Quantitative retinal imaging with optical coherence tomography

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2020

Chapter 1 |

Introduction

1.1 General Introduction

The most vital sense for all perceptions in everyday life is vision. It is estimated that we gather 80% of all sensory information through our visual sense [1]. It is a fundamental requirement for many professions, means of transportation, leisure activities and our regular routines. It is therefore not surprising that the loss of vision has a much bigger impact on a person's life than the loss of any other sense [2]. We see the world around us with our eyes. Photons, scattered from the objects around us, are imaged onto the retina where photoreceptors absorb and convert them into electrical signals. Those are guided through the optic nerve to the brain where they are finally interpreted. Any obstruction in this signal path can result in impairment of vision. Being embryologically part of the brain [3], the retina it is a very complex organ which can be damaged in the course of a number of diseases. Many of them occur during aging of the once healthy tissue [4]. Estimations of the WHO come to the conclusion that 80% of vision impairments can be avoided [5]. Amongst them retinal diseases are the most challenging to treat or cure but early and reliable diagnosis can help to increase chances for impairment prevention [6-9].

Optical Coherence Tomography (OCT) has been established as imaging technology for the human eye [10, 11] since the 1990s. It delivers primarily structural images and since the first devices were demonstrated much work has been done for improvements in imaging speed, sensitivity, combinations with other imaging techniques and functional extensions. The latter is also in focus of the work presented in this thesis. One important topic is the analysis of flow in blood vessels and it is discussed how flow velocities of moving particles can be extracted from monitoring changes in repeated acquisitions of sample volumes. The second topic is the detection and estimation of birefringence in tissue which is an optical property that is characteristic for fiber bundles such as collagen and nerve fibers and can be an indicator for scar formation or damage to nerve tissue.

1.2 The Eye

The human eye has caught the interest and fascination of researchers for a long time and made it one of the best studied organs of the human body [12]. It has an approximately spherical shape and its size can vary (17 — 33 mm) but the average size for adults is 23 mm [13]. A schematic drawing of the eyeball can be found in Fig. 1.1. The most outer layer is the sclera, a dense structure of collagen layers which give mechanical support to the eye. It blends in the anterior one-sixth of the eyeball into a transparent dome, the cornea. Another gap in the sclera is located in the back where the optic nerve enters through the laminar cribrosa. The cornea encloses together with the iris the anterior chamber. The iris has the pupil in its center through which is transparent for light and its diameter is controlled by muscles sphincter pupillae and dilator pupillae. It regulates how much light can go to the retina by dilation and contraction and is therefore also a limit for any beam diameter to be sent into the eye for measurements. The lens is located behind the iris and forms together with the anterior chamber and cornea the refractive elements of the eye which are necessary to transform the incoming light from outer objects to an image. The accommodation of the lens and with it the focusing on various distances is controlled by the ciliary muscles. The retina and choroid are located at the back of

the eyeball and the space between that and the lens is filled with an avascular gelatinous body, the vitreous [14].

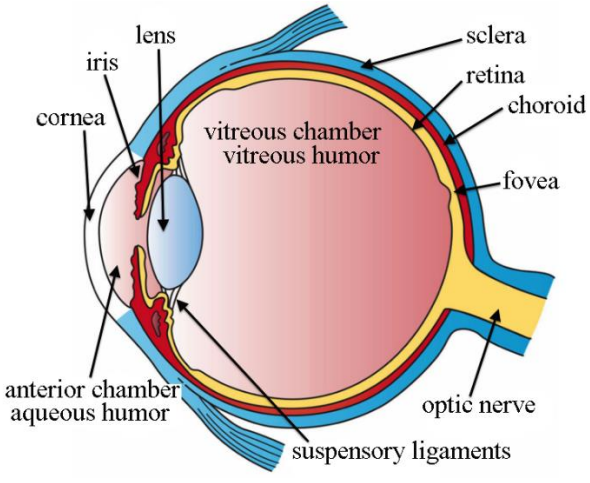

Fig. 1.1. Anatomy of the eye. Image acquired from Wikimedia Commons, created by Holly Fischer and published under the Creative Commons Attribution 3.0 Unported license with the ticket #2013040410011627

1.3 The retina

As imaging of the retina is specifically in the focus of the work in this thesis the anatomy of the retina is also described here in more detail than the rest of the eye. Fig. 1.2 shows a structural cross sectional image of the retina with layers indicated in the area of the posterior pole acquired with OCT. It is centered on the fovea and about 4.5-6 mm in diameter [3]. Characteristic for the fovea is a depression in the retina and is the region which delivers highest visual acuity. Photoreceptors in the retina are classified in rods and cones. The fovea has the highest density of cone receptors while rods are not present [15]. The cone receptors are sensitive to distinct colors but need higher light intensities than the rod receptors which cannot mediate color vision. Starting from the innermost towards the outer layers (as incoming light propagates) the retina is separated from the vitreous by the inner limiting membrane (**ILM**) which is formed by the flattened end of Müller cells. Often the first layer which can be resolved by OCT is the retinal nerve fiber layer (**NFL**) through which the axons of ganglion cells travel and is therefore the layer through which the electrical signals are sent to the optic nerve head. Behind the RNFL the ganglion cell layer (**GCL**) follows. Next to ganglion cells it also contains a number of other cells, such as amacrine cells, astrocytes, endothelial cells and pericytes. It is absent in the fovea itself. A dense network between bipolar, amacrine and ganglion cells is located in the inner plexiform layer (**IPL**) and acts as a processing layer. The inner nuclear layer (**INL**) contains Müller cells and the interneuron cells: horizontal, bipolar, amacrine, innerplexiform cells which are responsible for the initial processing of the photoreceptor signals. The bipolar and horizontal cells form connections in the outer plexiform layer (**OPL**) with the nuclei of the photoreceptors from the outer nuclear layer (**ONL**). Junctional

complexes between Müller and photoreceptor cells form the external limiting membrane (**ELM**). Together with the photoreceptive parts from the rods and cones it forms the photoreceptor layer. The last layer in the retina is the retinal pigment epithelium (**RPE**), a single-cell layer representing the blood-retina barrier [3]. The separation between retina and choroid is realized by Bruch's membrane. The choroid is a vascular layer between sclera and retina and is one of the sources of blood supply for the retina [3]. The other source are vessels directly in the retina which is discussed in the next paragraph.

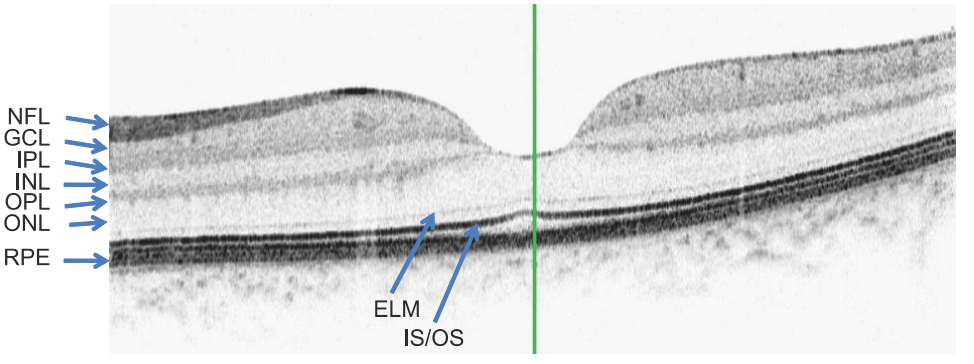

Fig. 1.2. A cross-sectional image from the posterior pole acquired with OCT with indicated retinal layers. NFL: nerve fiber layer, GCL: ganglion cell layer, IPL: inner plexiform layer, INL: inner nuclear layer, OPL: outer plexiform layer, ONL: outer nuclear layer, ELM: external limiting membrane, RPE: retinal pigment epithelium, IS/OS: inner/outer segment junction. Reproduced with permission of the Springer Nature Customer Service Centre (SNCSC) from [3].

1.4 Vascular network of the eye

As mentioned in the previous paragraph, the blood supply of the retina consists of two vascular systems: 1) a retinal system which is supplied by a central retinal artery, entering the eye with the optic nerve and 2) the choriocapillaris which supplies the RPE and outer retina by diffusion [16]. A schematic drawing of the different vascular layers is shown in Fig. 1.3. The choroid has three interconnected layers: the innermost choriocapillaris, the intermediate Sattler's layer, and the outermost Haller's layer. The vasculature in the retina can be separated into two to four plexuses [17]. In Fig. 1.3a three layers are drawn as an example and 1.3b shows the projection of an OCT angiography (OCTA) data volume of four different layers. The radial peripapillary capillary plexus (RPCP) is most superficial, found in the NFL, and contains in particular the largest arterioles branching out from the optic nerve head. The superficial vascular plexus (SVP) is primarily located in the GCL. The intermediate plexus (ICP) and deep capillary plexus (DCP) have a very similar appearance in the structure of their capillaries. The ICP is considered to be partially in the ganglion cell complex (GCC=NFL+GCL+IPL) and partially in the INL while the DCP is attributed partially to the INL and partially to the OPL. In OCTA images the ONH can be located as the origin of the central artery and vein and the fovea can be recognized by the avascular zone [17]. The supply of the photoreceptors with oxygen and nutrients in the avascular zone largely relies on diffusion [3].

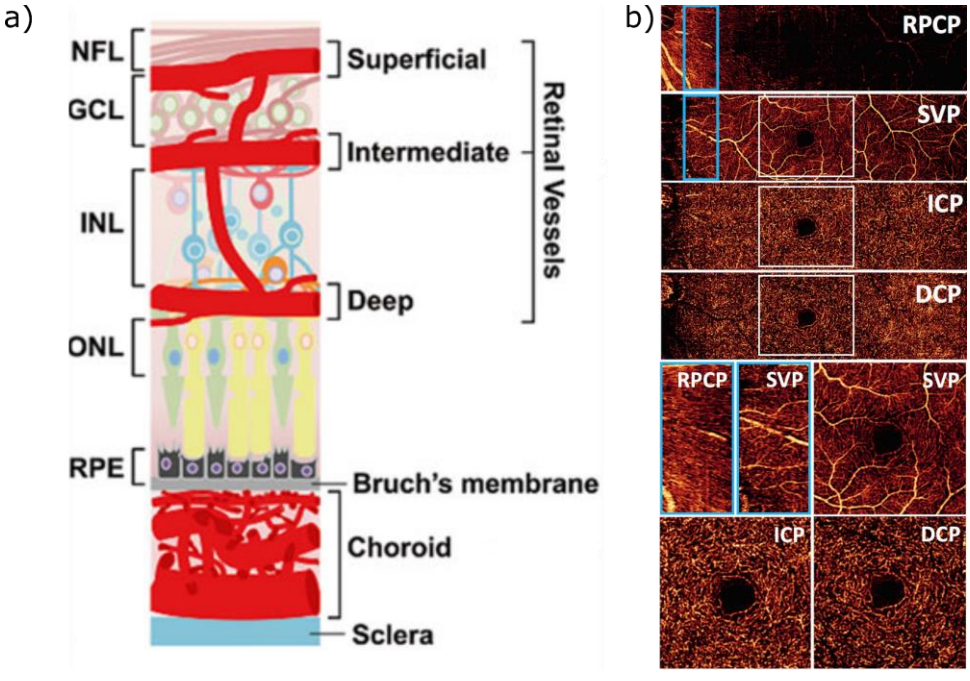

Fig. 1.3. The retinal vascular network. (a) A schematic drawing of the retinal vascular systems. Three layers are indicated in the retina. Adapted from [18], reproduced with permission of the SNCSC. (b) projection of an OCTA data set with four segmented layers. RPCP: radial peripapillary plexus, SVP: superficial vascular plexus, ICP: intermediate capillary plexus, DCP: deep capillary plexus. Adapted from [17], reproduced in accordance with the Creative Commons Attribution 4.0 International License http://creativecommons.org/licenses/by/4.0/.

Many diseases which affect the retina either induce damage through changed blood flow and damaged vessels or altered blood flow indicates them. In exudative age-related macular degeneration (AMD) new vessels grow (neovascularization) which can even penetrate the RPE and Bruch's membrane and cause leakage and inflammations [19]. In diabetic retinopathy high blood sugar levels can cause damage of the vessel walls leading to microaneurysms, macular edema and retinal ischemia which also trigger neovascularization [16]. The analysis of blood flow and retinal vasculature is not just limited to the evaluation of the state of health of the retina itself but the effect of various diseases on human vasculature can be investigated in general. For such studies the retina allows non-invasive imaging as the eye is designed to be transparent for visible and infrared light. It was shown in that in patients with Alzheimer's disease (AD) blood flow is reduced in comparison to healthy volunteers as well as in comparison to other cognitive impairment [20, 21] and altered arteriolar tortuosity was found in AD patients [22]. It was found that in open angle glaucoma patients not only vessels in the eye but also capillaries in the nailfold can be affected [23]. Abnormalities were found in the microcirculatory stimulus response [24] and vessel density of coronary heart disease patients [25]. These are only a few examples of a much larger spectrum of diseases which affect blood circulation in the human body and for which flow quantification might be a valuable indicator.

1.5 Other Biomarkers

The complexity of pathologies can vary and just blood flow is not enough to identify and follow their progression in the required detail. Several other techniques have been introduced as biomarkers. Many endogenous fluorophores can be found in the human body and fluorescence lifetime imaging is used to investigate alterations in the generation of metabolic byproducts [26]. Oxygen saturation of arterial and venous blood is another interesting biomarker as oxygen consumption is related to the metabolic rate of cells. Effects of diabetic retinopathy, central retinal occlusion, retinis pigmentosa, glaucoma and AD on the oxygen saturation levels have been reported [27]. Biological tissue which forms organized structures as aligned fibers exhibits another useful optical effect: birefringence. It influences the polarization state of the light which can be exploited to detect it. It is present in nerve and collagen fibers and was observed and quantified in tissues such as the NFL [28, 29], fibrotic lesions of AMD patients [30] or in other scar tissues such as scars in skin [31]. The excellent compatibility of polarization sensitive detection with OCT makes it particularly suitable to include polarization sensitivity in a phase stable system which can subsequently be used for birefringence detection as well as flow quantification. This circumstance has also been used in the work of this thesis to combine in one system the ability for birefringence measurements and flow quantification measurements.

1.6 Outline of the thesis

OCT has been developed into a standard device for clinical practice in ophthalmology. Its capability for three-dimensional imaging of the structure of the retina make it a great tool to detect pathological changes to the retinal layers. With the addition to visualize blood flow, OCTA represents an important step towards measuring changes in the blood supply of the tissue which is otherwise difficult to detect based on structural imaging. However, alterations to the retinal structure and blood supply can only indicate when damage has already been done by pathologies. In order to address changes even earlier in the development of pathologies, blood flow quantification is an interesting candidate as a potential future addition as a diagnostic tool and has therefore been the focus of research, but so far has not made it into clinical devices. One goal of the work in this thesis is the further development of flow quantification and its optimization to bring it closer to *in vivo* applications.

Another way to investigate pathological changes in the retina which is difficult to monitor based on just structural imaging or OCTA is the investigation of changes in fibrous tissues such as the formation of subretinal fibrosis or changes to the nerve fiber bundles. Polarization-sensitive (PS) OCT is a promising candidate for those tasks as it can exploit the birefringent nature of those tissues. A second goal in this thesis is the use of PS-OCT to detect and localize the presence of subretinal fibrosis in AMD patients.

This thesis is structured in the following way: in two chapters existing techniques are reviewed which are used for the above-mentioned goals. In **Chapter 2** existing approaches for flow quantification are described. In literature many approaches have been introduced and also techniques which are not based on OCT are mentioned for comparison. Then the principles of Fourier domain OCT are introduced, and flow quantification approaches based

on it are described. In **Chapter 3** the concept of birefringence and polarization-sensitive imaging is introduced. The measurements and calculation of important parameters are described for later use.

The following three chapters contain the main work to address the above-mentioned research goals. In **Chapter 4** an established flow quantification method is revisited for phased-based flow velocity estimations. It is described theoretically and from this theory the potential for the precision optimization is derived in order to reduce the required number of measurements because this is one of the main obstacles for *in vivo* applications. Flow quantification methods exist for amplitude-, phase-based and complex techniques. In **Chapter 5** the approach from Chapter 4 is generalized to analyze the precision of all three regimes resulting in a method to extract the maximum content of information for flow quantification from OCT measurements. The theory of Chapter 4 and Chapter 5 is validated with phantom measurements. **Chapter 6** addresses the second research goal. A PS-OCT system is used to scan patients suffering from AMD who partially developed subretinal fibrosis. The reliability of the detection and localization of fibrotic tissue is evaluated and compared to current techniques for the diagnosis of subretinal fibrosis.

Chapter 7 concludes the scientific content of this thesis with a general discussion with an outlook for further development of the described techniques and potential for clinical applications.

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