent structures and offers an intuitive way to display and localize them in depth. The metric local birefringence is used to analyze local changes in the polarization state of the propagating light and enables the quantification of the refractive index difference of the birefringent medium. The metric cumulative double-pass phase retardation delivers a value related to of how much birefringent material the light has passed through when it is scattered back in a certain depth. It also showed high sensitivity to birefringent media but is difficult for localizations of birefringent structures in depth because it is determined by the material from which photons are scattered but also by the material they have passed earlier.

In a general discussion in **chapter 7** aspects are considered which might be of importance for the translation of the applied methods in this thesis to clinical practice. The following questions are discussed: How much diagnostic value does the technology add in comparison to currently available devices in clinical practice? How much does it increase the complexity of the current technology and therefore, add costs? How user- and patient friendly is it and therefore how suitable for frequent measurements?

Velocimetry, as it is investigated here, can be directly used with standard OCT devices under the condition that enough measurements can be acquired. The work in this thesis has been focused on the minimization of the number of necessary measurements which can be a significant limitation for measurements times and therefore user- and patient friendliness. Although it is known that many diseases influence the blood flow, it is not clear at this point how much added value velocimetry or flow quantification might deliver. This aspect must still be evaluated in future.

The situation is different for birefringence imaging. Not only has it been shown in this thesis but also in other publications, that it would have a significant benefit for the diagnosis and monitoring of fibrosis development and perhaps even more value might be in the analysis of the birefringence of the retinal nerve layer. Also, user- and patient friendliness are hardly influenced in comparison to standard OCT. However, a more diverse signal detection would need more complex setups which currently poses one of the biggest limitations. But also here the theory and measurement analysis are being improved in order to reduce the setup complexity which might help to overcome this limitation.