Quantitative retinal imaging with optical coherence tomography

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Chapter 7 |

General discussion & outlook

Detailed discussions are included in the chapters 4, 5 and 6 addressing the results, limitations and potential for future developments. This chapter is dedicated to a more general discussion of the potential meaning of this work for future advances in clinical practice. Closely connected to such an assessment is the question how flow quantification and birefringence imaging can find its way into products, which are used for standard clinical procedures and diagnostics. For this discussion three factors might be of importance:

- **Added value**: How does the new technology add diagnostic value to the portfolio of devices which are currently available? This influences whether it is worth to invest into studies and the development of new devices.
- **Complexity**: Does the new technology increase significantly the complexity of currently available devices? Can it be integrated in existing technologies or combined with other technologies for multimodal imaging? This factor highly influences added costs which come with the new technology.
- **Tolerability** for the patient and **user friendliness**: What does the new technology require from patients and practitioners? How invasive is it? This influences how often the technique can be used.

Flow quantification and birefringence imaging are discussed separately while a closer look is taken at these three factors. It might be important to find a balance between them in order to become successful in clinical practice.

7.1 Flow quantification

Most approaches in flow quantification with OCT aim at the estimation of the flow velocity of blood particles. This has also been used in the work of this thesis. OCT in its most basic implementation delivers only structural images which give information about tissue structures and layers in the retina. More functional information is required for more detailed investigations of the health state of the retina. Flow quantification might be an important candidate as such a functional imaging modality as blood flow is linked to the metabolic rate. In this work the improvement of velocity estimations with OCT measurements, in particular the estimation precision has been investigated.

On the one hand, flow will be affected by many retinal diseases and systematic diseases which affect the retinal vasculature. Several examples have been mentioned in sections 1.4, 4.1 and 5.1 [1-15]. Therefore, flow quantification can be considered a promising tool for early diagnosis of diseases. On the other hand, is currently still difficult to answer how much **added value** flow quantification can deliver in comparison to techniques which are used to investigate the integrity of the healthy vasculature such as OCT angiography (OCTA) [16] and related vessel density analysis [17]. Future studies will be necessary to clarify this aspect.

Regarding the **complexity**, in Chapter 4 and Chapter 5 algorithms were chosen which do not require hardware modifications to the most common existing raster-scanning implementation of OCT. This implementation is also realized in current standard OCTA devices [18]. An advantage of this implementation is that it is well compatible with other

technologies for multimodal imaging, for instance OCT combined with spectroscopy or fluorescence imaging. Through closely bundled fibers [19] or if double-clad fibers are used in the sample arm, the single-mode core can be used simultaneously for OCT imaging and excitation of fluorescence while the fluorescence is collected through the cladding [20]. When a spectrum in the visible is used for OCT, the oxygen saturation of blood can be evaluated due to different absorption spectra of oxygenated and deoxygenated blood [21]. Furthermore, visible OCT can also be used for the combination of OCT with fluorescence imaging [22]. The combination of Raman- and OCT-imaging for tissue characterization has been reported [23]. OCTA and polarization-sensitive OCT in a joint system have been shown [24, 25]. The realization of such multimodal combinations benefit from a low level of complexity of the flow sensitive OCT.

The algorithms used here, are based on the decorrelation of the measured E-field. The E-field changes in a random walk manner in a complex plane when scattering particles in the detection volume move. In order to extract information about the type and direction of motion, statistical properties about this random walk need to be determined. This is only possible if enough measurements are recorded from nearly the same location in the tissue. This poses the main challenge in decorrelation estimation based algorithms for flow quantification. OCTA algorithms, which only visualize flow, usually need only a low number of measurements [26-28]. This makes it possible to acquire whole volume scans in only a few seconds which is very **tolerable** for patients if the technology is used for regular checkups and screenings for unhealthy developments. For flow quantification, the number of measurements was increased in several studies to 100 or several hundred or more of measurements per flow estimation [29-34]. This represents an increase of the measurement duration by a factor of one to two orders of magnitude. It makes the measurement significantly more challenging for the patient on one side and for the data analysis on the other side because motion artifacts such as drift, tremor and micro-saccades [35, 36] can corrupt the velocity estimations as they can induce the same decorrelation to the signal as flow itself. Therefore, the main objective in Chapter 4 and Chapter 5 has been to minimize the amount of measurements which are needed for each velocity estimation. This was done through the analysis of the uncertainty of the estimations. Those quantities are connected through the information content (Fisher-Information [37, 38]) of the measurements. It is shown in an example in Chapter 5, if an uncertainty of 18-20 % is considered acceptable (and pure flow is considered) velocity estimations might be possible with only 25 measurement pairs per estimation through the use of the complex E-field decorrelation. In the following, this number is compared to previously reported algorithms and commercial devices. In the algorithm of VISTA [39, 40] the intensity information of five repeated scans is used and in a report of flow quantification with SSADA [41] the recorded spectrum was split into five spectral bands in post-processing. A combination of both could already be designed to result 25 measurements which can then be used to create 24 measurement pairs. If additionally complex data are used instead of intensity speckle decorrelation, the uncertainty level of 20% might be reachable. In this case the uncertainty should be analyzed again to check if the measurements from a split spectrum can be treated as independent information. Also binning pixels along A-scans to ensembles might be an alternative to splitting the spectrum but the same considerations must be made regarding

independency of information. Comparing the required number for pairs of measurements to those in implementations for commercially available devices, similar numbers can be found as used in VISTA and SSADA. Heidelberg Spectralis can acquire up to seven repeated scans for the OCTA algorithm [42], the Optovue Angiovue uses the SSADA approach with two repeated B-scans [18], a swept-source OCTA device from Topcon uses four repeated scans [18] and Zeiss Angioplex uses four repeated scans [43]. Commercial devices currently work often with a repetition rate of A-scans of 68-100 kHz [18]. Potentially faster acquisition might be possible in the introduction of faster swept-sources e.g. sources based on Fourier Domain Mode Locking (FDML) [44]. At a central wavelength of 1060 nm, repetition rates of up to 3.35 MHz have been reported [45] which might give a chance on a significant increase of measurements pairs per ensemble without the need to increase measurement times.

A challenge to apply velocity estimates through decorrelation in human eyes is given by aberrations and therefore not diffraction-limited beam spots. In Chapter 4 and Chapter 5 decorrelation parameters were estimated which have a (constant) relation to velocity and beam radius. This relation was obtained by the evaluation of Eq. (4.5) under the assumption that Gaussian beams are used. Through the effect of aberrations in human eyes the beam spot on the retina might deviate from a Gaussian spot and the size might change which changes the relation between beam decorrelation parameter and velocity. This might also vary from patient to patient. An investigation of those effects to the accuracy of velocity estimates will be necessary. For this purpose other techniques might help, such as fluorescent particle tracking [46, 47] which is not as suitable for frequent use as OCT based methods due to their invasive nature.

Other flow quantification techniques based on OCT which are competing with decorrelation based methods and were described briefly in section 2.2.3 will not be compared at the same level of detail but more general aspects of advantages and limitations are discussed in the following. *En face* plane DOCT [48, 49], vessel segmentation in DOCT [50], multiple beam illumination [51] and digital filtering in FF-SS-OCT [52] are all based on the axial velocity component through the (average) Doppler phase difference. On one hand, this has the advantage that those are more independent on the beam radius than decorrelation-based approaches. As an illustration it can be noticed that the mean phase difference in Fig. 4.2a and 4.2b is independent on transversal motion. Phase noise due to low signal-to-noise ratios (SNR) only create symmetrical phase difference distributions [24] which does not change the mean but is expected to influence the accuracy of decorrelation based approaches. On the other hand, DOCT suffers from phase wrapping as indicated in Fig. 2.4 when motion is too strong while decorrelation approaches only reach a saturation as shown in Fig. 5.6. While in DOCT a careful analysis whether phase wrapping occurred might be necessary, in decorrelation approaches a detection of a saturation limit might be sufficient. Another point which must be considered, is that decorrelation noise from transversal motion leads to a broadening of the phase difference distribution. While in decorrelation approaches this can be used to estimate motion, it represents an obstacle in DOCT. Revisiting Fig. 4.2b illustrates the problem. A flow measurement with DOCT with a strong lateral velocity component (as it is common for vessels far away from the optic nerve head [53]), can result a phase difference which differs significantly from the average Doppler phase difference. In such a situation more

measurements would be necessary to find the average Doppler phase difference which means that the DOCT approaches would lose their advantage of less measurements to a certain degree. In the multiple illumination beam approach and in the digital filtering of FF-SS-OCT an angle between different illumination directions can always be ensured but this is limited by the numerical aperture of the eye. FF-SS-OCT with its massive parallelization of A-line acquisition represents a possibility to compare decorrelation and multiple illumination with each other in one system and investigate in which situation each of the technologies is beneficial. Through it high effective A-line rate, sufficient numbers of measurements can be acquired for decorrelation estimation and through digital filtering multiple beam illumination can be simulated. In its original implementation the imaging depth of FF-SS-OCT is more limited in comparison to raster scanning devices due to cross-talk [54, 55] but it has been shown recently that this can be reduced by breaking the spatial coherence in the sample arm [56].

In summary, in this thesis an investigation is presented how flow quantification by decorrelation estimation can be optimized to extract information from measurements most efficiently, but it has yet to be shown which technique will be most effective for standard clinical applications.

7.2 Polarization sensitive imaging

The aim in polarization-sensitive (PS) imaging in OCT is to find birefringent structures. In the human body birefringence can be found in fibrous tissues such as nerve fiber bundles [57, 58] and collagen fibers [59]. In this work in Chapter 6, PS-OCT has been used to detect fibrotic tissue in retinas of patients who suffer from age-related macular degeneration (AMD). A standardized method is currently missing for this purpose. Different processing modalities have been tested and it was found that the use of optic axis uniformity (OAxU) [60, 61] was particularly sensitive for the axial and lateral localization of fibrotic tissue.

For the **added value** to current clinical procedures two main aspects can be identified: the diagnostic value and the value for future research. For the diagnostic value it has been mentioned that currently a reliable method is missing to distinguish fibrotic from non-fibrotic tissue. PS-OCT can significantly improve the reliability and to help making a diagnosis regarding presence or absence in otherwise doubtful cases. For the value for future research it can play an important role in the studies of the development of fibrosis. The formation of fibrotic tissue in the retina is a scarring process and often a result of inflammation and neovascularization in the progression of exudative AMD [62]. In order to preserve vision, treatment aims to delay the formation of fibrosis. Different treatment strategies exist [63] and the use of PS-OCT could help to monitor the development of fibrosis to evaluate the effectiveness of treatment options. Furthermore, if also quantification of birefringence e.g. through the analysis of local birefringence, is used, additional possibilities are created to study the progression of other diseases. An example is that is has been shown that glaucoma also affects the birefringence of the retinal nerve fiber layer [57, 58].

Regarding the **complexity** of the setup the discussion will focus on the SS-OCT setups for Jones-based analysis, as it was also used in Chapter 6. Two main changes to a regular phase

stable setup can be mentioned: A polarization delay unit (PDU) is inserted in the sample arm to generate two different input polarization states, and in the detection an additional detector must be used while the interference signal is split into two orthogonal polarization states. The use of two input states and two detected states became necessary when fiber based PS-OCT was introduced and the stress-induced birefringence in optical fibers [64] made a control of the polarization state significantly more difficult in comparison to bulk optics systems [65]. Recent studies have shown that it is possible to correct for the polarization state in post-processing leaving the possibility to work either without a PDU or the second detector [66]. This would reduce the complexity of the setup.

Regarding the **tolerability** for the patient it can be mentioned that the implementation of PS-OCT as used in this work does not significantly increase the time required for a volumetric scan in comparison to other phase-stable systems [67] and is also non-invasive with low risk for any harm. Furthermore, the compatibility with other modalities such as angiography has been shown [24, 25]. For the **user friendliness** a disadvantage is the reduced imaging depth due to the splitting of the input into two polarization states in the PDU. This makes the alignment for clinicians during imaging session more difficult. The imaging depth is primarily limited by the roll-off. The development of sources with long roll-off, such as VSCEL-sources [68] might be used as an approach to solve this problem as polarization states can be separated better. Limitations to this are set by higher noise and therefore lower sensitivity due to a larger required electronic bandwidth. Another challenge is that components such as the PDU and the separation into two polarization states in detection introduced additional bulk optics which lowers the stability. Polarization-sensitive components have been demonstrated as photonic integrated circuits (PIC) [69]. PICs can be connected directly to single-mode fibers. This can significantly improve the stability.

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