1 Introduction

More than 80 % of the information received in daily live are perceived visually, e.g., via reading, recognizing people or observing the environment [1]. Thus, even slight impairments of the quality of vision significantly affect the quality of life. As a consequence, numerous ophthalmic examination and treatment procedures aim at characterizing and curing the defects of vision. Within the last decades, laser radiation has evolved into a versatile tool in ophthalmology, e.g., to characterize the aberrations of the eye [2]. Besides those applications using continuous wave radiation, the development of short pulse lasers has enabled precise ablation of tissue [3], e.g., aiming at refractive correction of the eye. With already more than 28 million treatments performed worldwide and an annual turnover of about 200 million euro solely in the German market, the Laser-Assisted in-Situ Keratomileusis (LASIK) is one of the most successful ophthalmic procedures [4, 5]. In this treatment, the ablation of stromal tissue of the cornea by means of focused ultraviolet (UV) nanosecond (ns) laser pulses provides a fast and enduring correction of hyperopia, myopia and astigmatism [6].

For surgical interventions in deeper eye segments, the recent development of compact and reliable laser systems emitting ultrashort pulses of few tens to hundreds of femtoseconds (fs) has enabled inducing modifications within the bulk of the transparent ocular tissue at comparatively low pulse energies of few µJ [7]. Here, the extreme intensities at the vicinity of the focal volume trigger nonlinear absorption and plasma formation [8, 9]. The subsequent energy transition to the surrounding material causes the formation of a µm-sized cavitation bubble, which locally disrupts the tissue, while a scanning of the focal spot allows for extended cuts within the transparent tissue [10]. Here, new strategies such as the refractive lenticule extraction (ReLEx®) or the small incision lenticule extraction (ReLEx® SMILE) aim at more gentle and reliable refractive surgery, e.g., avoiding the sensitive corneal flap cut required in the conventional LASIK [11,12]. Moreover, focused fs-laser pulses are currently evaluated to fragment the aged opaque lens tissue to facilitate its extraction in cataract surgery [13, 14]. Additionally, recent investigations revealed an improved precision of the laser-assisted opening of the capsular bag (capsulorhexis) prior to the lens tissue extraction [15].

Due to the advancing demographic change of our society, the demand for treating age-related disorders is constantly growing, since, for example, a reliable treatment of the age-related loss of the near sight (presbyopia) is still missing. Here, the fs-laser based tissue fragmentation is currently discussed as a potential therapy aiming at softening the aged crystalline lens to increase its flexibility [16–18]. Besides those lenticular treatments, further surgical approaches in the vitreous chamber are under investigation. For instance, tensile stress of the ageing vitreous body can lead to a detachment of the vitreous membrane or even the retina, which severely threatens the vision [1]. Therefore, fs-laser induced cuts within the ageing vitreous body may reduce those tractions to provide a preventive therapy.

Although the application of µm-sized disruptions into the ocular tissue by means of ultrashort laser pulses features negligible thermal or mechanical side effects, there are still fundamental uncertainties to be clarified prior to a clinical application. First, while for longer pulses in the ns-range the disruption and dissociation of the crystalline lens fibers results in an opacification of the lens (*cataract*), recent studies suggest that the more precise energy deposition of ultrashort laser pulses reduces this risk [19–21]. However, because even a low probability for cataractogenesis would preclude the lenticular fs-laser surgery, thorough long-term studies must clarify the tissue response. Additionally, a high number of µm-sized disruptions is required to cut extended areas of tissue. Since the optical properties of each single disrupted spot differ from the surrounding untreated tissue, the persistent spot distribution influences the light propagation within the eyeball and may impair the quality of vision. As a consequence, a significant amount of patients who underwent LASIK suffer from side effects such as an increased sensitivity to glare, halos, starbursts and rainbow glare [22–25], which might be further intensified in lenticular treatments due to the shorter distance to the retina.

For treatments in the central or posterior section of the eye, the numerical aperture (NA) of the focusing is limited by the required focal length and the iris of the eye to ~ 0.1. As a consequence, the resulting laser-induced modifications are strongly elliptically shaped due to the enlarged Rayleigh length. Moreover, because the weak focusing causes high intensities already far in front of the focal plane, the complex interplay of self-focusing and filamentation of the pulse elongates the modification volume [26, 27]. Thus, while >100 μm long streaks were already observed in corneal tissue for a low pulse energy of 1 μJ [28], the restricted focusing and higher pulse energies in lenticular or vitreoretinal surgery might further aggravate this problem. The resulting elongated disruptions do not only reduce the precision of the induced cuts, but may also state a risk for near sensitive membranes such as the retina or the capsular bag. Additionally, the long propagation distance of the ultrashort laser pulse within the ocular tissue triggers the generation of a broadband super-continuum [29], which might be disturbing in a surgical treatment.

The aim of this thesis is to examine and reduce those side effects for fs-laser surgery in the central and posterior eye segment. Since ocular surgery commonly requires the application of extended disruption distributions, the temporal development of the applied structures within the tissue and their influence onto the objective and subjective quality of vision will be investigated initially. Further, the arrangement of the applied modifications will be optimized to reduce the potential visual impairments. Additionally, because the application of laser spot patterns is accompanied by self-focusing and filamentation owing to the restricted focusing conditions, the temporal breakdown formation is studied in detail. Moreover, simultaneous spatial and temporal focusing (SSTF) is investigated as a tool to decrease detrimental nonlinear pulse-material interactions and enhance the surgical precision for intraocular surgery [30, 31].

After this introduction, **chapter 2** provides an overview on recent applications of ultrashort pulses in ocular surgery and the respective limitations. Thereafter, **chapter 3** illustrates the fundamentals of ultrashort laser pulses and the nonlinear interactions during the propagation through the transparent media. Due to their fundamental importance in fs-laser surgery, the nonlinear absorption processes and the resulting laser-induced optical breakdown (LIOB) and disruption formation will be depicted in detail. Because the tissue response after lenticular fs-laser surgery is of crucial importance for potential clinical applications, the cataractogenesis and modification permanence after a laser treatment of the crystalline lens is studied in **chapter 4**. Here, minipigs act as an adapted animal model for the human lens in a clinical trial, in which the potential healing and cataract formation of laser-treated crystalline lenses was observed over a comparatively long observation period of 12 months. Because healing is weak in ocular tissue and the persistent modification pattern may induce scattering and diffraction, the impairment of the objective and subjective visual quality after fs-laser surgery is studied in **chapter 5** by means of an artificial model eye and a clinical trial using laser-treated contact lenses, respectively. Since the weak focusing in fs-laser surgery in the central and posterior eye sections results in strongly elongated disruptions decreasing the surgical precision, SSTF is evaluated as a tool to reduce the detrimental non-linear pulse material interactions in **chapter 6**. In this technique, the ultrashort pulse duration is restricted to the focus and continuously increases outside, which strongly confines the intensity distribution to the focal volume and prevents side effects such as self-focusing and filamentation [30,31]. Finally, **chapter 7** provides a summary of the thesis, resumes the fundamental findings on fs-laser surgery in the central and posterior eye segment and gives an outlook on future enhancements in the field of ophthalmic fs-laser surgery.

2 Fs-laser surgery in ophthalmology

The development of stable and compact pulsed laser systems providing high peak powers has enabled new therapeutic treatments within the last years, e.g., aiming at the refractive correction of the eye by precise cutting and ablation of tissue [32]. Here, the extreme intensities of focused picosecond (ps) and femtosecond (fs) laser pulses allow a precise energy deposition within transparent media, which for instance can be used for minimally invasive surgical approaches deep within the eyeball. In the following chapter, the various types of the laser-tissue interactions are introduced. Thereafter, recent applications of fs-laser surgery as well as several new surgical approaches will be presented, while moreover their particular limitations will be discussed.

2.1 The human eye

The human eye is a complex optical system (Fig. 2.1a) with the purpose of imaging the visual field within a wide range of environmental conditions. Anatomically, it can be structured into an anterior and a posterior segment, while the average axial length of the adult eye is ~24 mm [1]. The composition of the light refracting anterior eye segment is illustrated in Fig. 2.1b. The human eye features a total refractive power of $D \approx 60$ dpt, of which $^2/_3$ are caused by the front surface of

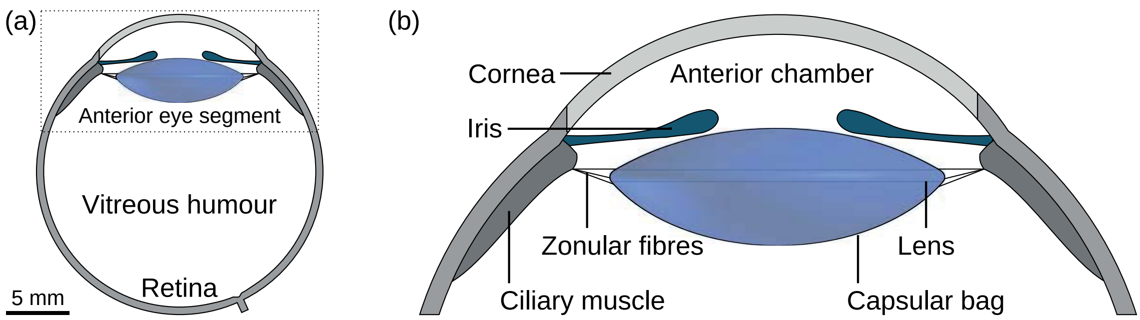

Fig. 2.1 Sketch of the human eye (a) and the anterior eye segment (b).

the cornea. In addition, 1/3 is induced due to refraction at the back surface of the cornea and the surfaces and the gradient refractive index profile of the crystalline lens. To focus for near objects, the refractive power of the lens can be varied due to the process of *accommodation* [33]. Hence, the ciliary muscle decreases its inner diameter, thus relieving the tension onto the zonular fibres and the crystalline lens. As a result, the elastic capsular bag turns the soft lens into a more spherical shape, increases its refractive power by up to ~15 dpt and enables focusing to near distances. After passing the jellylike vitreous humour of the posterior eye segment, the photosensitive retinal layers convert the incident photons into electrochemical impulses, which are transmitted to the brain by the optical nerve.

2.2 Laser-tissue interactions

Various impairments such as retinal detachment or refractive errors (ametropia) may decrease the image quality [1]. Thus, several laser treatments have been established in order to cure those disorders [32]. The particular reaction of the illuminated tissue crucially depends on the characteristic properties of the incident laser pulses such as the center wavelength λ_0, the pulse duration τ, the pulse energy E, the peak power P and the intensity I at the focal plane. The resulting laser-tissue-interactions can be classified into five main mechanisms: *photochemical*, *thermal*, *photo-ablative* and *plasma-induced ablative* as well as *disruptive interactions* (see Fig. 2.2) [34]. For low intensities < 1 W/cm^2 and long-lasting exposure durations in the range of several seconds to minutes, e.g., due to continuous-wave laser sources, linear absorption initiates or accelerates *photochemical processes* and reactions such as photosynthesis. With increasing intensity linear absorption of the water molecules, proteins and pigments as well as the non-radiative decay of excited states cause a local heating of the irradiated area. Depending on the temperature rise of the tissue hyperthermia (42 - 50 °C), coagulation (> 60 °C), vaporization (> 100 °C), carbonization or melting (> 300 °C) can result, which can be summarized as thermal processes and may finally cause a modification or the necrosis of the cells.

When applying laser pulses with durations of microseconds (µs) to nanoseconds (ns) and intensities of 10^7 - 10^8 W/cm^2, *photo-ablation* occurs at the surface of the irradiated tissue. Hereby, the absorbance of photons induces a transfer of the

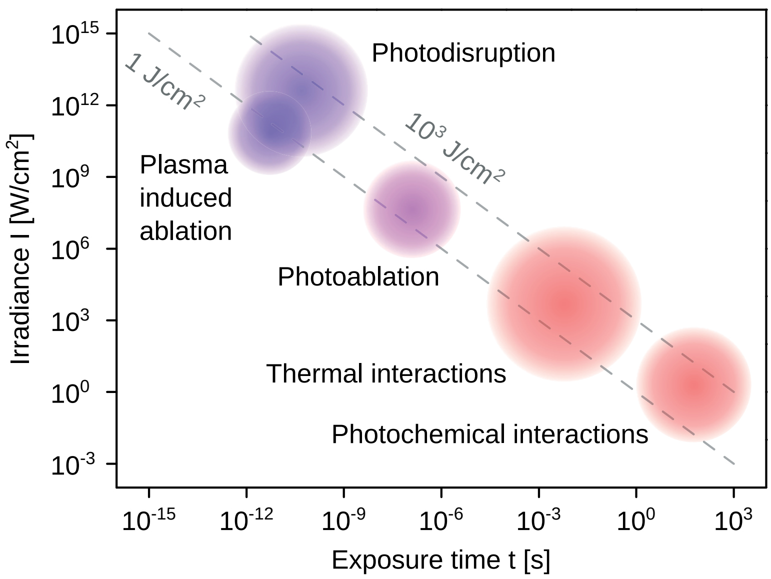

Fig. 2.2 Types of laser-tissue interactions: While for long pulse durations and low intensities thermal processes prevail, short pulses of several pico- to femtoseconds allow precise and non-thermal ablation or disruption of tissue, according to [34].

macromolecular polymer chains of the tissue into excited states. If the photon energy $E_{ph} = h\nu$ exceeds the energy of the chemical bonds, the resulting dissociation of the molecular bonds and the acceleration of the molecule fragments away from the surface enables a fast and precise removal of tissue. For pulse durations shorter than the thermal relaxation time of the tissue, heat diffusion away from the focal volume during the pulse incidence is negligible, thus localizing the laser-material interaction to the focal spot [32]. Since recently, photo-ablation has been applied in the ophthalmic LASIK-treatment in order to reshape the cornea and to provide a refractive correction of the eye [34].

For ultrashort pulses of only several ps to fs, the intensity at the focal spot can exceed values of ~10^{12} W/cm^2 even with comparatively low pulse energies of only few µJ. Thus, absorption due to avalanche ionization or nonlinear tunnel- and multiphoton ionization triggers the *laser-induced optical breakdown* (LIOB) [10]. Subsequent to the absorption process and the resulting formation of a µm-sized plasma, the energy of the free electrons is transferred to the surrounding tissue. The rise in temperature and pressure causes vaporization and *plasma-induced ablation* at the surface. When the focal spot is placed within the bulk of transparent material such as the cornea, the local energy deposition and the resulting pressure waves lead to the formation of a cavitation bubble and to local *disruption*. Due to the importance of this process in fs-laser surgery, the fundamentals of LIOB will be presented in more detail in Sec. 3.6. Since LIOB enables minimally invasive surgery within the bulk of transparent tissue with low side effects, numerous novel applications such as femto-LASIK and fs-laser cataract surgery have been established in the last years [14,35], which will be depicted in the following chapter.

2.3 Refractive fs-laser surgery

The most common aberrations of the eye are *hyperopia* (farsightedness) and *myopia* (nearsightedness), which are caused by a mismatch of the refractive power of the anterior eye segment and the length of the eyeball. While in the past these ametropia were mainly treated by compensating refractive elements such as glasses or contact lenses, new surgical approaches aim at a permanent refractive correction of the eye itself [32]. Currently, one of the most successful refractive treatments is the *LASIK* [5]. In this procedure, a corneal flap with a thickness of few 100 µm is created initially by means of a mechanical microkeratome and temporary fold away to access the intracorneal stroma layer. Then, predefined parts of the stromal tissue are precisely photo-ablated due to focused ultraviolet (UV) ns-laser pulses. After repositioning the flap, the change of shape of the cornea's front surface yields the refractive correction of the eye.

In the last decade, the development of compact and reliable fs-laser systems triggered new medical applications, as LIOB has enabled precise and gentle cuts within the bulk of transparent tissue [7]. Thus, in the novel *femto-LASIK* procedure, the mechanical microkeratome is replaced by focused fs-laser pulses in order to

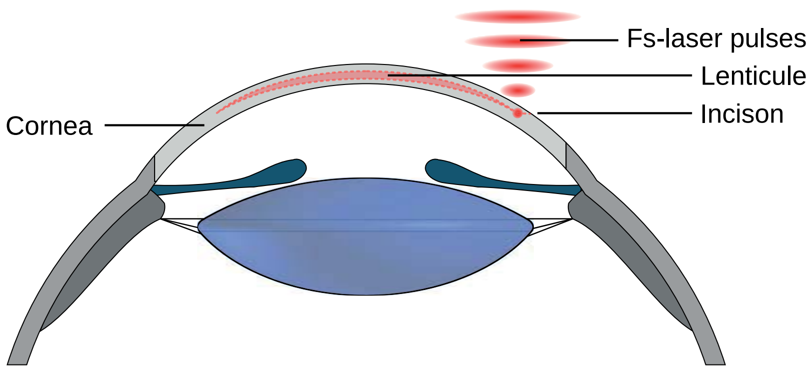

Fig. 2.3 Illustration of the 'ReLEx® SMILE' treatment: Due to the creation and removal of a thin lenticule within the stromal cell layer, the shape of the cornea is changed to provide the refractive correction of the eye.

enhance the precision of the flap cut, while the refractive correction is typically still obtained by ns-laser based photo-ablation. However, new techniques such as *ReLEx*® (Refractive Lenticule Extraction) aim at an even more gentle and faster treatment using only a single surgical device [36]. Here, focused fs-pulses are used to apply two stacked cut layers into the stromal tissue creating a thin lenticule. After opening the cornea by an additional circular side wall cut, the lenticule is removed yielding the desired refractive correction. A further reduction of tissue injury is achieved by continuative approaches such as *ReLEx*® *SMILE* (small incision lenticule extraction), where the circular side cut is replaced by a narrow side incision to extract the lenticule (see Fig. 2.3) [11].

2.4 Fs-laser cataract surgery

Besides aberrations, also metabolic changes of the lens tissue can impair the visual quality, e.g., due to *cataract formation*. Here, an age-related opacification of the crystalline lens fibres causes a diffuse scattering of the incident light and impairs the proper image formation of the eye [37]. As a consequence, cataract patients initially report on increasing halos and sensitivity to glare. The progressive opacification of the lens significantly impairs the visual acuity and contrast sensitivity and, finally, leads to entire blindness. To more than 90% cataract is caused by the age-related denaturation and degradation of the lens proteins, while additional factors such as diseases and environmental conditions cause an abatement of the restorative and protective mechanisms of the lens [1]. Moreover, a damage of the lens capsule or severe blunt trauma may result in the swelling of crystalline lens fibres likewise inducing their opacification.

With about 20 million treatments per year, cataract surgery is one of the mostly performed surgical interventions worldwide [14]. Currently, the *small incision phaco-emulsification* is the most common treatment technique. After manually opening the capsular bag by a circular cut (capsulorhexis) through a small incision in the sclera, the emulsification and removal of the opaque lens tissue is realized by means of a suctioning ultrasonic tip. Finally, an intraocular lens (IOL) is implanted into the capsular bag to restore the refractive power of the eye. Although new implants such as accommodative IOL aim at providing both near and far vision, the restoration of a satisfying accommodation ability is yet to be gained [38].

In recent years, precise fs-laser surgery has been of increasing interest for cataract surgery, as in the conventional treatment the precision of the manual capsulorhexis cut is limited and may lead to irregular cuts or capsular tears, which impede the correct positioning of the IOL [15]. Furthermore, phaco-emulsification by means of an ultrasonic tip induces stress to surrounding tissue such as the sensitive corneal endothelium [13]. In contrast, LIOB enables a fast and precise cutting of the capsular bag as well as the perforation of the lens tissue with low side effects. Hence, studies on the fs-laser induced capsulorhexis show an increased accuracy regarding the intended diameter, the circularity and the centration of the cut [15]. Due to the fragmentation of the opaque lens tissue by a three-dimensional grid-like cut pattern prior to its extraction, the effective phaco-emulsification time and the applied phaco energy are significantly reduced compared to the conventional treatment, thus reducing stress onto surrounding tissue [39].

2.5 Fs-laser presbyopia treatment

To adapt from far to near fixation, the human eye features the adjustment of its optical power due to a change of the crystalline lens shape. However, with increasing age the flexibility of the crystalline lens is hampered [40]. The resulting loss of the accommodation width causes a displacement of the near point up to distances > 50 cm at the age of ~ 50 years (Fig. 2.4), thus hampering the close vision ability, e.g., required for reading [1]. Although the complex ageing processes of the human eye are not entirely clarified, yet, current research states the loss of the lens

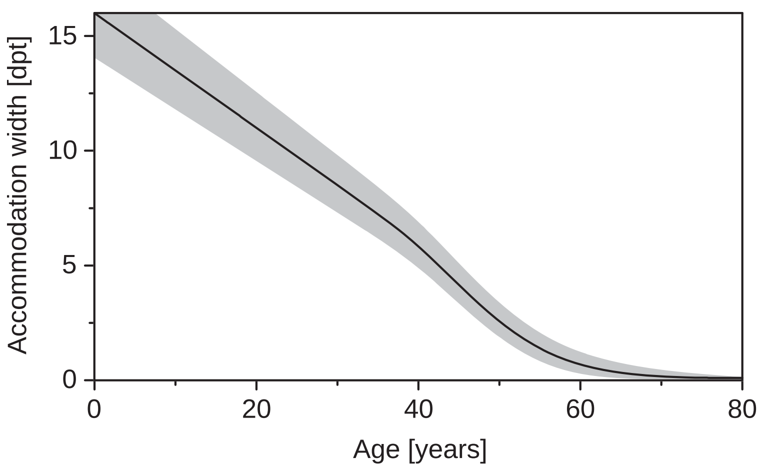

Fig. 2.4 Age-depending loss of the eye's accommodation width, according to [1].