Design, Validation and Application of an Ocular Shack-Hartmann Aberrometer

by

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DEDICATION

Gewidmet meinen Eltern Lonia and Karl Straub.

Para mi esposa Alejandra por ser mi inspiración
durante los años de mis estudios.
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ABSTRACT

The design and testing of an ocular Shack-Hartmann aberrometer is presented. The aberrometer objectively measures optical aberrations in the human eye in vivo. The sensor was successfully tested for measurements of refractive error (sphere and cylinder) and spherical aberration. Vignetting limits the measurement range of the wavefront to a range of -10 D to +15 D. Large refractive errors and decentration of the measurement induce aberrations in the test wavefront. Analytical tools to correct for these systematic errors were developed.

A clinical study was conducted assessing visual performance in 158 eyes of 89 subjects before and after LASIK refractive surgery. The main results of the study were that refractive surgery corrects refractive errors very accurately. A slight regression in refraction during the 12 months after surgery was noted. Measurements of ocular aberrations using the Shack-Hartmann aberrometer revealed that refractive surgery introduced large amounts of higher order aberrations, mainly spherical aberration and coma. The amount of aberrations changed significantly during the 12 months wound healing period.

The dark adapted pupil diameter of the eye increased significantly during the first 6 months after surgery. The changes in ocular aberrations and pupil diameter were correlated to changes in contrast sensitivity in the human eye.
The analysis of corneal topography showed that while the anterior corneal curvature changed due to surgery, we also saw a change in the posterior corneal curvature as a biomechanical response to surgery.

A Customized Eye Model was designed and tested based on the clinical measurements. The model used conic surfaces and modeled defocus and spherical aberration. This computer eye model was then used in optical lens design software to calculate an optimal Customized Ablation Pattern for individual eyes.
CHAPTER 1

INTRODUCTION

Laser refractive surgery has been a popular elective surgery for several years. Current research and development efforts have been moving towards customized refractive surgery that is expected to provide an individually tailored treatment for every eye which would result in improved visual quality. Visual quality is expected to improve beyond the outcome of current refractive surgery and when compared to naturally emmetropic eyes.

The goal of our research was to investigate the changes to the human eye due to current laser refractive surgery and wound healing. We conducted a clinical study enrolling almost 100 subjects that had laser refractive surgery (LASIK, laser in situ keratectomy). The subjects were seen before surgery and at five visits up to 12 months after surgery. At each visit, we assessed a number of subjective and objective metrics for the visual performance of the subject’s eyes. The measurements included manifest refraction, visual acuity, contrast sensitivity, corneal topography, and ocular aberrations. The analysis of the data collected throughout the study provided valuable insight in surgery and wound healing changes to the human eye in a large population.

The only measurement instrument in our study that was not available commercially was a wavefront sensor to measure ocular aberrations. We designed and tested a Shack-Hartmann wavefront sensor (aberrometer) to objectively measure the aberrations in the
human eye in vivo. Our aberrometer is compact and easy to use and has been in clinical use for over three years now. Chapters 2 though 4 in this dissertation are dedicated to the design and testing of the Shack-Hartmann aberrometer.

In Chapters 6 and 7, we present an algorithm to calculate a customized ablation pattern for individual eyes. Based on the measurements of the eyes of the subjects in the clinical study, we designed a Customized Eye Model. For the model, we used measurements of topography and of the total aberrations of the human eye. The Customized Eye Model can be used to model the eye before surgery, or based on measurements before and after surgery. Based on the Customized Eye Model we can calculate a Customized Ablation Pattern for every individual eye. This Customized Ablation Pattern will provide the eye with the best possible optical performance.
CHAPTER 2

DESIGN OF A SHACK-HARTMANN ABERROMETER

Shack-Hartmann Wavefront Sensor

A Shack-Hartmann wavefront sensor is a modification of the Hartmann screen test that is widely used in astronomical applications and optical testing [7]-[10]. Instead of a screen with apertures, the Shack-Hartmann wavefront sensor uses an array of lenses [8]. An incoming wavefront is divided by the sub-apertures of the lenslet array and each lens of the lenslet array focuses its part of the wavefront onto the imaging plane. A plane wave creates an evenly distributed grid pattern on the image plane. For an aberrated wavefront, the focus spots of each lenslet are shifted by an amount related to the wavefront aberrations [7], [10]. Figure 1 shows spot patterns created by a plane wavefront and an aberrated wavefront.

![Diagram of focus spot patterns](image)

Figure 1: Focus spot patterns created in the focal plane of the lenslet array by a plane wavefront and an aberrated wavefront.
Design of a Shack-Hartmann Aberrometer for the Human Eye

In order to measure the aberrations of the human eye with a Shack-Hartmann wavefront sensor, we focus a laser source on the retina to create a point source. The wavefront emerging from this point source passes through the eye and is aberrated by the optical components of the eye. The wavefront aberrations are measured with the Shack-Hartmann wavefront sensor. There are several design characteristics that are specific to the human eye. The aberrometer needs to be mounted on a chin rest assembly with easy alignment possibilities. The distance between the eye and the instrument should be a minimum of two inches; else the patient might feel uncomfortable. The exposure of the eye with laser light has to be controlled carefully in order to keep the eye safe and comfortable from a brightness standpoint.

Shack-Hartmann wavefront sensors have been shown to be fast and precise instruments for the objective measurement of monochromatic aberrations of human eyes in vivo [1]-[5]. However, the measurement procedure potentially involves some inconvenience for the subject that could limit the use of this technique in a clinical environment. Early Shack-Hartmann wavefront sensors for the eye used a bright HeNe laser at an exposure time between 100ms and 2s. The subject’s eye has to be aligned prior to the measurement, using a fixation target, and only after the exposure can it be decided if alignment and measurement were successful. Some studies also report the use of dilating drops or drugs to paralyze the accommodation of the eye.
In this chapter, the design of a compact Shack-Hartmann aberrometer is presented. The aberrometer shows two live images simultaneously on a computer screen, one image of the subject’s eye and one of the Shack-Hartmann grid pattern. The operator has instant feedback and can align the aberrometer to the best possible position before measuring. The actual measurement only requires freezing and saving the live images. The subject’s pupil size is controlled by the ambient lighting conditions, since near infrared laser light is used for the measurement. During the measurement, the subject fixates the slightly visible collimated laser beam and the eye accommodates for infinity. The alignment of the system takes only about a minute and no eye drops or drugs are necessary. There is no discomfort for the subject involved in the measurement. Our Shack-Hartmann aberrometer is very small and light enough to be mounted on a standard ophthalmic chin rest assembly. The mechanical design is such that the aberrometer is portable without the need for realignment after transport. Corrections of the alignment of the optical components can be done very easily [12].

The aberrometer is shown in Figure 2. It is mounted on a standard ophthalmic chin rest assembly and is 500mm long, 200mm wide, and 150mm high. Figure 3 shows the entire aberrometer mounted on the chin rest assembly together with the laptop computer that is used to capture and process the images.
Figure 2: Photograph of the first generation Shack-Hartmann aberrometer. The aberrometer is mounted on a standard ophthalmic chin rest assembly and is 500mm long, 200mm wide, and 150mm high.

Figure 3: Photograph of the first generation aberrometer in the clinic. This photograph shows the entire aberrometer mounted on the chin rest assembly together with the laptop computer that is used to capture and process the images.
The first version of the aberrometer was put in the clinic in August 2000. Over the following three years, five additional aberrometers have been built. The design was constantly improved and the original aberrometer was rebuilt in August 2002, taking all the design changes into account. The discussion in this chapter refers to the most recent design, although some of the photographs or figures might show older versions. Figure 4 shows photographs of the latest generation Shack-Hartmann aberrometer.

Figure 4: Photographs of the latest generation Shack-Hartmann Aberrometer.
Optical Design of the Aberrometer

The Shack-Hartmann aberrometer consists of three optical paths that are combined into one instrument, sharing some of the optical components. The illumination path focuses the laser on the retina. The sensor path images the aberrated wavefront from the pupil of the eye onto the lenslet array of the Shack-Hartmann sensor. Finally, the imaging path is used to show a live picture of the eye and is used for alignment purposes. A laptop computer with two frame grabbers is used to operate the aberrometer.

Figure 5 shows a schematic of the optical design of the aberrometer, showing the illumination path (red), sensor path (yellow), and imaging path (green).
The Illumination Path

A laser beam is focused on the retina where it creates a point source that illuminates the eye. As a light source, we use a near infrared diode laser with beam shaping optics (laser class IIIb, 5mW, 780nm). The laser has a short coherence length which reduces problems with diffraction and speckle. The laser beam is linearly polarized and has a circular shape with a diameter of about 1mm. The laser is slightly decentered relative to the optical axis and the apex of the cornea in order to avoid light reflected from the front corneal surface from entering the aberrometer. Because the near infrared wavelength is still slightly visible, the subject uses the laser light as a fixation target. Figure 6 shows a schematic of the decentered laser light entering the eye (red), creating a point source on the retina and light propagating out of the eye’s pupil (yellow).

Figure 6: Schematic of the laser entering the eye (red) and focusing on the retina. A diffuse reflection directs the light back (yellow). This creates a point source that is collimated by the optics of the eye. When the light exits the eye the wavefront has been aberrated by the optical components of the eye. The incoming laser is decentered in order to avoid that the light reflected at the anterior corneal surface enters the aberrometer.
To the patient's eye, the parallel laser beam appears as a target at infinity, thereby relaxing the accommodation of the eye. The patient does not note the decentration. The subject is looking at its far point. The perceived brightness of the near infrared light is, on the other hand, dim enough that the pupil dilates naturally in a dark environment. Figure 5 shows that before entering into the eye, the laser is deflected twice. The first deflection is at a mirror that folds the illumination path by 90 degrees and puts it perpendicular to the sensor path. This saves space and provides extra degrees of freedom for beam alignment. The second deflection is at a pellicle beam splitter that transmits 92% of the light. Only 8% of the laser power is actually directed into the eye.

For laser safety reasons, the maximum permissible exposure (MPE) for the laser in our Shack-Hartmann was calculated [11]. For the near infrared wavelength of 780nm, the MPE for an 8hr exposure (3·10^4 seconds) is

\[ MPE = 320 \cdot C_A \frac{\mu W}{cm^2} \]  

(1)

with \( C_A \) increasing semi-logarithmically between 1 for 700nm and 5 for 1050nm. For a conservative estimate, we chose \( C_A = 1 \).

\[ MPE = 320 \cdot 1 \cdot \frac{\mu W}{cm^2} \cdot \frac{0.7cm)^2}{4} = 125 \mu W \]  

(2)

A linear polarizer is placed behind the laser to control the power of the laser beam. The laser power was set to a level well below the MPE where it gives good measurement results for subjects with significantly different reflectivities of the retina. The reflectivity
varies largely with the pigmentation of the retina, which is related to the color of the skin of the patient. The laser power that enters the eye was measured to be $9\mu W$. This is approximately 14 times less than the American National Standards Institute’s maximum permissible exposure (MPE) of $125 \mu W$. The measurement of the laser power was made using a Coherent hand-held laser power meter. Our Shack-Hartmann aberrometer is approved by the Radiation Control Office of the University of Arizona as a Laser Class 1 product with an embedded Class IIIb laser.

If the subject’s eye has a refractive error, the collimated laser beam will not be focused on the retina. This error decreases the quality of the wavefront created at the retinal laser spot. We designed a zoom system that was placed in the illumination path. This zoom system consists of two lenses that are aligned as a Keplerian telescope. The eye is placed at the back focal plane of zoom lens 2. By moving zoom lens 1 along the optical axis to decrease or increase the separation between the lenses, the zoom system corrects for myopia and hyperopia, respectively. We found that a focal length of 120mm for zoom lens 1 and 100mm for zoom lens 2 gives us a linear tuning of 1 diopter per centimeter. The mechanical constraints allow corrections in a range of $-10$ to $+10$ diopters. Figure 7 shows the geometry of the zoom system and the relation between the displacement of lens 1 and the correction. The mechanical mounts give us the opportunity to move lens 1 without altering the alignment of other optical components.
Figure 7: The zoom system is a Keplerian telescope with the eye placed at the back focal plane of zoom lens 2. By displacing zoom lens 1, the zoom system corrects for the refractive errors of the eye. To correct for myopia, lens 1 has to be shifted towards lens 2. To correct for hyperopia, lens 1 has to be shifted away from lens 2. The relation between the displacement and the correction is linear (1D/cm). The mechanical design allows corrections of −10D to +10D.
The Sensor Path

The laser spot on the retina creates a spherical wavefront that propagates through the eye that is accommodated to infinity. For an emmetropic eye, the wavefront after the eye is a plane wave that has been aberrated by the eye’s optical system. A telescope system with a telecentric aperture stop is used to image the wavefront onto the lenslet array as shown in Figure 5. The stop acts as a spatial filter to block reflected and scattered light. The aperture stop may not be closed down too much, because it will also block strongly aberrated parts of the wavefront.

The lenses used for the telescope are achromatic lenses with a focal length of 120mm. They were chosen to minimize spherical aberration introduced by the telescope system. A reference measurement had been taken of a perfectly plane wave and is used to correct for systematic errors in the measurement. For a perfectly aligned system we introduce 0.004 waves of spherical aberration for a 6 mm pupil size, and 0.5 waves at full aperture (25.4 mm). Therefore, we have to make sure that we have the eye’s pupil well centered when taking the measurements. Because the eye is placed at the front focal plane of the first lens, the eye relief of the patient depends on the focal length of the lens. On the other hand, the optical system is four times the focal length long. A focal length of 120mm provides a good compromise between patient comfort and total system length.

The lenslet array used in our system has a focal length of 24mm and a lenslet size of 400 microns. Our choice was limited by commercially available lenslet arrays. We need a long focal length in order to mount the lenslet array in front of the CCD camera without
the need of custom mounts. Standard C-mount CCD cameras have a flange distance of 17mm, so lenslet focal lengths longer than that distance are acceptable. The diameter of individual lenslets has influence on the amount of light collected into each single focal spot. A larger number of lenslets (i.e. choosing smaller lenslets) increases the sampling of the wavefront and therefore the accuracy of the measurement. On the other hand, it decreases the brightness of the focus spots, making it necessary to use a more sensitive CCD camera. A longer focal length increases the sensitivity of the sensor because the focus spots are further displaced by a small change in wavefront curvature or tilt. As a disadvantage, this might cause spots crossing over for highly aberrated wavefronts [17], [18]. In our case, we deal mainly with defocus, astigmatism, and spherical aberration. Our arrangement is suitable for most regular aberrations. However, this setup has limited capabilities for highly irregular eyes like those associated with patients with keratoconus and penetrating keratoplasty.

We use a 2/3” monochrome CCD camera with a sensitivity of 0.5 lux to grab the grid image. The size of the CCD chip is 6.6mm by 8.8mm, allowing a pupil of 6 mm diameter to be imaged completely. For pupil sizes larger than 6.6 mm diameter we will encounter some cropping. The video image from the camera is digitized and displayed on the computer screen. Brightness and contrast are adjusted to get a crisp image with bright white dots and a black background. The operator sees a live image with a repetition rate of 2-3 pictures per second and a resolution of 300x400 pixels. The pupil is sampled with a 400 micron grid of focus spots. Figure 8 shows a grid image of a human eye.
Six LEDs at 880nm are mounted to the front of the aberrometer. These are needed to illuminate the external portions of the eye to facilitate alignment. Measurements can therefore be taken in complete darkness to allow maximum natural pupil dilation. To ensure corneal reflections of the LEDs do not corrupt the Shack-Hartmann grid image, a short wave pass filter is used. A cutoff wavelength of 850nm eliminates any effect from the LEDs in the measurement.
Limits of the Optical Design: Cropping the Wavefront / Vignetting

For eyes free of refractive error, a plane wave emerges from the eye. For eyes with refractive error, the wavefront emerging from the eye is spherical. In the case of myopia, the spherical wavefront converges to the far point in front of the eye (FP). For hyperopia, the spherical wavefront is diverging and appears to come from a far point behind the eye. Figure 9, Figure 10, and Figure 11 show how wavefronts are created by emmetropic, myopic, and hyperopic eyes.

**Emmetropic Eye**

Figure 9: Wavefront emerging from an emmetropic eye. The far point FP of this eye is at infinity.

**Myopic Eye**

Figure 10: Wavefront emerging from a myopic eye. The far point is in front of the eye.

**Hyperopic Eye**

Figure 11: Wavefront emerging from a hyperopic eye. The far point is behind the eye.
The far point of the eye is inversely related to the eye's refractive error if $FP$ is the distance from the far point to the front principal plane of the eye, then the refractive error of the eye is $\Delta\Phi$.

$$\Delta\Phi = -\frac{1}{FP} \quad (3)$$

For an emmetropic eye the far point is at infinity. The wavefront emerging from the eye is relayed by an afocal imaging system to the lenslet array. Since plane, converging or diverging wavefronts are encountered for emmetropia, myopia and hyperopia respectively; the afocal relay must allow the wavefront to propagate through the system without being vignette. The illustration in Figure 12 shows a plane wave propagating through the system.

![Figure 12: Propagating a plane wavefront through the system.](image)

For emmetropia, the maximum clear aperture for each element is the diameter of the eye pupil. For dilated pupil, 8-9mm is about the maximum seen. The yellow color indicates the wavefront in the exit pupil of the eye and its image on the lenslet array. One of the pellicle beam splitters in this drawing has been rotated by 90 degrees so that now all the cross sections of all limiting apertures are drawn in the same plane. Because the beam splitters are crossed in the actual setup, they limit the unvignetted field of view in
both, x- and y- directions. The size of the elements used is limited by the mechanical system that we used to build the aberrometer.

Figure 13: Propagating a converging wavefront through the optical system. Limiting apertures are the stop and the second telescope lens. The wavefront (red) is imaged onto the lenslet array and vignetted.

Figure 13 shows the propagation of a converging wavefront from a myopic eye. Again, the yellow color indicates the wavefront in the exit pupil of the eye and its image on the lenslet array. Vignetting will occur at the aperture stop and the second telescope lens. Opening the aperture stop and using a larger diameter for the second telescope lens can solve this problem.

Figure 14: Propagating a diverging wavefront through the optical system. Limiting apertures are the edges of the pellicle beam splitters.

Figure 14 shows the propagation of a diverging wavefront from a hyperopic eye through the optical system. The limiting apertures are now the edges of the pellicle beam splitters and the aperture stop. While opening the aperture achieves an unvignetted
propagation, mechanical constraints limit the size of the pellicle beam splitters in the aberrometer.

Table 1 shows the clear apertures of the current setup. To find the limits of our measurement range, we trace a single ray, starting at the edge of the exit pupil of the eye (4 mm high) with an angle corresponding to the divergence or convergence angle of the refractive error.

<table>
<thead>
<tr>
<th></th>
<th>Clear Aperture (mm)</th>
<th>Limit to the Measurement Range (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pellicle 1</td>
<td>17.8</td>
<td>+10</td>
</tr>
<tr>
<td>Telescope Lens 1 (120mm)</td>
<td>25.4</td>
<td></td>
</tr>
<tr>
<td>Pellicle 2</td>
<td>17.8</td>
<td></td>
</tr>
<tr>
<td>Stop (Iris Diaphragm)</td>
<td>4.8, 9.6, 14.4, 19.2</td>
<td>+/- 5, +/- 10, +/- 15, +/- 20</td>
</tr>
<tr>
<td>Telescope Lens 2 (120mm)</td>
<td>25.4</td>
<td>-15</td>
</tr>
</tbody>
</table>

Table 1: Clear apertures of the optical system in the aberrometer. Pellicle 1 limits the measurement range to 10 D hyperopic; telescope lens 2 limits the range to 15 D myopic. All this is dependent on the adequate stop size.

For unvignetted measurements, pellicle 1 limits the range to 10 D of hyperopia. Telescope lens two limits the measurement range to 15 D of myopia. While this range is acceptable for standard clinical use, the stop size limits the unvignetted measurement range even further. If we want to use the whole range of our optical system, we have to
practically remove the stop. The disadvantage of this is that we then lose our spatial filter that ensures acceptable contrast in the grid image. A compromise has to be found between measurement range and spatial filter size. We found a stop size of about 5 to 6 mm to still be a good filter, though limiting the measurement range to +/- 5 or 6 D, respectively. This stop size is adequate, since most eyes in our study have undergone refractive surgery, and these eyes ideally are free of refractive errors.
Limits of the Optical Design: Induced Aberrations

We used an afocal imaging system to image the wavefront at the exit pupil of the eye onto the lenslet array of the wavefront sensor. Figure 15 shows the afocal imaging system. The object plane is at the front focal plane of telescope lens 1 (L1), while the image plane is at the back focal plane of L1. The magnification of the afocal imaging system is the ratio of the focal length of the two lenses, or negative unity in our case. The location of the stop at the common focal point of L1 and L2 makes the imaging system doubly telecentric.

Figure 15: Afocal imaging system.

The afocal imaging system is a telescope system that uses two achromats in order to minimize the introduction of spherical aberration by the imaging lenses. The system is designed for a plane wave in the object plane, so the achromats are placed back-to-back, as can be seen in Figure 16.
If the patient’s eye has a refractive error, then the wavefront emerging from the exit pupil of the eye is not a plane wave, but instead either diverging or converging. In the first order design discussed earlier, the defocused wavefront was imaged from the exit pupil onto the lenslet array. We could also think of a diverging or converging wavefront as a point source placed at the far point of the eye. This changes our object location and the imaging system consisting of the two achromats is no longer well corrected for this imaging task.

In this chapter, we evaluate the aberrations induced by propagating aberrated wavefronts, develop some correction algorithms for individual aberrations, and present a procedure to calculate the real wavefront error for a given wavefront error measurement.

To evaluate aberrations induced when imaging aberrated wavefronts with the afocal imaging system, a Zemax model was designed, consisting of a the two achromat lenses discussed above, a phase plate to create an aberrated wavefront, and a paraxial lens simulating the wavefront sensor (Zemax Optical Design Program, Zemax Development Corporation, San Diego). Figure 17 shows a sketch of the model eye showing the Zernike phase plate and the paraxial lens with its image plane.
Figure 17: Imaging an aberrated wavefront (red) created with the Zernike Standard Phase surface. A paraxial lens is introduced to create an image plane where we can analyze the aberrations.

We evaluated two causes for induced aberrations. The first is inducing aberrations when imaging aberrated wavefronts. We limit our initial aberrated wavefronts to defocus and spherical aberration because defocus is the largest aberration present in the human eye and spherical aberration is elevated after laser refractive surgery. We analyze initial defocus in the range of up to -10 D myopia, and initial spherical aberration up to 1.0 micron. The other cause for induced aberrations is decentration of the measurement. We analyze decentration up to 5 mm. The analysis is done for a 6 mm pupil diameter.

Figure 18 shows a plot of induced defocus for decentered measurements. The plot shows a family of curves for different amounts of initial defocus. The induced defocus increases with decentration and initial defocus. The reason for this introduction of defocus into the wavefront is that the image plane of the afocal imaging system is not plane, but has some curvature, i.e. field curvature, or Petzval curvature. Field curvature is a field-height-dependent aberration and we can think of it as a defocus term that changes with field height or decentration as we can see in Figure 18.
Figure 18: Induced defocus for imaging a defocused wavefront with different amounts of decenteration.

Figure 19: Induced Astigmatism when imaging a defocused wavefront for decentered measurements.

Figure 19 shows the induced astigmatism when imaging a defocused wavefront for decentered measurements. This figure is plotted at the same scale as Figure 18 showing that the amount of induced astigmatism is larger than the amount of induced defocus. If we consider 0.25 D the smallest measurement unit for refractive error, we see that
induced defocus and astigmatism can cause a substantial systematic error in the measurements of refractive error. Both Figure 18 and Figure 19 show that no defocus or astigmatism is induced if the measurement is not decentered. Even a slight decenteration of up to 1 mm is tolerated very well. For decentrations of 2 mm and larger, we notice a substantial increase in induced defocus and astigmatism.

We induce a continuously increasing amount of defocus and astigmatism for increasing amounts of decenteration. Because we will not be able to maintain perfect centration for every single measurement, we need to determine a criteria to determine what amount of induced aberrations we can tolerate. The Rayleigh criteria states that a wavefront error of 0.25 waves peak-to valley is acceptable for diffraction limited performance [61]. This gives us the limit of about ±0.2 microns of peak to valley wavefront error that we can tolerate. This wavefront error corresponds to ±0.2 D of refractive error. This confirms that we can tolerate induced defocus and astigmatism for decentrations up to 1mm.

Figure 20 shows induced spherical aberration when imaging a defocused wavefront for different decentrations. The induced spherical aberration is negative and its magnitude increases with larger initial defocus in the wavefront. The amount of induced spherical aberration decreases with decenteration, indicating some aberration balancing for decentered measurements. Because induced spherical aberration is present even for well-centered exams, we determined a correction algorithm for this systematic error that will be presented later.
Figure 20: Induced spherical aberration when imaging a defocused wavefront for decentered measurements.

Figure 21 shows induced coma when imaging defocused wavefronts. Unlike in the previous charts we now see a steep increase in induced coma with slight decentrations. Coma is the main higher order aberration induced by decentration of the measurements. Note the larger scale as compared to induced spherical aberration.

Figure 22 shows induced trefoil when imaging defocused wavefronts for decentered measurements. The amount of trefoil increases with larger initial defocus and increasing decentration, but is still small compared to the induced spherical aberration or coma. Note the different scale when compared to induced coma or spherical aberration.
Induced Coma when Imaging
Defocused Wavefronts

![Graph showing induced coma for different decenterations and diopters.]

Figure 21: Induced coma when imaging defocused wavefront for decentered measurements.

Induced Trefoil when Imaging
Defocused Wavefronts

![Graph showing induced trefoil for different decenterations and diopters.]

Figure 22: Induced trefoil when imaging defocused wavefronts for decentered measurements.
When imaging wavefronts with spherical aberration, we encounter a number of induced aberrations. Again, we induce defocus for decentered measurements, due to the Petzval field curvature of the afocal imaging system. We also induce astigmatism and spherical aberration. The largest induced aberrations are defocus and coma. Induced spherical aberration, trefoil, fourth order astigmatism, and quadrafoil are very small.

We found that the most dominant of the induced aberrations are defocus induced by decenteration (Figure 18) and spherical aberration induced by initial defocus (Figure 20, zero decenteration). We present two formulas to correct these for these systematic errors in the measurements.

The first correction formula is used to calculate the real refractive error $\Phi_{\text{REAL}}$, or defocus, for a given measured defocus term $\Phi_{\text{MEASURED}}$ for a known amount of decenteration $d$.

$$\Phi_{\text{REAL}} = (1 + 0.0029 \cdot d + 0.0048 \cdot d^2) \cdot \Phi_{\text{MEASURED}}$$

This formula can be used to correct for induced defocus errors in measured refraction data. Note that the real refraction is always larger or equal to the measured refraction, depending on a quadratic function of decenteration $d$. 
The second formula corrects for spherical aberration induced by imaging defocus. The induced spherical aberration is a function of the refractive error $\Phi_{REAL}$ and the decentration $d$.

$$a_{40, \text{INDUCED}} = (0.0287 - 0.0045 \cdot d) \cdot \Phi_{REAL} \tag{5}$$

These two formulas give us the tools to correct for the systematic error of the most dominant induced aberrations, i.e. defocus induced by decentration and spherical aberration induced by defocus. These formulas will be used to correct the data presented in the chapter entitled Whitaker study.

The simulation that lead to the above results was quite simplified. We created wavefronts that would either contain only defocus or only spherical aberration. In reality, we will always encounter a combination of a number of different aberrations in every single wavefront. If we image a wavefront with the afocal imaging system, especially if the measurement is decentered, then the induced aberrations are usually too complex to correct for the systematic error analytically. Instead, we can use the same Zemax model that we have used for the calculation of induced aberration to back-trace the measured wavefront to the original wavefront. In order to do this, we reversed the order of the elements and the sign of the measured wavefronts. We also took the magnification of negative unity into account. We propagated this wavefront through the afocal system with the known decentration. The resulting wavefront is the original wavefront.
The Imaging Path

The imaging path consists of a camera that is imaging the pupil of the eye. Its main purpose is to give the operator a live image of the eye that can be used for alignment. We designed the pupil camera to be telecentric in object space. If the eye is not placed exactly at the front focal plane of the first lens, the image appears out of focus, but the blur is centered on the in-focus image. This gives us the opportunity to also use the instrument as a pupillometer [13].

Figure 23: Layout of the imaging path, showing rays for on-axis and 3 mm object height.

Figure 23 shows the layout of the imaging path with ray bundles for an on-axis as well as a 3 mm height object point (edge of a 6mm pupil). The stop is set to a quarter inch diameter and is placed at the rear focal point of the first lens, thereby creating a telecentric system. The small pupil size reduces the amount of spherical aberration introduced by the shorter focal length lens. For the telecentric design, the first lens is actually mounted backwards, with the stronger curved surface towards the diverging bundle of rays. This is because the first lens is oriented to image the wavefront, and we have to accept it. The image quality is still quite good, as can be seen in Figure 24.
Figure 24: Image of a pupil taken with the telecentric pupil camera. The scene is illuminated by NIR light from six 880nm LEDs. The reflection of these LEDs can be seen on the image. The dim spot in the center is some reflection from the decentered laser. The edge of the image shows that this optical design suffers from vignetting at the first pellicle beam splitter.

Figure 25 shows the spot diagram of the pupil camera. The solid circle represents the Airy disk diameter. The system is very well corrected, although the first achromat is mounted backwards. For increasing object height, we introduce astigmatism. The image is recorded by a 1/3” CCD camera with a very high sensitivity of 0.01 lux. This is 50 times more sensitive than the 2/3” CCD camera used for the grid image.

Figure 25: Spot diagram for the imaging path. On-axis point (left) and 3mm object height corresponding to the edge of a 6mm pupil (right). Scale bar in microns. Solid circle represents airy disk diameter.
Mechanical Design of the Aberrometer

We had built a first Shack-Hartmann aberrometer using C-Mounting components (Edmund Scientific). The optical components were mounted in tubes that were connected to one another and mounted on posts. These posts were then mounted on a base plate which made the whole setup portable. While we were working with this already comparatively compact setup (base plate 400x500mm, 200m high) in a clinical environment, we found that the following criteria are critical for the design of a reliable Shack-Hartmann aberrometer. The aberrometer is very sensitive to optical alignment. This requires a high mechanical stability of the mounting components. Although the measurement is in real-time with live images on the computer screen, it is necessary for the subject to rest his head on a chinrest for the measurement.

In order to meet all these requirements, a second aberrometer was built based on the Microbench system (Linos Photonics). This system uses a set of four rods that are mounted parallel to each other. All components (i.e. lenses, filters, mirrors, laser, etc.) are mounted in mounting plates that can be moved along these rods. This has the advantage that all components are perfectly centered relative to the optical axis and cannot be tilted. The setup supports itself and does not need to be mounted on a base plate or on posts. The Microbench system provides mechanical interfaces to mount the complete system on an ophthalmic chin rest assembly or connect it with custom made parts or stock optical components of other manufacturers. Casing and cover plates can be mounted directly onto the mounting plates to protect the optical components from dust and mechanical
damage and also to improve the looks of the setup. The mounting on the four rods is very stable and gives the opportunity to move and adjust single components without moving other parts. When building the Shack-Hartmann aberrometer, we used mainly stock optical and mechanical components that were available at a reasonable price.

Figure 26 shows the mechanical design of the Shack-Hartmann Aberrometer. This drawing refers to the initial design using 100mm achromats in the telescope system. The drawing is to scale. The current version of the aberrometer uses a 120mm achromat in order to increase the eye relief. This drawing illustrates the source of vignetting at the circular pellicle beam splitters. The system drawn here does not contain the zoom system described in the section of the illumination path.

Figure 26: Mechanical design of the Shack-Hartmann Aberrometer (Side view).
Figure 27: Mechanical design of the Shack-Hartmann Aberrometer (Top view).
The Shack-Hartmann Aberrometer in Clinical Use

When taking a measurement with the Shack-Hartmann aberrometer, the subject waits in a dark room until his pupils are dilated and then rests his head on the chinrest and fixates the collimated dim red laser beam. The operator aligns the aberrometer relative to the subject's eye. On the computer screen, the operator sees two live images: an image of the subject's eye and the Shack-Hartmann grid image. Figure 8 and Figure 24 show images of a typical measurement showing the eye and the Shack-Hartmann grid image respectively. The system is designed so that if the pupil of the eye is in focus in the imaging path then the pupil is conjugate to the lenslet array. By focusing the image of the eye, the operator assures that the aberrometer and the eye are aligned properly and takes a measurement. The operator can take a measurement at any time. The images are then automatically recorded and referenced in a database.

After taking the images, the user can process the image. The results of a processed measurement are shown in Figure 28. The top left shows the grid image with the green lines indicating the displacement of every single spot. Based on the displacement, the wavefront error and refractive error maps are calculated. The software contains different tools to visualize the aberrations and the point spread function of the eye. It displays the wavefront error using the proposed standard Zernike set [19].
Figure 28: Analysis of the measured grid pattern (top left), display of the 27 Zernike coefficients (top right), the wavefront error map (bottom left), and the refractive error map (bottom right) [20].
Summary

The Shack-Hartmann aberrometer provides real-time measurements of the aberrations of the human eye. We present a Shack-Hartmann aberrometer that is small, compact and light weight, so that it can be mounted on a standard ophthalmic chin rest assembly. The mounting and alignment of the optical components is very stable which makes the aberrometer portable. In more than three years of clinical use, it has proven to be quick and easy to operate as well as reliable. The time for a measurement of both eyes of a subject is usually less than 5 minutes. Because the aberrometer provides live images of both the eye and the Shack-Hartmann grid image in order for the operator to get instant feedback during alignment, it can be aligned very quickly. Measurements can be repeated in seconds if a correction of the alignment is necessary. In addition, the aberrometer is safe and comfortable because the subject’s eyes are dilated naturally in a dark room with no eye drops or drugs administered.

Vignetting limits the use of the aberrometer to a maximum range of -15 to +10 D. This can only be achieved if the stop is removed. In the current clinical setting, the aberrometer is reliable in a range of +/- 6 D. The impact of defocus, spherical aberration, and decentration on induced aberrations has been shown. We can correct analytically for induced aberrations caused by initial defocus and decentration. To correct for all induced aberrations, we can propagate the measured wavefront back through the afocal relay system.
CHAPTER 3

TESTS WITH AN OPTICAL MODEL EYE

Introduction

The aberrometer enables us to measure aberrations in human eyes in vivo. One of the problems of measuring aberrations in human eyes is that there is no independent way to verify the measurements. In order to characterize the accuracy, reliability, and repeatability of our measurements, we first conducted measurements with an optical model eye. This model has the advantage that we can measure or characterize the components by independent measurements and compare them to our measurements. We conducted tests of pupil diameter, defocus, astigmatism, and spherical aberration. We designed two different optical model eyes. The first was built to model the eye including the most important components like the optical components of the eye, the pupil, and the retina. We call this model eye the passive optical model eye. We also built an optical model eye that is more of a wavefront generator and does not really mimic the anatomy of the human eye. This second model proved more useful for our purposes. We call this model eye the active model eye.
The Passive Model Eye

The passive model eye consists of a lens, an iris diaphragm and a model retina. This model can be used to test the complete setup, including the laser illumination of the eye. We call it the passive model eye because it does not provide its own light source, but uses the aberrometer's laser light source. Figure 29 and Figure 30 show a schematic drawing and some photographs of the passive model eye.

Figure 29: Schematic drawing of the passive model eye

Figure 30: Photographs of the passive model eye and its components (from left to right: iris diaphragm, lens and model retina).
The advantages of the passive model eye are that it is small, compact and can easily be mounted on the chinrest assembly. This way, it is an easy tool to test if the aberrometer works correctly. Another feature of the passive model eye is that it can model different pupil sizes.

The passive model eye has a number of limitations. First, the distance between the lens and the retina cannot be exactly determined. The retina should be placed at the back focal plane of the lens in order to model an eye with no refractive error. Any displacement of the retina along the optical axis will cause a refractive error in the model.

The second limitation is the reflectivity of the model retina. The model retina should model the diffuse and specular reflection characteristics of the human retina as close as possible. When looking for a model retina, we tried several different materials. We found that a mirror reflection is too specular. White paper reflects lambertian, but the reflectivity is far too high. Black cardboard or a dollar bill work well as shown in Figure 31, but the reflected beam is not very uniform due to the roughness of the surface, resulting in large differences in intensity in the grid pattern spots and in speckle. When we move the retina at high speeds perpendicular to the optical axis, we create a uniform beam profile. We tried this manually and showed that the intensity of the grid pattern becomes very uniform as can be seen in Figure 32.
The third limitation of the passive eye model is the presence of a center reflection from the surfaces of the lens. The appearance of the center reflection with the passive model eye is due to the fact that the lens is flatter than the human cornea. The laser in the aberrometer has been decentered to avoid center reflection in human eyes. When a human pupil is centered relative to the optical axis of the aberrometer, the laser enters decentered and no center reflection is present. In order to avoid the center reflection with the passive
model eye, we grossly decentered the pupil of the passive model eye in order to increase the decenteration of the laser beam relative to the apex of the lens in the model eye. This results in cropped and therefore incomplete measurements as seen in Figure 32.

The fourth limitation of the model eye is that it is difficult to model cylindrical refractive errors or higher order aberrations like spherical aberration, coma, etc. We did not optimize the passive model eye after we achieved very good results with the active model eye.
The Active Model Eye

The active model eye consists of a monomode fiber point source and a collimating lens (120mm achromat). Figure 33 shows sketches of the active optical model eye a) when modeling an emmetropic eye, b) when modeling a myopic eye, and c) when modeling an emmetropic eye with spherical aberration. Figure 33a shows the collimation of the laser light from the monomode fiber and the stop that models the pupil size. When we place a positive ophthalmic lens in front of the stop, we model a myopic eye as shown in Figure 33b. We can also replace the collimating lens with a test lens. This setup still collimates the laser light, but the wavefront will contain spherical aberration.

Figure 33: Sketches of the active optical model eye for a) an emmetropic eye, b) a myopic, and c) an emmetropic eye with spherical aberrations.
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Laser guided in monomode fiber

Collimating lens (achromat) or test lens

Aperture Stop of different sizes (3.8mm, 5.2mm, 8.0mm or iris diaphragm)

Ophthalmic lens to model refractive error (sphere and cylinder)

Figure 34: Photograph of the active optical model eye showing the fiber chuck for the monomode fiber, the collimating lens, the aperture stop and an ophthalmic lens to model refractive error.

Figure 35: Sample measurements for sphere, cylinder, and spherical aberrations in a human eye (top line) and the optical model eye (bottom line).
Figure 34 shows a photograph of the active optical model eye. It shows the fiber chuck that holds the monomode fiber, the collimating lens, the aperture stop and an ophthalmic lens to model refractive error. Figure 35 shows sample grid images of human eyes compared to the active optical model eye.

When building the active model eye, we test the collimation of the beam with a shear plate. Aberrations in the collimated beam are less than a quarter wave of spherical aberration for an 18mm aperture.

**Calibration**

Several measurements were performed in order to calibrate the aberrometer. We used the active optical model eye without a stop to record a reference grid image filling the entire CCD of the grid image camera. This image is used as a reference in the analysis and accounts for aberrations that are induced by the afocal imaging system when a plane wave is imaged. This image is also used to calibrate the aspect ratio of the pixels of the CCD camera.

We further determined the exact distance between the lenslet array and the CCD camera by measuring wavefronts with known defocus, created with the active optical model eye and ophthalmic lenses. If the distance between lenslet and CCD is too large, we will measure more defocus than there is present, if the distance is too short, we will measure too little defocus. The exact distance between lenslet array and CCD is a calibration constant that can be entered in the analysis software.
Pupil Size

The representation of the measured wavefront in Zernike coefficients depends highly on an accurate measurement of the pupil size. We tested the accuracy of this measurement with the aberrometer and the passive model eye with different known fixed pupil sizes. We measured 8.0mm, 6.35mm and 4.8mm pupils. We achieved very good results for a 6.35mm pupil size. The measurement error for the 6.35mm pupil was 0.12 mm. The measurement errors for the 8mm and the 4.8mm pupil were -0.34 and -0.62 mm respectively. The 8mm pupil is too large for the CCD camera and too many grid image dots get lost, causing a decrease in accuracy of pupil size measurement. For the smaller pupil size of 4.8mm, we reach the limit of accuracy caused by the 400 micron sampling of our lenslet array. The overall measurement error of pupil diameter with the passive model eye was 0.14 ± 0.17 mm.

In order to verify this observation, we used the simulation tool of the analysis software [20] to simulate grid images for different pupil sizes and measure them. The measurement errors achieved with the simulated pupil sizes are shown in Figure 36. The simulated data show that there is a theoretical limit to the measurement error which is 0.2 mm in the measurement range of 2 through 8 mm pupil diameter.

We also used the simulation tool of the analysis software to simulate eyes with different refractive errors and pupil sizes. The average measurement error when using the simulation is 0.14 ± 0.06 mm.
The simulated data presented in Figure 36 show that for large pupil diameters the measurement errors increase dramatically as we reach the limit of the CCD size. The measurement error increases for pupil sizes above 8mm. The simulated data do not show the problem for smaller pupil sizes that we observed using the passive model eye. This might be due to the even distribution of the grid pattern in the simulation as compared to the grid pattern achieved in the test measurements.
**Ophthalmic Lenses: Sphere and Cylinder**

We conducted tests with the active model eye where we put ophthalmic lenses in front of the active model eye in order to simulate an eye with refractive error. We tested spherical error in the range of ± 20 D and cylindrical error in the range of zero to + 8 D at different angles. Figure 37 shows the correlation of the measured sphere to the wavefront error created with the spherical ophthalmic lenses. A quadratic error is present, resulting in measurements that are too large for measurements outside the ± 10 D range.

![Measurement of Sphere Ophthalmic Lenses](image)

Figure 37: Measurement of ophthalmic lenses with the aberrometer and the active model eye. Spherical error in the range from -20 to +20 D.

The measured sphere in Figure 37 was calculated based on the 2\textsuperscript{nd} order defocus term \(a_{2,0}\) and does not include higher order terms that might contain defocus. In the section about induced aberration we had shown that we induce large amounts of spherical
aberration when imaging wavefronts with large amounts of defocus. We calculated the amount of defocus that will be represented by the higher order terms due to induced spherical aberration. This analysis gives us the following correction formula where $\Phi_{REAL}$ is the real defocus and $\Phi_{MEASURED}$ is the measured defocus.

$$\Phi_{REAL} = -0.0055 \cdot \Phi_{MEASURED} + \Phi_{MEASURED}$$  \hspace{1cm} (6)$$

Using this correction formula, we achieve a much better correlation between the sphere of the ophthalmic lenses and the measured sphere as shown in Figure 38.

![Corrected Measurement of Sphere Ophthalmic Lenses](image)

Figure 38: Corrected measurement of ophthalmic lenses with the aberrometer and the active model eye. Spherical error in the range from $-20$ to $+20$ D.

The test of spherical refractive error validated the accuracy of the aberrometer in detecting defocus when using well defined standard lenses. Table 2 summarizes the
results of the analysis of the spherical ophthalmic lenses. It presents the average measurement error for different measurement ranges. The cylinder error in this table is the amount of astigmatism detected, although we used only spherical lenses, i.e. the aberrometer detects astigmatism where there is none. The three measurement ranges presented are ±10 D, ±14 D, and ±20 D. The results for the measurement of sphere are very good for all measurement ranges with the measurement error slightly increasing for the ±14 D and ±20 D ranges.

<table>
<thead>
<tr>
<th>Measurement Range</th>
<th>Sphere Error (D)</th>
<th>Cylinder Error (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>±10 D, n = 24</td>
<td>-0.01 ± 0.17</td>
<td>0.10 ± 0.13</td>
</tr>
<tr>
<td>±14 D, n = 31</td>
<td>0.08 ± 0.29</td>
<td>0.14 ± 0.17</td>
</tr>
<tr>
<td>±20 D, n = 37</td>
<td>0.13 ± 0.38</td>
<td>0.26 ± 0.40</td>
</tr>
</tbody>
</table>

Table 2: Measurement of Ophthalmic lenses: Spherical lenses up to +/- 20 D. Cylinder should read zero.

The average measurement error when measuring cylindrical lenses of up to + 8 D at different angles is -0.07 ± 0.19 D (n = 14). When measuring pure cylinder power, we detected spherical power of -0.02 ± 0.07 D (n = 14). The axis measurement was very accurate with a measurement error of 0 ± 1 degree (n = 14).
The measurement range of the current setup is limited by three factors: vignetting, spot quality, and software algorithm. Vignetting of the wavefront occurs in the aberrometer for high myopes and hyperopes like discussed earlier. The spot quality of the grid image decreases for high myopes. Figure 39 shows the spot quality for a -20 D myope. This decrease in spot quality does not occur for hyperopia.

The software algorithm had to be refined because of the large displacement of the spots for high myopia or hyperopia. When testing the software algorithm with simulated data, we find the limit of the analysis to be -20 D for spherical refractive error. The limit for pure negative astigmatism is -15 D. For hyperopia, the algorithm is stable for both spherical and astigmatic refractive error, but the grid image soon becomes too large for the CCD and the outer portion of the wavefront is cropped. The grid image cropping does not have an influence on the measurement of the refractive error, but it will influence the accuracy of measurements of higher order aberrations and limits the region of the pupil that is analyzed.
Spherical Aberration

In order to test the accuracy of the measurement of spherical aberration with the Shack-Hartmann aberrometer, we tested some lenses with known amounts of spherical aberration. In order to create a plane wave with spherical aberration, we replaced the collimating lens in the active optical model eye with a single element, e.g. bi-convex, plano-convex, or convex-plano. Lenses with short focal length naturally carry large amounts of spherical aberration. When mounted “backwards” the amount of spherical aberration increases. Table 3 shows the different lenses and orientations used.

<table>
<thead>
<tr>
<th>Lens</th>
<th>Setup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thorlabs 25mm biconvex</td>
<td><img src="image" alt="Thorlabs 25mm biconvex" /></td>
</tr>
<tr>
<td>Linos 20mm biconvex</td>
<td><img src="image" alt="Linos 20mm biconvex" /></td>
</tr>
<tr>
<td>Linos 40mm plano-convex</td>
<td><img src="image" alt="Linos 40mm plano-convex" /></td>
</tr>
<tr>
<td>Linos 40mm plano-convex w/ stop</td>
<td><img src="image" alt="Linos 40mm plano-convex w/ stop" /></td>
</tr>
<tr>
<td>Linos 40mm convex-plano</td>
<td><img src="image" alt="Linos 40mm convex-plano" /></td>
</tr>
<tr>
<td>Linos 40mm convex-plano w/ stop</td>
<td><img src="image" alt="Linos 40mm convex-plano w/ stop" /></td>
</tr>
</tbody>
</table>

Table 3: Different setups to generate collimated wavefronts with spherical aberration.
The optical fiber has a certain divergence angle. This angle determines the diameter of the collimated beam as a function of the focal length of the collimating lens. The beam diameter for short focal lengths lenses was too small to test the collimation with the shear plate. In this case, we first measured the defocus in the beam with the aberrometer and adjusted the lens until we measured zero diopters for refractive error (defocus). We then recorded the measurement.

The wavefronts created with the active optical model eye and the test lenses contain spherical aberration up to 0.460 microns at an 8.5mm pupil. Because of this large amount of spherical aberration, we could not make a comparison measurement using simple interferometric measurement techniques. Instead, we used raytrace software (Zemax) to model the lenses. All of the lenses that we used were off-the-shelf components, and therefore were available in the Zemax lens database. Because we do not suspect manufacturing errors to be large enough to be detected with our wavefront sensor, we can use the simulation for comparison.

Zemax calculates the aberrations in the image plane and lists the Zernike coefficients (Zernike Standard Coefficients). The active model eye creates an aberrated plane wave which has its image plane at infinity. We modeled the entire active optical model eye in Zemax, including the fiber tip as an object point. We introduced an aberration free paraxial lens into our Zemax model that images the plane wave into an image plane that can be evaluated by Zemax.
We had aligned the active optical model eye so that the aberrometer measurement was zero diopters, but the wavefront created by the active optical model eye might still contain some defocus. We manually altered the distance between the object point (light source) and the lens in Zemax until we matched the amount of defocus simulated in the Zemax model with the defocus measured with the aberrometer.

After this, we compared the spherical aberration of the measurement with the spherical aberration of the simulation. The measurements were corrected for systematic errors using the algorithms presented in the previous chapter. The average measurement error for measurements of spherical aberrations up to +0.460 microns was 0.026 ± 0.023 microns (n = 18).

The Zemax model indicated that in a perfect system only spherical aberration and defocus are present because we only test on-axis and do not have any field angles. The aberrometer measurement, though, showed some coma and astigmatism. The measurements were well centered, so the coma and astigmatism cannot be due to induced aberrations. They are caused by alignment errors in our active optical model eye. These alignment errors are very hard to avoid due to the limitations of our mechanical mounting system. But spherical aberration does not depend on field angle, only on the marginal ray height. Therefore, we can measure spherical aberration with high accuracy even in the presence of other aberrations that were caused by misalignment, decenteration or tilt of the optical elements.
Using the active optical model eye and test lenses, we tested wavefronts with spherical aberration up to 0.460 microns at an 8.5mm pupil. The spherical aberration that we expect in the human eye, especially after refractive surgery, might be higher than that. We therefore had to extend the range of our test measurements in order to test the aberrometer properly.

In order to extend our test measurements for spherical aberration to about 1-2 microns of spherical aberration, we also tested a set of six spherical aberration phase plates. The phase plates had been designed using Zemax and were diamond turned in PMMA on a lathe. The profile follows a fourth order polynomial. A schematic profile is shown in Figure 40. We tested three plates with positive spherical aberration and three plates with negative spherical aberration.

![Phase Plate for Positive Spherical Aberration](image1)

![Phase Plate for Negative Spherical Aberration](image2)

Figure 40: Surface profiles of the phase plates for positive (left) and negative (right) spherical aberration.

The procedure for the testing of the phase plate was similar to the tests with ophthalmic lenses. We used an achromat in the active optical model eye to create a plane wave and then added the phase plate to introduce spherical aberration. We used different stop sizes to get multiple measurements using the same phase plates. We could not confirm the shape of the phase plates by independent measurements. In our analysis, we therefore compared the spherical aberration of the phase plates measured with the
aberrometer to the Zemax simulation. We had to assume that the phase plates were machined perfectly. The measurement range for this test was ± 2.5 microns. Figure 41 shows the relationship between the simulated and the measured spherical aberration for the six phase plates. There are two or three measurement values for each phase plate, taken at different pupil sizes. The average error for this test was 0.050 ± 0.250 microns. When fitting all measurements to a linear function, we get a very good correlation with an error of only 2.8%. The variability of individual measurements, though, is very large. In the plot in Figure 41, we can also see differences in measurement errors between individual plates. While plates 1 and 3 show a good correlation between calculated and measured spherical aberration, other plates show either a constant offset (plate 2) or a very large variability (plates 4 and 6), especially for larger amounts of spherical aberration. Note that in this test we measured both positive and negative spherical aberration. We had determined in a previous section, that imaging wavefronts with spherical aberration does not induce further spherical aberration. A correction was therefore not necessary. The measurements had been well centered, so correction for decentered measurements was also not necessary.
Spherical Aberration Phase Plates

Figure 41: Spherical aberration as calculated from the Zemax model compared to the measured spherical aberration.

Our tests of spherical aberration with test lenses have shown that the aberrometer is very accurate when measuring spherical aberration in the range of up to +0.460 microns at an 8.5mm pupil. Measurements of larger amounts of spherical aberration using phase plates show less accuracy and high variability in the measurements. Some of these errors, though, might be due to manufacturing tolerances or errors that we could not verify by independent measurements. The amount of spherical aberration that we will encounter in post-LASIK eyes are up to 0.5 microns for a 6 mm pupil or up to 0.8 microns for a 7 mm pupil. Therefore, our instrument is well suited for measuring spherical aberration in human eyes, both pre- and post-operatively.
Summary

In order to characterize the accuracy of measurements with our Shack-Hartmann aberrometer, we conducted several tests with optical model eyes. We tested the measurements of pupil size, spherical and cylindrical refractive error, as well as spherical aberration. Table 4 summarizes the test results.

<table>
<thead>
<tr>
<th>Test</th>
<th>Measurement Range</th>
<th>Measurement Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pupil Diameter: Passive Model Eye</td>
<td>4.8 – 8.0 mm</td>
<td>0.14 ± 0.17 mm</td>
</tr>
<tr>
<td>Pupil Diameter: Simulated</td>
<td>2.0 – 8.0 mm</td>
<td>0.14 ± 0.06 mm</td>
</tr>
<tr>
<td>Refractive Error: Sphere</td>
<td>± 10 D</td>
<td>-0.01 ± 0.17 D</td>
</tr>
<tr>
<td></td>
<td>± 14 D</td>
<td>0.08 ± 0.29 D</td>
</tr>
<tr>
<td></td>
<td>± 20 D</td>
<td>0.14 ± 0.38 D</td>
</tr>
<tr>
<td>Refractive Error: Cylinder</td>
<td>0 to + 8 D</td>
<td>-0.07 ± 0.19 D</td>
</tr>
<tr>
<td>Refractive Error: Axis</td>
<td>0, 45, 90, 135 degrees</td>
<td>0 ± 1 degree</td>
</tr>
<tr>
<td>Spherical Aberration: Test Lenses</td>
<td>0.0 – 0.460 microns</td>
<td>0.026 ± 0.023 microns</td>
</tr>
<tr>
<td>Spherical Aberration: Phase Plates</td>
<td>About ± 2.5 microns</td>
<td>0.050 ± 0.250 microns</td>
</tr>
</tbody>
</table>

Table 4: Summary of test results with the active optical model eye.
CHAPTER 4

TESTS WITH HUMAN EYES

Introduction

The tests with the active optical model eye described in chapter two have characterized the accuracy of the aberrometer when used to measure wavefronts that are created by optical components. We also have to make sure that we obtain accurate, reliable, and repeatable measurements when testing human eyes. Several tests were designed to test the aberrometer with human eyes. The first test used a single eye with paralyzed accommodation. We placed ophthalmic lenses of different power in front of the eye to test the measurements of sphere and cylinder with this eye. For a second test, we conducted a study where we compared the refraction of 22 eyes of 11 subjects when measured with the aberrometer and with a Zeiss Humphrey autorefractor. Both measurements are objective. In the next study, we tested reliability and repeatability of the measurements. 66 eyes of 66 subjects were measured between 7 and 9 times with the aberrometer.

The aberrometer measures the wavefront aberrations of the human eye. We can calculate the refractive error in plus cylinder notation based on the wavefront aberrations. This corresponds to the prescription of a contact lens that is placed directly on the cornea. When we calculate the prescription for spectacles, we have to adjust the power. The
following formulas are used to transform the contact lens power to a lens power. $\Phi_L$ denotes the power of a corrective lens; $\Phi_C$ denotes the power of the corresponding contact lens. The distance between the cornea and the lens is $d = 12$ mm.

\[
\Phi_C = \frac{\Phi_L}{1 - d \cdot \Phi_L}
\]  

(7)

\[
\Phi_L = \frac{\Phi_C}{1 + d \cdot \Phi_C}
\]

(8)

In the following chapters, we will compare measurements of refractive error that were obtained by different means. In order to compare them, we have to describe both measurement results in the same prescription, either spectacle or contact lens. Another key to good results in prediction of the refractive error based on wavefront measurements with our aberrometer is to take the correction for induced defocus, as presented in the chapter about induced aberrations, into account.

In order to compare large numbers of refraction measurements, we used the power vector method [14]. The positive cylinder prescription is transformed into a spherical equivalent and two crossed cylinder powers. These can be compared and the measurement error can be determined directly. The results are then back-transformed to the positive cylinder prescription.

We transform the sphere $S$, cylinder $C$ and axis $\varphi$ from the plus cylinder prescription to the Jackson Crossed Cylinder form with spherical equivalent power (SEP) $M$, and the
crossed cylinder terms $J_0$ and $J_{45}$. The cylinder $C$ is decomposed into two components at 0 and 45 degrees. We can then analyze these terms directly.

Forward transformation:

$$M = S + \frac{C}{2}$$  \hspace{1cm} (9)

$$J_0 = \frac{C}{2} \cdot \cos \left( 2(\varphi - 90) \cdot \frac{\pi}{180} \right)$$  \hspace{1cm} (10)

$$J_{45} = \frac{C}{2} \cdot \sin \left( 2(\varphi - 90) \cdot \frac{\pi}{180} \right)$$  \hspace{1cm} (11)

Back transformation:

$$S = M - \sqrt{J_0^2 + J_{45}^2}$$  \hspace{1cm} (12)

$$C = 2 \cdot \sqrt{J_0^2 + J_{45}^2}$$  \hspace{1cm} (13)

$$\varphi = \frac{1}{2} \cdot \arctan \left( \frac{J_{45}}{J_0} \right) \cdot \frac{180}{\pi} + 90$$  \hspace{1cm} (14)
Cyclopleged Eye

A test of the measurement of refractive error with the aberrometer was performed on a single eye wearing ophthalmic lenses. The eye had a manifest refraction of -0.5 D sphere and therefore was almost emmetropic. The pupil was dilated and accommodation paralyzed with two drops of 0.5% tropicamide. A set of ophthalmic lenses was placed in front of the eye in order to model different refractive errors. We used ophthalmic lenses in the range of -7 D to +7 D and cylindrical lenses of +1.5 D at four different angles. The results are plotted in Figure 42.

![Diagram](image)

Figure 42: Aberrometer measurement compared to the refractive error of the subject wearing ophthalmic lenses. The solid line is the 45 degree line.

The measurement error in this test was -0.12 ± 0.42 D (n = 16) for sphere and 0.10 ± 0.14 D (n = 4) for cylinder. The measurements of the cylinder axis are off by an average of 10 ± 4 degrees. This might be due to poor alignment of the trial lens frames that were holding the ophthalmic lenses and head alignment during the test.
Aberrometer vs. Autorefractor

In order to evaluate the accuracy of the aberrometer when measuring human subjects, we conducted a small study where we measured the subject’s refractive error using the aberrometer, a Zeiss-Humphrey autorefractor, and also measured the subject’s spectacle prescription with a lensometer. At the time, we had no resources available to measure the subject’s manifest refraction. Spectacle prescription is inherently unreliable since subjects may be functioning with an inaccurate prescription. Following are the conditions and results of the study.

• 11 subjects, 22 eyes; 7 female, 4 male
• No drugs administered, i.e. accommodation possible
• Prescription range sphere 0.0 to -9.5 D, cylinder 0.0 to +3.5 D

<table>
<thead>
<tr>
<th>Measurement Difference (D) Between Spectacle and Aberrometer</th>
<th>Autorefractor and Aberrometer</th>
<th>Spectacle and Autorefractor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sphere</td>
<td>-0.06 ± 0.62</td>
<td>-0.14 ± 0.63</td>
</tr>
<tr>
<td>Cylinder</td>
<td>0.68 ± 0.38</td>
<td>0.56 ± 0.31</td>
</tr>
</tbody>
</table>

Table 5: Measurement difference between spectacle and aberrometer, autorefractor and aberrometer, as well as spectacle and autorefractor.

The results in Table 5 show a good correlation for all three comparisons with a difference of less than a quarter diopter for the measurements of sphere. The measurement differences for cylinder are about a half diopter for all three comparisons. The standard deviation of the measurement differences is higher for the measurement of sphere than for the measurement of cylinder. The most important comparison is the one between autorefractor and aberrometer because they are both objective.
Refraction in 110 Myopic Human Eyes

In this section, we analyze the refraction measured with the aberrometer for a large population of people with myopia. The subjects are participants of a study that evaluates the impact of laser refractive surgery (LASIK) on the aberrations in the human eye. The details of the study will be discussed in the next chapter. Here, we compare the preoperative manifest spherical equivalent power of 110 eyes measured by an ophthalmologist with the measurements of the aberrometer (refraction study).

![Figure 43: Scattergram of manifest spherical equivalent power versus the spherical equivalent power measured with the Shack-Hartmann aberrometer. The solid line is the 45 degree line.](image)

Figure 43: Scattergram of manifest spherical equivalent power versus the spherical equivalent power measured with the Shack-Hartmann aberrometer. The solid line is the 45 degree line.

Figure 43 shows the scattergram of manifest spherical equivalent power versus the spherical equivalent power measured with the Shack-Hartmann aberrometer. The solid line is the 45 degree line. The data were corrected for induced defocus and vertex-
adjusted. The following equation is the result of fitting a linear function. This linear fit has an offset of 0.213 D and a slope of almost one. The correlation is $R^2 = 92.2\%$. The mean error of the measurement of spherical equivalent power is $0.29 \pm 0.42$ D.

$$y = 0.980x + 0.213$$  \hspace{1cm} (15)

While the data clearly follow the trend and no residual systematic error is present, the variability is quite large. A correction for defocus and astigmatism induced by decentration of the measurements did not improve the results significantly, because the average decentration was 0.77 mm and the refractive error induced by this decentration is only 0.5\% of the initial refractive error.

The cylinder measurements were analyzed in the same way. The measurement error for the cylinder is $-0.18 \pm 0.40$ D. The analysis was done using the power vector method. The aberrometer measurements were corrected for induced aberration and vertex-adjusted. Because of the lower amount of astigmatism as compared to defocus, the influence of induced aberration cannot be noted as clearly as in the defocus measurements.

The correlation plot in Figure 43 can be used to perform a Bland-Altman test of bias and confidence interval. The bias of the measurement of refractive error with the aberrometer as compared to a manifest refraction is the average of the measurement difference, i.e. 0.29 D. The 95\% confidence interval is 0.82 D. This value can be compared to bias and confidence interval of the Topcon autorefractor that is considered
the standard autorefractor commercially available today. A study including 14 measurements, comparing the Topcon to the manifest refraction has shown a bias of 0.05 D and a 95% confidence interval of 0.96 D for the measurements of spherical equivalent power [28]. Our measurements of refractive error with the Shack-Hartmann aberrometer achieve a comparable confidence interval as the current industry standard, although our bias is slightly higher. This bias can be removed analytically when using the aberrometer as an autorefractor.

The source for the bias in measurements of refractive error with the Shack-Hartmann aberrometer is chromatic aberration. The aberrometer measures the eye using the near infrared wavelength of 780nm. Manifest refraction is measured using white light. The chromatic aberration between 780nm and 500nm is in the order of the bias determined for measurements of human eyes with the Shack-Hartmann aberrometer.
Reliability

A study was conducted including 66 eyes of 66 subjects including normal patients, patients with dilated pupils and post LASIK as well as post IOL patients. Of every eye, about 7 to 9 measurements were taken. The purpose of the study was to analyze the repeatability of measurements with the Shack-Hartmann aberrometer. While analyzing the data, we found some problems that give us indications of the reliability of the aberrometer.

Some of the images taken could not be analyzed by the current software algorithm. Problems occurred if a center reflection was present or if the background noise in the image was too large. In our study, we had a total of 419 exams. Out of these, 360 could be examined well (85.9%). After some basic image processing on the exams that did not process well (adjusting brightness, contrast, and black level), we were able to analyze 411 exams (98.0%). There were still some exams that we were not able to analyze. It is recommended that the operator take several measurements of the same eye while doing the exam and analyzes the measurement while the patient is still present so that the measurement can be repeated if necessary.
Repeatability

We tested the repeatability of the measurements by analyzing the results of 7 to 9 repeated measurements of 66 eyes of 66 subjects. For each exam, we analyzed the repeatability of the measurement presented in Zernike coefficients up to 6th order (28 Zernike coefficients). We began with 66 eyes and an average of 6 measurements each. For every measurement, we calculated a subset of Zernike coefficients with discrete pupil diameters between 4.0 and 8.0 mm in 0.5 mm steps [24]. Each of these subsets included 28 Zernike coefficients (a_{0,0} to a_{6,8}). For each of the eyes, we calculated the mean and standard deviation for each discrete diameter subset and each Zernike coefficient. The analysis also indicated if the measured value was significantly different from zero.

The standard deviation achieved over repeated measurements of the same eye is a good measure to quantify the repeatability of our measurements. We can use the average of all standard deviations from the measurements of the individual eyes to define the error bar or confidence interval of our measurements.

For every eye, we analyzed up to 9 measurements. Over these measurements, we calculated the standard deviation for each of the Zernike coefficients of every eye, and for all the diameter subsets. We then calculated the average over all the standard deviations for individual Zernike coefficients. This gives us the average error bar half width for the measurements with the Shack-Hartmann aberrometer. We included all datasets in our analysis because if there are no aberrations present, we want to be sure that we get a zero measurement.
We excluded all data sets that had a number of measurements \( n \) of less than 3 per eye because calculating a standard deviation does not make sense for less than 3 values. We also excluded all data sets for the Zernike coefficients \( a_{0,0}, a_{1,-1} \) and \( a_{1,1} \) (piston and tilt) because they have no physical meaning for the wavefront measurement. This left us with 5,424 data points.

Table 6 shows the results of the analysis. The average error for all aberrations is \( \pm 0.026 \) microns. This number compares very nicely to the error of 0.023 microns that we had determined for the measurement of spherical aberration with an optical model eye. The standard deviation of the error bar is 0.060 microns.

We noticed that the error bars for the higher order aberrations are much smaller than for the lower order aberrations. For this reason, we calculated the average and standard deviation for the two sets of Zernike coefficients \( a_{2,-2} \) to \( a_{4,4} \) and \( a_{5,-5} \) to \( a_{6,6} \) separately. Table 6 also shows the total number of measurements and the percentage of statistically significant non-zero values in each of these groups [15].

<table>
<thead>
<tr>
<th>Zernike Coefficients</th>
<th>Error Bar (microns)</th>
<th>Standard Deviation of the Error Bar (microns)</th>
<th>Number of Data</th>
<th>Non-Zero Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>( a_{2,-2} - a_{6,6} ) (all aberrations)</td>
<td>( \pm 0.026 )</td>
<td>0.060</td>
<td>5424</td>
<td>48.60 %</td>
</tr>
<tr>
<td>( a_{2,-2} - a_{4,4} ) (low order aberrations)</td>
<td>( \pm 0.044 )</td>
<td>0.082</td>
<td>2486</td>
<td>61.06 %</td>
</tr>
<tr>
<td>( a_{5,-5} - a_{6,6} ) (high order aberrations)</td>
<td>( \pm 0.011 )</td>
<td>0.017</td>
<td>2938</td>
<td>38.05%</td>
</tr>
</tbody>
</table>

Table 6: Error bars of the Zernike coefficients.
Summary

In order to quantify the accuracy of the measurements with our Shack-Hartmann aberrometer, we conducted several tests with human eyes. We tested the measurements of refraction, i.e. spherical and cylindrical refractive error, and compared them to the manifest refraction with ophthalmic lenses (cyclopleged eye), to an autorefractor measurement (aberrometer vs. autorefractor) and to the manifest refraction (refraction study). Table 7 summarizes the test results.

<table>
<thead>
<tr>
<th>Test</th>
<th>Measurement Range (D)</th>
<th>Measurement Error (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclopleged Eye: Sphere</td>
<td>± 7.0</td>
<td>-0.12 ± 0.42</td>
</tr>
<tr>
<td></td>
<td>1 eye, 16 measurements</td>
<td></td>
</tr>
<tr>
<td>Cyclopleged Eye: Cylinder</td>
<td>1.5 at 4 angles</td>
<td>0.10 ± 0.14</td>
</tr>
<tr>
<td>Aberrometer vs. Autorefractor: Sphere</td>
<td>0 to -9.5</td>
<td>-0.14 ± 0.63</td>
</tr>
<tr>
<td></td>
<td>22 eyes</td>
<td></td>
</tr>
<tr>
<td>Aberrometer vs. Autorefractor: Cylinder</td>
<td>0 to 3.5</td>
<td>0.56 ± 0.31</td>
</tr>
<tr>
<td></td>
<td>22 eyes</td>
<td></td>
</tr>
<tr>
<td>Refraction Study: Sphere</td>
<td>0 to -8.25</td>
<td>0.29 ± 0.42</td>
</tr>
<tr>
<td></td>
<td>110 eyes</td>
<td></td>
</tr>
<tr>
<td>Refraction Study: Cylinder</td>
<td>0 to 2.75</td>
<td>-0.18 ± 0.40</td>
</tr>
<tr>
<td></td>
<td>110 eyes</td>
<td></td>
</tr>
</tbody>
</table>

Table 7: Summary of the test results for sphere and cylinder with human eyes.
Table 7 shows that we achieve a very good mean measurement error in the range of about a quarter diopter, which is the smallest unit for a prescription. The standard deviation of the measurement error is in the range of about a half diopter. This could probably be improved when taking induced astigmatism by decentration into account.

When comparing the results from the aberrometer vs. autorefractor study to the results of the refraction study, we find that the mean error and standard deviation are more consistent in the refraction study. The sphere measurement in the aberrometer vs. autorefractor study has a larger standard deviation, and the mean error of the cylinder measurement of the same study is quite large. This might be due to the much smaller number of subjects, with only 22 eyes in the first study as compared to 110 eyes in the refraction study. Another reason for a larger mean error and standard deviation is the presentation of the prescription in quarter diopter increments. All measurements in the aberrometer vs. autorefractor study were presented in the plus cylinder notation. The limits to accuracy when presenting data in quarter diopter increments may cause the above mentioned larger measurement errors and standard deviations. The refraction data in the refraction study was analyzed using the Zernike coefficients of the wavefront aberrations. Therefore, the rounding off to quarter diopters is only present in the manifest refraction. In addition to the much larger number of eyes examined, this explains the smaller measurement errors and standard deviation in the refraction study.

About 86% of measurements that were perceived "good" by the operator analyzed well. With simple image processing, we can bring the reliability up to 98%. For operation
in the clinic, it might be advisable to process the images while the patient is still present, so that a second measurement can be taken if necessary.

The repeatability of the aberrometer was tested by taking repeated measurements of 66 subjects (66 eyes). 3 to 9 measurements were analyzed for each eye. 24 Zernike coefficients were analyzed for each measurement. We quantify the repeatability of the measurement using the standard deviation of the repeated measurements of individual eyes. Table 6 summarizes the results for all Zernike coefficients and for lower and higher order coefficients separately. The overall repeatability is ±0.026 microns for all coefficients, ±0.044 microns for the lower order coefficients (a_{2,2} to a_{4,4}, i.e. defocus, astigmatism, spherical aberration, coma, trefoil), and ±0.011 microns for the higher order coefficients (a_{5,5} to a_{6,6}).
CHAPTER 5:
THE WHITAKER STUDY:
ASSESSMENT OF VISUAL PERFORMANCE
PRE- AND POST-LASIK

Introduction

LASIK (laser in situ keratomileusis) is an elective laser refractive surgery that aims to correct the patient’s refractive error by reshaping the anterior surface of the cornea. Current technologies achieve very good results, but some patients complain about glare, haloes, and ghost images, especially during night vision [39], [40], [41].

While the current surgery technology increases the visual acuity of the patient, i.e. the ability to read the eye chart, a loss of contrast sensitivity occurs that diminishes the ability to see low contrast scenes, especially at night. This is caused by aberrations that are introduced during the surgery which are detrimental for large pupils. A new generation of refractive surgery lasers is becoming available that allow the cornea to be reshaped with an individualized pattern. Customized ablation can be used to re-treat patients with post-operative vision problems as well as to treat new patients with an optimized ablation pattern [42], [43], [44].

To improve current surgery technologies, we must first understand how current laser refractive surgery affects the optics of the eye. We therefore designed and conducted a clinical study that provides data to thoroughly understand the impact of LASIK surgery
and wound healing. Figure 44 illustrates the purpose of the study. We took measurements before surgery and at multiple time periods post-operatively up to 12 months. Comparing the measurements gives us information about the

- Impact of surgery: Comparing pre-op to 1 week post-op.
- Impact of wound healing: Comparing post-op 1 week to 12 months.
- Progression over time: Comparing all post-op measurements.

Figure 44: Exams in the Whitaker study.
Once the influence of surgery and wound healing are determined, we can design a computer model of the eye for all available visits and determine an optimized anterior corneal surface.

In summary, the goals of the Whitaker study are:

1. To understand the impact of surgery and wound healing on the visual performance and the aberration structure of the human eye.

2. To present a computer eye model that can model any individual eye and its individual aberration structure before and after surgery and to use the individual computer eye model to propose a customized anterior corneal surface that optimizes the performance of each individual eye.
Design of the Whitaker Study

The clinical study was designed to determine the impact of LASIK surgery and wound healing to the human eye. It also included measurements that are necessary to build the computer eye model for modeling each individual eye. The following are a list of measurements taken and the instruments used:

- Manifest Refraction: surgeon pre-op and 1 week post-op; Zeiss Humphrey Autorefractor for all other post-op visits.
- Contrast Sensitivity: Vector Vision CSV-1000 contrast sensitivity chart
- Anterior and Posterior Corneal Topography, Pachymetry: Orbscan topographer.
- Total Aberrations of the eye: Shack-Hartmann Aberrometer.
- Axial Length and Anterior Chamber Depth: Biometry, Carl Zeiss IOL master.
- Pupil Size: Pupillometer and Shack-Hartmann Aberrometer.

While the measurements of visual acuity, manifest refraction, and contrast sensitivity are used to assess visual performance before and after LASIK surgery, the measurements of aberrations, corneal topography, anterior chamber depth, axial length and pupil size are necessary to both characterize the surgical and healing changes to ocular aberrations, and for the customized computer eye model. Most of the measurement devices were available as commercial systems prior to starting the study. The design and testing of the Shack-Hartmann aberrometer to measure the total aberrations of the eye has been presented in the previous chapters. We had also designed, built and tested a pupillometer that gives exact and repeatable measurements of the pupil size, both in complete darkness and in a brightly lit room [13].
The goal of the Whitaker study was to enroll 100 patients that undergo LASIK refractive surgery and follow up for 12 months. Surgery was performed with a VISX Star S2 and the standard nomograms. The participants were volunteers and agreed to have several measurements taken before surgery as well as 1 day, 1 week, 1 month, 3 months, 6 months, and 12 months post-operatively. Approval for the study was obtained from the Institutional Review Board of the University of Arizona and informed consent was obtained from each participant. The first patients were enrolled in August 2000. The data collection was finished at the end of August 2002.

Table 8 lists the number of subjects and eyes that were examined at each visit. 48 subjects were female, 41 subjects male. The treatment range was up to -9.25 D myopia, averaging at -4.65 ± 1.79 D sphere. Cylinder treatment was performed up to +3.25 D, averaging at 0.79 ± 0.72 D cylinder. Table 9 lists age and gender for all subjects in the Whitaker study. Figure 45 shows the number of eyes in different age groups in 5 year increments.

<table>
<thead>
<tr>
<th>Visit</th>
<th>Subjects</th>
<th>Eyes</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-op</td>
<td>89</td>
<td>158</td>
<td>Before surgery</td>
</tr>
<tr>
<td>1 week post-op</td>
<td>87</td>
<td>154</td>
<td>7 ± 2 days</td>
</tr>
<tr>
<td>1 month post-op</td>
<td>81</td>
<td>145</td>
<td>32 ± 8 days</td>
</tr>
<tr>
<td>3 months post-op</td>
<td>73</td>
<td>131</td>
<td>99 ± 20 days</td>
</tr>
<tr>
<td>6 months post-op</td>
<td>59</td>
<td>105</td>
<td>200 ± 30 days</td>
</tr>
<tr>
<td>12 months post-op</td>
<td>74</td>
<td>132</td>
<td>415 ± 52 days</td>
</tr>
</tbody>
</table>

(11 to 16 months)

Table 8: Number of subjects and eyes at the different visits of the study. The average and standard deviation of the time after surgery is also listed.
Table 9: Age and gender of the subjects in the Whitaker study.

<table>
<thead>
<tr>
<th>Subject Group</th>
<th>n</th>
<th>Average Age (years)</th>
<th>Range (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>89</td>
<td>42.9 ± 7.2</td>
<td>22 – 59</td>
</tr>
<tr>
<td>Female</td>
<td>48</td>
<td>42.9 ± 7.1</td>
<td>28 – 55</td>
</tr>
<tr>
<td>Male</td>
<td>41</td>
<td>43.0 ± 7.4</td>
<td>22 – 59</td>
</tr>
</tbody>
</table>

Figure 45: Number of eyes in different age groups.

Surgery was usually performed on both eyes. A total of 17 eyes were excluded from the study. Ten of these eyes were excluded because the subjects had an enhancement surgery performed on these eyes during the course of the study. One subject had their fellow eye treated one month later, so only one eye was followed up. Three subjects had no surgery done at all on one of their eyes. Three subjects were treated with the goal of achieving myopia for monovision on one of their eyes. The exclusion of the eyes with enhancements biases our results towards better results for the manifest refraction than what is actually the case, but one of our major goals is to look at the changes in aberrations during the wound healing period. Therefore, limiting our data to eyes with a “successful” treatment is justified.
Drop-Outs from the Study

Subjects are defined as “drop-out” if they participated in the first part of the study, but did not show up for the 12 months follow-up visit. Table 8 lists the fifteen subjects that dropped out from the study. For the validity of the study, it is important to know the reasons why subjects drop out. If subjects drop out because they move, it does not have any impact on the results of the study, other than that we miss their follow-up data. But if the subjects decide to drop-out because they are unhappy with the surgery or encounter post-operative difficulties, it is important for the study to note how many of our subjects drop-out because of such a reason. For most of the drop-outs, we do not know the reason for leaving the study. Some subjects have moved during the course of the study and could not be located for the 12 months follow-up visits.

Four subjects had their surgery done after August 2002. The data assessment for the Whitaker study ended August 2003, so that these subjects could not have their 12 months follow-up exams taken before the data assessment for the study ended. We know of two subjects that decided to drop-out due to dissatisfaction. One had serious problems with dry eye after surgery, while the other was unhappy because of a strong decrease in visual acuity after surgery. For the other nine subjects, we attempted to analyze the data to find out the reason why they might have dropped out or were unhappy with the outcome of the surgery.
<table>
<thead>
<tr>
<th>Subject</th>
<th>Reason for drop-out</th>
<th>Last visit</th>
<th>Measurements below average</th>
</tr>
</thead>
</table>
| W0010   | 6 months            | Visual Acuity OD (-1.25σ)  
Contrast sensitivity OD (-2σ) |
| W0018   | 6 months            |            |                            |
| W0024   | 3 months            |            |                            |
| W0034   | 6 months            |            |                            |
| W0060   | 1 month             | Visual acuity OU (-1.5σ)   |
| W0068   | Unhappy with outcome of surgery | 3 months | Visual acuity OU (-1.5σ) 
Manifest Refraction OS (-1σ) |
| W0070   | 1 week              | Manifest Refraction OU (-1σ) 
Contrast Sensitivity OD (-1.25σ) |
| W0096   | 1 month             | Visual Acuity OU (-3σ, -1σ) 
Manifest Refraction OD (-2σ) |
| W0098   | 1 month             |            |                            |
| W0099   | 1 week              |            |                            |
| W0101   | Problems with dry eye | 1 day     | Manifest Refraction OU (-3σ) |
| W0103   | Surgery was performed after 08/31/01. No 12 months follow-up visit could be scheduled after 08/31/02 because data collection for the study was closed. |

Table 10: List of subjects that dropped out of the study, reasons for the drop-out, and measurements below average after surgery (OD: right eye, OS: left eye, OU: both eyes, (-1.25σ): value was 1.25 standard deviations σ below the average).

Table 10 shows a quantitative judgment of the outcome of the surgery based on measurements of visual acuity, manifest refraction, and contrast sensitivity. The exams of the subjects that dropped out were compared to the average outcome of all eyes in the study. The average manifest refraction for all subjects after surgery was -0.50 ± 0.60 D sphere and 0.35 ± 0.35 D cylinder. The average uncorrected logMAR visual acuity after
surgery was $0.05 \pm 0.12$. The average log contrast sensitivity was $1.65 \pm 0.22$ for 3 cycles per degree, $1.82 \pm 0.22$ for 6 cycles per degree, $1.45 \pm 0.27$ for 12 cycles per degree, and $1.06 \pm 0.26$ for 18 cycles per degree. In Table 10, we denote if any of the measurements for visual acuity, manifest refraction, or contrast sensitivity are below average at the last time the subject had their exam taken. The number in parenthesis indicates how many standard deviations, $\sigma$, the measurement was below average. For contrast sensitivity, we indicate below average if the measurements for at least three out of four frequencies are below average. We also indicate which eye is affected: OD for the right eye, OS for the left eye or OU for both eyes.

Of the remaining nine subjects, four had below average visual acuity, manifest refraction, or contrast sensitivity in one or both eyes. The other five had their measurements in the average range; some even exceeded the average range. Of course, some of these five subjects might still have dropped out because they were unhappy with anything related to the study, but based on the measurements we can assume that they were not unhappy and have simply moved away or chosen not to continue participation. This totals our 15 drop-outs to six subjects that dropped out because of complications with the surgery and the outcome, and nine subjects that dropped out without surgery-related reasons. The six subjects that we suspect to drop-out because of problems with the surgery are 6.74% of the 89 total subjects.
Data Analysis

In the following section, we will present the results of the data analysis from the Whitaker study. The analysis will be divided into visual acuity, manifest refraction, contrast sensitivity, pupil diameter, corneal topography, pachymetry, and aberrations. For these individual exams, we usually plot the measurement results over a time scale representing the healing process. The change between the pre-op and the 1 week follow-up exam is due to the impact of the surgery; any changes after the 1 week visit are due to a wound healing response. The exam at 1 week after surgery is chosen because at this stage the patient has sufficiently recovered from the surgery to produce stable wavefront examinations. To evaluate the statistical significance of the changes, we performed a two-tailed Student T-test assuming two samples with unequal variance. We compare the pre-op measurement with the 1 week post-op measurement to evaluate the impact of surgery, and the 1 week post-op measurements to the 12 months post-op measurements to evaluate the overall impact of wound healing. In order to evaluate the progression over time, we also compare all consecutive measurements after 1 week, i.e. we compare 1 week post-op to 1 month post-op, 1 month post-op to 3 months post-op, 3 months post-op to 6 months post-op, and 6 months post-op to 12 months post-op. In summary, these statistical analyses indicate: (1) if any significant changes occur due to surgery, (2) if any significant changes have occurred in the 12 months after surgery, and (3) if any significant changes occur between consecutive exams during wound healing.
For some analysis, we split the data into two groups of mild and high myopia based on the manifest refraction before surgery. The cutoff point was arbitrarily chosen at -5 D spherical equivalent power. This cutoff point is slightly higher than the average of -4.07 D spherical equivalent power for all subjects. Therefore, there are more eyes in the mild myopia group than in the high myopia group. The relatively high cutoff enables us to see effects that are mainly due to the treatment of high myopia. Usually, we will present the data for three cases: all myopia, mild myopia, and high myopia. The total of myopic eyes in the study is 157. In the mild myopia group with less or equal -5 D spherical equivalent power (SEP) we have 107 eyes. In the high myopia group with higher than -5 D spherical equivalent power we have 50 eyes. Figure 46 shows a histogram of the refraction in our subject group.

![Figure 46: Number of eyes in groups of different spherical equivalent power (SEP). The cutoff point is -5 D. Less and equal -5 D in the mild myopia group, greater than -5 D in the high myopia group.](image-url)
Visual Acuity

Visual acuity was measured using a Vector Vision logMAR visual acuity chart. The visual acuity measurement is the only measurement that was also taken at the 1 day post-op visit. The plot in Figure 47 shows the average visual acuity of all eyes over the time scale. The pre-op measurement is arbitrarily plotted at 1 month before surgery to separate the data points on the plot. The error bars are the standard deviation of the measurements. The pre-op visual acuity is the best-corrected visual acuity, whereas all follow-up values are for uncorrected visual acuity.

![Visual Acuity Graph](image)

Figure 47: Visual acuity before and after surgery. The data points indicate the average logMAR visual acuity for all eyes at their consecutive visits. The pre-op measurement is plotted at 1 month before surgery in order to separate the data points on the plot. The error bar is the standard deviation of the measurements.

A two-tailed Student T-test assuming two samples with unequal variance was performed comparing the exams at the different visits. The only change found to be
statistically significant was the decrease in visual acuity, represented by a higher logMAR value, between pre-op and 1 day post-op ($p < 0.001$). All other changes during wound healing that can be noted in Figure 47 are not statistically significant.

During the healing period the visual acuity undergoes some changes. Although they are not statistically significant, a trend can still be seen in Figure 47. Visual acuity is worst at 1 day after surgery. It then constantly increases up to the 3 months visit. After that it slightly decreases for the 6 and 12 months visit.

The visual acuity in Figure 47 is the average over the total number of eyes, depending on the visit. There are some outliers in the distribution. Some eyes had a bad visual acuity (higher logMAR value) right after surgery that stayed constant over time. Others experienced a regression in visual acuity in the healing period after surgery. These outliers strongly influence the average and standard deviation of the visual acuity. The logMAR visual acuity after 12 months is $0.07 \pm 0.16$. When we exclude the 14 worst outliers from the analysis, we achieve an average logMAR visual acuity after 12 months of $0.02 \pm 0.10$. 
**Manifest Refraction**

To analyze the impact of surgery and healing on the manifest refraction, we use the measurements of all subjects at all visits. The comparison of the exam before surgery (pre-op) with the exam at 1 week after surgery (post-op) quantifies the changes due to refractive surgery. Comparing the 1 week post-op exam to the consecutive exams quantifies the changes due to the healing response.

Manifest refraction for the pre-op and 1 week post-op exams was assessed by a physician, the other time periods with a Zeiss-Humphrey autorefractor. The prescription was recorded in the positive cylinder notation. Three quantities are used to quantify the changes in manifest refraction: the spherical refractive error, the cylindrical refractive error and the spherical equivalent power. Table 11 shows the results for the average manifest refraction for sphere, cylinder, and spherical equivalent power.

Due to surgery, the average spherical equivalent manifest refraction changes from $-4.07 \pm 1.98 \text{ D}$ to $-0.33 \pm 0.61 \text{ D}$. Laser refractive surgery greatly reduces the refractive error for a wide range of pre-op refractive errors ranging from $-8.10$ to $+2.25 \text{ D}$ spherical equivalent power. During the wound healing period, a slight regression in manifest refraction between the 6 months and 12 months visits can be noted and will be analyzed later. Figure 48 shows the plot of the spherical equivalent power plotted over time.

Figure 49, Figure 50, and Figure 51 show the distribution of the manifest refraction for the measurements of sphere and cylinder and for the spherical equivalent.
Distributions are shown pre-op and for 1 week and 12 months post-op. The histograms in Figure 49, Figure 50, and Figure 51 were normalized and are presented in percent. The pre-op charts are based on 154 measurements. The 1 week post-op charts are based on 148 measurements. The 12 months post-op charts are based on 86 measurements.

<table>
<thead>
<tr>
<th>Time after Surgery (months)</th>
<th>Sphere (D)</th>
<th>Cylinder (D)</th>
<th>Spherical Equivalent (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pre-op</td>
<td>-4.47 ± 2.01</td>
<td>0.80 ± 0.74</td>
<td>-4.07 ± 1.98</td>
</tr>
<tr>
<td>1 week post-op</td>
<td>-0.50 ± 0.63</td>
<td>0.33 ± 0.32</td>
<td>-0.33 ± 0.61</td>
</tr>
<tr>
<td>1 month post-op</td>
<td>-0.50 ± 0.65</td>
<td>0.34 ± 0.31</td>
<td>-0.33 ± 0.61</td>
</tr>
<tr>
<td>3 months post-op</td>
<td>-0.46 ± 0.65</td>
<td>0.35 ± 0.36</td>
<td>-0.29 ± 0.58</td>
</tr>
<tr>
<td>6 months post-op</td>
<td>-0.46 ± 0.73</td>
<td>0.40 ± 0.42</td>
<td>-0.26 ± 0.63</td>
</tr>
<tr>
<td>12 months post-op</td>
<td>-0.61 ± 0.66</td>
<td>0.41 ± 0.35</td>
<td>-0.40 ± 0.61</td>
</tr>
</tbody>
</table>

Table 11: Average manifest refraction for sphere, cylinder and spherical equivalent power before and at 1 week, 1 month, 3 months, 6 months, and 12 months after laser refractive surgery (LASIK).

Figure 48: Spherical equivalent power of the manifest refraction before and after surgery.
Figure 49: Distribution of sphere (refractive error) before surgery and at 1 week and 12 months after surgery.
Figure 50: Distribution of cylinder (refractive error) before surgery and at 1 week and 12 months after surgery.
Figure 51: Distribution of spherical equivalent power (refractive error) before surgery and at 1 week and 12 months after surgery.
Figure 48 shows the changes in manifest refraction during wound healing. We further investigated these changes by splitting the group of patients into two groups, mild myopes with a spherical equivalent power of up to -5 D and high myopes with a spherical equivalent power over -5 D.

![Manifest Refraction After Surgery](image)

Figure 52: Manifest refraction (spherical equivalent power) during wound healing, starting at the 1 week post-op visit. Manifest refraction is plotted for all exams, for mild and for high myopes separately.

All three curves show the same regression during wound healing. The higher myopes are in average more undercorrected than the mild myopes. All groups a regression of manifest refraction between the 6 and 12 months exams. The regression is statistically significant ($p = 0.0043$, paired T-test). The sign test shows that 53% of the changes in manifest refraction between 6 and 12 months post-op are negative and 27% positive. No changes occur in 20% of the analyzed eyes. Table 12 shows the manifest refraction for the three groups. The number in parenthesis is the number of eyes. Note that the standard deviation is quite large compared to the average refraction. The numbers for “all myopia”
differ slightly from the numbers in Table 11 because now we only look at myopia excluding the small number of hyperopic treatments in the study.

<table>
<thead>
<tr>
<th>Status</th>
<th>All myopia</th>
<th>Mild myopia</th>
<th>High myopia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-op</td>
<td>-4.10 ± 2.00 (157)</td>
<td>-3.32 ± 1.04 (107)</td>
<td>-6.26 ± 1.25 (50)</td>
</tr>
<tr>
<td>1 week post-op</td>
<td>-0.33 ± 0.61 (152)</td>
<td>-0.27 ± 0.57 (104)</td>
<td>-0.57 ± 0.60 (48)</td>
</tr>
<tr>
<td>1 month post-op</td>
<td>-0.34 ± 0.62 (144)</td>
<td>-0.33 ± 0.58 (95)</td>
<td>-0.44 ± 0.65 (49)</td>
</tr>
<tr>
<td>3 months post-op</td>
<td>-0.26 ± 0.57 (130)</td>
<td>-0.20 ± 0.42 (89)</td>
<td>-0.51 ± 0.70 (41)</td>
</tr>
<tr>
<td>6 months post-op</td>
<td>-0.27 ± 0.63 (105)</td>
<td>-0.24 ± 0.48 (73)</td>
<td>-0.48 ± 0.76 (32)</td>
</tr>
<tr>
<td>12 months post-op</td>
<td>-0.39 ± 0.67 (128)</td>
<td>-0.33 ± 0.59 (84)</td>
<td>-0.61 ± 0.70 (44)</td>
</tr>
</tbody>
</table>

Table 12: Manifest refraction (spherical equivalent power) split into groups of mild and high myopia. The number in parenthesis is the number of eyes.

The statistically significant regression in manifest refraction in our group of patients might not be clinically significant because changes below 0.25 D do not affect vision noticeably. Still, the regression shows that refraction after LASIK surgery might not be stable. The PERK study, a long term study for another refractive surgery, radial keratotomy (RK), has shown that the regression after RK continues even after 10 years [56]. The PERK study determined an average change in refraction of +0.21 D per year between 6 and 24 months post-op, and 0.06 D per year thereafter. In RK, the surgeon cuts radial incisions in the cornea, thereby weakening and flattening the cornea. While the techniques of RK and LASIK are very different, they both have in common that major incisions are made that structurally weaken the cornea.

No long-term studies on the stability of LASIK for low and moderate myopes with a follow-up period and a number of eyes comparable to the PERK study are available as of today. Studies with shorter follow-up time periods or lower numbers of eyes come to
opposing conclusions regarding the stability of LASIK. Most of the studies report the refraction as percentage of eyes in the ±0.5 D or ±1.0 D range. These numbers cannot be directly compared to our numbers and are not sensitive enough to detect minor regression. Knorz et al. [58] have reported a two-year follow-up study for moderate to high myopia. They concluded that surgery is stable for corrections of -5 D to -10 D (18 eyes), but did not report the average manifest refraction in their patient group.

Magallanes et al. [59] found LASIK to be stable over a two year follow-up in the refraction group of -7 to -15 D (p = 0.2, 24 eyes). Sekundo et al. [60] have reported a six-year follow-up study for moderate and extreme myopia (-8 to -20 D) and found a regression from -0.25 D to -0.88 D at six years. They analyzed 33 eyes of 19 subjects.

We had mentioned earlier that the patients with enhancement surgery during the course of the study were excluded and that this biases our study towards better results in manifest refraction. We checked if there were any differences in the numbers of enhancements in the groups of mild and high myopia, as one would suspect that the treatment of high myopia with its stronger impact on the eye and the deeper ablation might cause a stronger regression. Of the ten eyes that had enhancements, there were three in the group of high myopia and seven in the group of mild myopia. The total number of eyes in the group of high myopia was 50 and 107 in the group of mild myopia. The percentage of enhancements for both groups was almost equal with 6.0% for the high myopia group and 6.5% for the mild myopia group. The average enhancement was -0.82 ± 0.20 D. Had we included these eyes in our analysis of regression during wound healing, we would have found an even larger regression.
Figure 53: Scattergram of the changes in manifest refraction due to surgery plotted over the pre-op manifest refraction (spherical equivalent power).

Figure 53 shows a scattergram of the changes in manifest refraction, i.e. the achieved correction 1 week post-op due to surgery plotted over the pre-op manifest refraction. Most eyes achieve the desired correction or are slightly undercorrected. A number of eyes were overcorrected, but the overcorrection was only in the range of 0.25 to 0.50 D. Performing a Bland-Altman analysis on the changes in manifest refraction due to surgery, we find a bias of 0.35 D, i.e. an average undercorrection of 0.35 D. The 95% confidence interval for the changes in manifest refraction due to surgery is 1.16 D.
**Contrast Sensitivity**

While visual acuity is a measure of the subject’s ability to read small high contrast letters, contrast sensitivity is a measure for the ability to detect small changes in contrast like they might occur during night vision. Contrast sensitivity is related to modulation transfer function (MTF) of the eye, i.e. higher order aberrations decrease the MTF and therefore the contrast sensitivity of the eye. Contrast sensitivity can therefore be used as an independent measure of aberrations in the human eye. A loss of contrast sensitivity after laser refractive surgery has been reported [39], [40], [41]. Because contrast sensitivity is a function of the aberrations in the eye, it is also a function of pupil size.

We measured the contrast sensitivity using the Vector Vision CSV-1000 contrast sensitivity chart and converted the readings to log units. Contrast sensitivity was assessed for four different spatial frequencies: 3, 6, 12, and 18 cycles per degree. Figure 54 shows a plot of contrast sensitivity for all visits. The black curve with error bars represents the population norm reported by the manufacturer of the chart [57], the colored curves are from our study. Figure 55 shows the same values referenced to the pre-op values plotted over time. Changes are more apparent in this plot.

In Figure 54, the blue curve represents the pre-op values. At the 1 week post-op visit, the contrast sensitivity is lowest. Interestingly, the contrast sensitivity increases during the 1, 3, and 6 months visits, but drops back down at the 12 months visit. While we did expect the contrast sensitivity to drop after surgery for the 1 week post-op visit, we were surprised by the changes that occur during wound healing.
Contrast sensitivity CSV-1000

Figure 54: Contrast sensitivity in log units plotted over the spatial frequency in cycles per degree (cpd) for all visits. The population norm was referenced by the manufacturer of chart [57].
The pre-op values in Figure 54 are in the lower range of the population norm. The reason for this can be found in the way the test was conducted in the clinic as compared to the manufacturer's guidelines. The contrast sensitivity chart shows eight pairs of circles for each spatial frequency. One of the circles in each pair contains a grating with the corresponding spatial frequency; the other circle is randomly filled with uniform gray. The circles are numbered 1 through 8 with decreasing contrast. During the test, the subject has to detect the circle with the grating, starting at circle 1 with the highest contrast. In our study, we recorded the highest number (i.e. lowest contrast) that was detected correctly in a row. If a subject for example detects the correct circle for 1, 2, 3, and 4, misses 5, and then detects 6 correctly, we recorded a 4, because the 5 was detected wrong. After finding that our results are in the lower range of the population norm, we asked the vendor of the chart how to treat the above mentioned example. The answer was that we should have re-tested the 6, and if the subject detected it right again, we should have recorded the 6 instead of the 4.

This difference in performing the test explains our overall lower measurements of contrast sensitivity. Our results are still valid, because we were consistent with our method throughout the study. The differences in the method of measurement of contrast sensitivity, though, have to be taken into account when comparing our results to the results of other researchers performed with the same equipment.
Figure 55: Changes in log contrast sensitivity as a result of surgery and wound healing. All values are presented relative to the pre-op values.

We statistically analyzed the differences in contrast sensitivity using the two-tailed T-test. We compared pre-op to 1 week post-op to evaluate the influence of surgery. We also compared the 1 week post-op to the 6 months post-op, and the 6 months post-op to the 12 months post-op to evaluate the influence of wound healing. The choice of the 6 months post-op was based on results from the aberration analysis that will be presented in a later chapter.

<table>
<thead>
<tr>
<th></th>
<th>3 cpd</th>
<th>6 cpd</th>
<th>12 cpd</th>
<th>18 cpd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-op vs. 1 week</td>
<td>0.024</td>
<td>0.004</td>
<td>0.025</td>
<td>0.008</td>
</tr>
<tr>
<td>1 week vs. 6 months</td>
<td>0.008</td>
<td>0.006</td>
<td>0.032</td>
<td>0.074</td>
</tr>
<tr>
<td>6 vs. 12 months</td>
<td>0.466</td>
<td>0.123</td>
<td>0.066</td>
<td>0.254</td>
</tr>
</tbody>
</table>

Table 13: P-values for the changes during surgery and during healing for the different spatial frequencies. Two-tailed T-test assuming unequal variances. Significant changes are in green, not significant changes in orange.
Table 13 lists the P-values for the T-test performed on the changes during surgery and during healing. The changes between the pre-op and the 1 week post-op values are statistically significant for all four frequencies. The changes between 1 week and 6 months post-op are significant for the lower frequencies of 3, 6, and 12 cycles per degree. The changes between the 6 and 12 months follow-up exams are not statistically significant. The individual measurements of contrast sensitivity are very widely scattered. A correlation between the changes in contrast sensitivity in individual eyes and their pre-op manifest refraction could not be found.

Contrast sensitivity drops significantly after laser refractive surgery. During wound healing, the contrast sensitivity recovers until, at the 6 months visit, it reaches almost pre-op values. There is a decrease in contrast sensitivity between 6 and 12 months post-op, but it is not statistically significant.

A loss in contrast sensitivity immediately after surgery followed by a recovery during the first 6 months has been reported by several authors. Fan-Paul et al. [41] and Hoffman et al. [40] reviewed a large number of papers. They both agree that there is a strong decrease in contrast sensitivity immediately after surgery, which was also reported by Montés-Micó et al. [39]. The results for changes in contrast sensitivity during the time after surgery differ. While some authors report an increase in contrast sensitivity almost back to pre-op values between 3 and 6 months, others report that the contrast sensitivity increases, but stays below pre-op values at 6 to 12 months or even longer post-op. Based on our results, we can agree with both groups.
When comparing the changes in contrast sensitivity for the two groups of mild and high myopes separately, we find that the contrast sensitivity in general is lower for the higher myopes. The changes during wound healing are slightly larger for higher myopes, but the pattern of behavior is the same, i.e. they decrease with higher spatial frequencies. Figure 56 shows the contrast sensitivity for high myopes.

Figure 56: Contrast sensitivity for high myopia.
Pupil Diameter

The pupil diameter of the subject’s eye is of great importance because most ocular aberrations have some higher order dependence on pupil diameter. For example, coma is proportional to the third power of pupil diameter, while spherical aberration is proportional to the fourth power of pupil diameter. If any of these pupil-size dependent aberrations are present, the optical performance of the eye is greatly decreased for larger pupil sizes. This can result in eyes that have excellent visual acuity in daylight conditions where the pupils are smaller, but experience problems with night vision like halos or decreased contrast sensitivity under darkened conditions when the pupils are larger.

We analyzed the natural dark-adapted pupil diameter in our group of subjects pre-op and at all visits in the study. The pupil diameter was measured with the Shack-Hartmann wavefront sensor in a dark room. Because some vignetting might have occurred in the pre-op measurements for eyes with strong refractive error, we only included pre-op exams with spherical equivalent power of up to -6 D.

Figure 57 shows the average dark-adapted pupil diameter for all visits. The average dark-adapted pupil diameter before surgery was 5.93 ± 1.19 mm (n = 122). At 1 week after surgery, the dark-adapted pupil diameter has increased to 6.35 ± 0.83 mm (n = 155). This increase of 0.42 mm is statistically significant (p < 0.001). The pupil stays large, decreasing slowly in diameter over time. The changes are not significant for the 1 and 3 months visits. At the 6 months visit, the pupil sizes have decreased to 5.75 ± 0.72 mm (n = 106). This change is statistically significant (p < 0.001). There is no statistically
significant difference between the pre-op and the 6 or 12 months post-op pupil diameters \( (p = 0.16) \).

![Dark-Adapted Pupil Diameter](image)

Figure 57: Dark-adapted pupil diameter. Analysis of pre-op eyes with spherical equivalent power of less than -6 D and all post-op eyes.

The change in pupil diameter after surgery indicates that night vision or contrast sensitivity 1 week after surgery might be substantially worse than 6 months after surgery if large amounts of pupil-size dependent aberrations like coma, spherical or higher order aberrations are present in the eye.

In summary, the analysis of the pupil size before and after surgery has shown that the pupil size of the subjects in this study increased by about 0.42 mm as an immediate response to surgery. This increase in pupil size is only temporary. At the 6 months post-op visit, the pupil diameter has decreased back to the pre-op values.
Pupil Diameter and Contrast Sensitivity

For an eye with aberrations present, the contrast sensitivity is a function of pupil size. The increased pupil size after surgery might therefore be one of the reasons for the decrease in contrast sensitivity immediately after surgery. The increase of contrast sensitivity during wound healing, reaching almost pre-op values at 6 months, also matches the behavior of the pupil size. The pupil size increases significantly as an immediate response to surgery and decreases back to pre-op diameters at the 6 months visit. We can therefore conclude that the changes in contrast sensitivity after laser refractive surgery and during wound healing are in part due to changes in pupil size that occur as a reaction of the eye to surgery. Several authors have reported on the relation between pupil diameter and contrast sensitivity. In their review, Fan-Paul et al. [41] conclude that there is a strong correlation between larger pupil sizes and decreased contrast sensitivity, but the increased pupil size cannot be the only reason for the decreased contrast sensitivity. If the increased pupil diameter were solely responsible for the decreased contrast sensitivity, then the contrast sensitivity should return to its pre-op values at the 6 months follow-up visit, as the pupil size does. The contrast sensitivity increases between the 3 and 6 months follow-up visits, but stays below the pre-op value for both the 6 and 12 months follow-up visits. We will show in the following chapters that corneal aberrations increase as a result of the surgery. This increase in aberrations also has an impact on contrast sensitivity. We will show later that the changes in aberration in conjunction with the changes in pupil diameter correlate with the changes in contrast sensitivity.
Pachymetry

Pachymetry measures the central thickness of the cornea. Laser refractive surgery for myopia flattens the central anterior corneal surface by ablating more tissue in the center than in the periphery. Therefore, the center thickness of the cornea decreases as a result of laser refractive surgery. The average central corneal thickness of the eyes in the Whitaker study before surgery was $0.541 \pm 0.033$ mm and $0.474 \pm 0.057$ mm at 1 week after surgery.

Figure 58: Changes in the central corneal thickness during wound healing. The first data point is the 1 week post-op exam and is set to zero. Figure 58 shows the changes in central corneal thickness over time. The average increase in corneal center thickness during wound healing measured at the 12 months post-op visit is about 20 microns ($p = 0.022$) for all eyes. Figure 58 also shows the increase in central corneal thickness for the two groups of mild and high myopia. The
increase is smaller for the mild myopia group and higher for the high myopia group. This indicates that the increase in central corneal thickness is related to the refractive correction achieved by the surgery.

Figure 59 shows a scattergram of the change in corneal center thickness between 1 week and 12 months post-op plotted over the pre-op refraction (spherical equivalent power), where the 1 week pachymetry was used as the reference. For the majority of eyes, we encounter an increase in corneal center thickness. This increase is only weakly dependent on the pre-op manifest refraction. This suggests that the increase in central corneal thickness during wound healing is a reaction to the cutting of the flap as well as a function of the attempted correction.

Figure 59: Scattergram of the change in corneal center thickness between 1 week and 12 months post-op, plotted over the pre-op refraction (spherical equivalent power).
Our results agree with findings by Kozak et al. [51] and Pallikaris et al. [21] that have found an increase in central corneal thickness after laser refractive surgery. Pallikaris et al. [21] have reported an increase in corneal thickness of 10 microns at the 2 months visit. This agrees with our results for mild myopia. The increase in corneal thickness for the high myopia group in our study is larger, indicating that the actual ablation depth also has its impact on the thickening of the cornea during wound healing.
Corneal Topography

At each exam during the Whitaker study, we assessed the corneal topography for the anterior and posterior corneal surfaces using the Orbscan Topographer. The output of the topographer is a height map with discrete elevation points. These height data were fitted to Zernike polynomials of 7th order with a 6 mm diameter [22]. This chapter presents the analysis of five entities derived from the measurements of corneal topography:

- **Changes to the anterior and posterior corneal curvatures**: Changes of the anterior and posterior radii of curvature due to surgery and wound healing are analyzed.

- **Changes to the corneal power**: The total power is calculated based on anterior and posterior corneal surfaces and pachymetry. Changes in corneal power due to surgery and during wound healing are analyzed.

- **Changes to the Zernike coefficients of the corneal surfaces**: The corneal surfaces are represented using Zernike polynomials. Changes to the Zernike coefficients due to surgery and wound healing are analyzed.

- **Changes to the corneal aberrations**: Average corneal aberrations for the anterior and posterior corneal surfaces are calculated using ray trace software. Changes due to surgery and during wound healing are analyzed.

- **Changes to the conic constant of the corneal surfaces**: Conic constant of the anterior and posterior corneal surfaces are calculated using a least square fit method. Changes due to surgery and during wound healing are analyzed.
This chapter contains two different kinds of analysis. One analysis is based purely on geometrical shapes, the other on optical properties. While we analyze corneal curvature purely based on geometry, we combine both corneal surfaces and the corneal center thickness to calculate the total corneal power. Changes in corneal power measured by the topographer can then be compared directly to changes in manifest refraction because both measurements independently measure the same changes in corneal power due to surgery and during wound healing.

The same distinction has to be made between the analysis of the corneal Zernike surface coefficients or the conic constants which are representatives of the geometrical shape of the anterior and posterior corneal surfaces, and the analysis of corneal aberrations. The latter uses the corneal surfaces to create a model cornea consisting of an anterior and posterior surface and the corresponding thickness. The aberrations of this model cornea are then analyzed using optical design software.
Changes in Corneal Curvature

We find differences in both the anterior and posterior radii of curvature between the pre-op and 1 week post-op visits. The changes of both radii are statistically significant \( (p < 10^{-8}) \). Table 14 lists the anterior and posterior radii of curvature pre-op and 1 week post-op.

<table>
<thead>
<tr>
<th></th>
<th>ROC Anterior Cornea (mm)</th>
<th>ROC Posterior Cornea (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-op</td>
<td>7.617 ± 0.261</td>
<td>5.978 ± 0.390</td>
</tr>
<tr>
<td>1 week post-op</td>
<td>8.141 ± 0.368</td>
<td>5.551 ± 0.392</td>
</tr>
<tr>
<td>Change</td>
<td>+0.524</td>
<td>-0.427</td>
</tr>
</tbody>
</table>

Table 14: Radius of curvature (ROC) for the anterior and posterior corneal surfaces before and 1 week after surgery.

The change in radius of curvature of the anterior corneal surface is a result of the reshaping of the anterior surface of the cornea. A flatter anterior corneal surface is the result of the correction for myopia. The posterior corneal surface after surgery is steeper than before surgery. This effect is unexpected, and although the changes in anterior and posterior corneal radii of curvature are both about 0.5 mm, the effect of the change in posterior curvature on refraction and aberrations is expected to be smaller due to the small change in index of refraction at the posterior cornea. This will be shown in the following chapters about corneal power and corneal aberrations.

Figure 60 plots the radius of curvature of the anterior corneal surface over time during the course of the study, including the pre-op radius. It also shows the differences in changes in anterior curvature for mild and high myopia separately. The changes due to
surgery differ significantly, resulting in a much flatter corneal surface in the case of high myopia. The changes in radius of curvature of the anterior corneal surface during wound healing are not statistically significant.

![Radius of Curvature of the Anterior Cornea](image)

Figure 60: Radius of curvature of the anterior corneal surface for mild, high, and all myopic eyes.

Interestingly, the anterior radius of curvature before surgery seems to be almost the same for all eyes. This indicates that in our patient group, myopia was mainly caused by differences in the axial length of the eye. Figure 61 shows a scattergram of the axial length of the eyes plotted over the pre-op refractive error (spherical equivalent power). On average, eyes with higher refractive error are longer.
Figure 61: Scattergram of the axial length of the eyes plotted over the pre-op refractive error (SEP, spherical equivalent power).

Figure 62 shows the radius of curvature of the posterior corneal surface for all eyes, and for mild and high myopia separately. Again, the pre-op radius of curvature is about the same for all eyes. One week after surgery, we measure a steeper posterior corneal surface, which relaxes slightly between the 1 week and 1 month visits. The reason for the steepening of the posterior corneal surface is not yet fully understood, but biomechanical models have been developed that help understand this change [23]. The change between pre-op and 1 week post-op posterior radius of curvatures is statistically significant. The only other change in this graph that is statistically significant is the increase in posterior radius of curvature between 1 week and 1 month (p = 0.028).
Figure 62: ROC of the posterior corneal surface for mild and high myopia and for all myopic eyes.

We can also look at the changes in anterior and posterior corneal surfaces during wound healing by referencing all measurements to the 1 week post-op measurement. Figure 63 shows the change in radius of curvature during wound healing for the anterior and posterior corneal surfaces for all eyes. The only significant change here is the increase in the radius of curvature, i.e. a flattening of the posterior corneal surface between 1 week and 1 month post-op. The anterior corneal curvature does not change significantly. What is interesting to note in this graph is what seems like a temporary change to both radii of curvature at the 6 months exam.
Figure 63: Change in radius of curvature during wound healing for the anterior and posterior corneal surfaces. The first data point is the 1 week post-op exam and is set as a reference. Positive values refer to a flattening of the surface.

Figure 64: Change in radius of curvature during wound healing for the anterior and posterior corneal surfaces for eyes treated for mild myopia. The first data point is the 1 week post-op exam and is set as a reference. Positive values refer to a flattening of the surface.
Figure 65: Change in radius of curvature during wound healing for the anterior and posterior corneal surfaces for eyes treated for high myopia. The first data point is the 1 week post-op exam and is set as a reference. Positive values refer to a flattening of the surface.

Looking at the mild myopia cases shows the same behavior as discussed above. The temporary changes of the radii at the 6 months exam is more pronounced, as can be seen in Figure 64. Figure 65 shows the changes in anterior and posterior corneal curvatures for the high myopia case. In this chart, we notice a flattening of both corneal surfaces between the 1 week and the 1 month exams.

Hernandez-Quintela et al. [50] have reported on changes in the posterior corneal curvature. In their study, they found the changes in posterior corneal curvature after laser refractive surgery to be in the range of the fluctuation in a non-surgery group.
Changes in Corneal Power

In order to quantify the impact of the changes in corneal curvature, we calculate the refractive power of the cornea including the curvatures of the anterior and posterior corneal surfaces as well as the corneal thickness. Due to surgery, the average anterior corneal power decreases from 49.51 to 46.32 D. This decrease in power by 3.19 D is needed to correct myopia. The posterior corneal power also changes from -6.64 to -7.15 D. The additional 0.51 D of negative power add to the myopic correction. The total power of the cornea decreases from 43.00 D to 39.28 D. This change of -3.72 D corresponds to the change in manifest spherical equivalent power that we have noted in the manifest refraction. Table 15 lists the total corneal and manifest spherical equivalent powers. Note that the negative change in corneal power (i.e. less power in the cornea) corresponds to a positive change in manifest refraction (i.e. less myopic).

<table>
<thead>
<tr>
<th></th>
<th>Total Corneal Power (D)</th>
<th>Manifest Spherical Equivalent Power (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-op</td>
<td>42.99</td>
<td>-4.07</td>
</tr>
<tr>
<td>1 week post-op</td>
<td>39.28</td>
<td>-0.33</td>
</tr>
<tr>
<td>Change</td>
<td>-3.72</td>
<td>3.74</td>
</tr>
</tbody>
</table>

Table 15: Changes in total corneal power and manifest spherical equivalent power.

The changes in corneal power that we discussed above are due to surgery. But wound healing also has its impact on the corneal power. Figure 66 shows a plot of the total corneal power plotted over time. In the three months following surgery, the total corneal
power increases by about a quarter diopter. This corresponds to a regression in the refractive error of a quarter diopter. At the 6 months visit, the total corneal power drops down to the 1 week post-op value and then rises again for the 12 months post-op visit. The corneal power after 12 months is about 0.40 D higher than directly after surgery.

Figure 66: Changes in total corneal power (anterior and posterior surface) during wound healing. The first data point is the 1 week post-op.

The myopic shift in Figure 66 can also be seen in the manifest refraction plotted in Figure 52. Both the corneal power and the manifest refraction show the regression in refractive error with time. With the corneal power and the manifest refraction measurements, we have two independent measures showing the same trend. The drop in corneal power at the 6 months post-op exam seems out of the ordinary and we do currently not have an explanation for it. It cannot be a systematic measurement error because the subjects were recruited over the course of one year and their 6 months follow-up visits are therefore also distributed over one year.
Figure 67 shows a scattergram of the changes in total corneal power due to surgery. While there is a general trend of the data points following the blue line of optimum correction, the data are very widely scattered. The distribution of the anterior corneal power is equally widely scattered. The scattergram in Figure 53 in the chapter about manifest refraction had shown measurements of the same power changes, but the distribution there was not as widely scattered. This suggests that the scattering in the plot of corneal power changes measured with the topographer is due to a large measurement uncertainty in the topography measurements when measuring corneal curvature.

![Changes in Total Corneal Power](image)

**Figure 67:** Changes in total corneal power due to surgery, measured with the corneal topographer.

Bland-Altman analysis of the changes in total corneal power shown in Figure 67 show a bias of 0.56 D and a 95% confidence interval of 2.72 D. While the bias of the
changes in corneal power is only slightly higher than the bias of the changes in manifest refraction with 0.35 D, the 95% confidence interval of 2.72 D is more than twice as large compared to the 1.16 D of manifest refraction. The measurements of corneal power using topographic height maps is as accurate, but less repeatable than measurements of manifest refraction.

![Changes in Posterior Corneal Power Pre-op vs. 1 week Post-op](image)

Figure 68: Changes in posterior corneal power due to surgery, measured with the corneal topographer.

In the previous section, we have presented changes in the posterior radius of curvature as a result of surgery. Figure 68 shows a scattergram of the changes in posterior corneal power due to surgery plotted over the pre-op manifest refraction. The red line is the best linear fit. The individual changes in posterior corneal power are very widely scattered and range from -0.5 to +1.5 D. In the best fit line, we see a trend for larger
power changes for higher pre-op manifest refraction. The above results suggest that the wide scatter of the measurements is due to the measurement uncertainty of the topographer. Because no independent measurement of the posterior corneal curvature is available, we cannot confirm this. Therefore, the widely scattered changes can also be due to a temporal variation of posterior corneal curvature in individual eyes.
Changes in the Zernike Coefficients of the Corneal Surfaces

The output of the topographer is a height map with discrete height data points. To analyze the height data, we decompose the height data in Zernike polynomials [22]. The Zernike decomposition represents the height data in a closed form mathematical set of functions and also smoothen high frequency noise or measurement errors. We can look at the behavior of the Zernike surface coefficients and find qualitative results about the wavefront aberrations that are introduced by the shape of the surfaces. The Zernike surface coefficients used here are labeled \( c_{n,m} \) in order to distinguish them from the aberration Zernike coefficients \( a_{n,m} \). The \( c \)-coefficients represent a surface; the \( a \)-coefficients represent wavefront aberrations.

Figure 69, Figure 70, and Figure 71 show the Zernike surface coefficients of the anterior corneal surface before surgery, at 1 week and at 12 months after surgery. Although these coefficients actually represent the shape of the cornea and are not aberration coefficients, they can be related to aberrations. In the figures present below, we show the coefficients related to 4\(^{th} \) and 6\(^{th} \) order spherical aberration (\( c_{4,0}, c_{6,0} \)), 3\(^{rd} \) and 5\(^{th} \) order coma (\( c_{3,1}, c_{3,1}, c_{5,3}, c_{5,3} \)), trefoil (\( c_{3,-3}, c_{3,3} \)), and 4\(^{th} \) order astigmatism (\( c_{4,2}, c_{4,2} \)).

Comparing Figure 69 with Figure 70, we see that surgery increases the Zernike surface coefficients \( c_{4,0} \) and \( c_{6,0} \) that for the anterior corneal surface are directly related to spherical aberration. The coefficients \( c_{3,1} \) and \( c_{3,1} \) that are related to coma also show an
increase, whereas the coefficients for trefoil \((c_{3,3}, c_{3,3})\), 4\({\text{th}}\) order astigmatism \((c_{4,-2}, c_{4,2})\), and 5\({\text{th}}\) order coma \((c_{5,-3}, c_{5,3})\) are almost unchanged.

Figure 69: Zernike surface coefficients of the anterior corneal surface pre-op.

Figure 70: Zernike surface coefficients of the anterior corneal surface 1 week post-op.
Figure 71: Zernike surface coefficients of the anterior corneal surface 12 months post-op.

No notable changes occur between the 1 week and the 12 months visits shown in Figure 70 and Figure 71, indicating that no major changes in corneal aberrations occur during wound healing. The changes to Zernike surface coefficients related to spherical aberration $c_{4,0}$ and $c_{6,0}$ are statistically significant between the pre-op and the 1 week post-op visits ($p < 0.001$). Changes in 3rd and 5th order coma are also significant ($p < 0.01$). An increase in higher order non-spherical aberrations can be noted. Eight out of 21 higher order Zernike surface coefficients change significantly ($p < 0.05$). We compared the 1 week post-op to the 6 months and the 12 months post-op exams. Changes in Zernike surface coefficients related to defocus, spherical aberration, and 4th order astigmatism are significant ($p < 0.05$); higher order coefficients do not change significantly.
Figure 72, Figure 73, and Figure 74 show the same Zernike surface coefficients for the posterior corneal surface. Note that the scale of these plots is larger than for the previous plots for the anterior corneal surface. We cannot relate the Zernike surface coefficients of the posterior cornea directly to individual aberrations because the anterior cornea has already refracted the light coming in from infinity. If we want to determine the aberrations of the posterior cornea, we have to evaluate every individual surface in a corneal model and analyze the aberrations using optical design software.

The Zernike surface structure of the posterior corneal surface is different from the surface structure of the anterior corneal surface. The posterior corneal surface shows large amounts for the $c_{3,3}$, $c_{3,3}$, $c_{4,-2}$, and $c_{4,2}$ coefficients. Because surgery changes only the anterior corneal curvature, the changes that occur in the posterior corneal surface during surgery must be due to a biomechanical response of the eye to surgery. The most important change to the Zernike surface coefficients of the posterior corneal surface is a change in sign in the coefficients $c_{4,0}$ and $c_{6,0}$, which are related to the $4^{th}$ and $6^{th}$ order spherical aberration ($p < 0.001$). Another change is an increase in $4^{th}$ order astigmatism coefficient $c_{4,-2}$ ($p < 0.001$). There is a wider distribution of coefficients in the posterior corneal surface, which can be seen by the larger error bars. Five out of 21 coefficients representing higher order surface variations change significantly between pre-op and 1 week post-op ($p < 0.05$). Figure 73 and Figure 74 show that the only significant change during wound healing occurs in $4^{th}$ order astigmatism $c_{4,-2}$ ($p < 0.05$).
Figure 72: Zernike surface coefficients of the posterior corneal surface pre-op.

Figure 73: Zernike surface coefficients of the posterior corneal surface 1 week post-op.
Figure 74: Zernike surface coefficients of the posterior corneal surface 12 months post-op.
Changes in Corneal Aberrations

In the previous section, we have analyzed the changes in the anterior and posterior corneal surfaces due to surgery and due to wound healing. The aberrations of the anterior corneal surface can be calculated by multiplying the Zernike surface coefficients with the change in refractive index [25]. The change in refractive index at the anterior corneal surface is positive, changing from \( n = 1.0 \) in air to \( n = 1.3776 \) in the stroma [26]. As an example of this analysis, Figure 75 shows a scattergram of the changes in anterior corneal spherical aberration due to surgery, i.e. subtracting the pre-op measurement value from the 1 week post-op value for every individual eye.

Figure 75: Changes in the spherical aberration of the anterior corneal surface (pre-op vs. 1 week post-op) plotted over the pre-op manifest refraction.

The distribution in Figure 75 is very widely scattered. No influence of pre-op manifest refraction is noted. We had seen an equally wide scatter in the analysis of
corneal power presented in Figure 67 and Figure 68. There could be several reasons for this wide scatter in both instances. One could be the measurement uncertainty when using the topographer data and the Zernike decomposition. Sudden changes in corneal curvature at the edge of the ablation zone might be a cause for these measurement errors. There might also be some temporal changes in the higher order aberration structure of individual eyes causing the wide scatter.

The method of calculating aberrations based on corneal surface data presented above can only be applied to the anterior corneal surface. To evaluate the total aberrations of the cornea as well as the contributions of the posterior corneal surface, we created a corneal model in optical design software and analyzed the aberrations. For the corneal model, we used the Arizona Eye Model [26] and removed the lens from the model because we only wanted to analyze corneal aberrations. The anterior and posterior corneal surfaces are replaced by Zernike surfaces calculated from the topography measurements. We also include the corneal thickness from the pachymetry measurements.

To analyze the total corneal aberrations, we import the anterior and posterior corneal surfaces as Zernike surfaces. The analysis gives us the total amount of corneal aberrations. To calculate the aberrations of only the anterior corneal surface, we also remove the posterior corneal surface. The corneal model now consists of only one air-stroma interface. This surface is imported as a Zernike surface from the topographer measurements. To calculate the aberrations of the posterior corneal surface, we replace the anterior corneal surface with a paraxial lens of 22 mm focal length. This lens has the
same power as the average anterior cornea, but does not introduce any aberrations. The posterior corneal surface is again imported from the topographer measurements.

Because of the large scatter that we have found in previous analyses of topography measurements, we did not import the corneal surfaces of every individual eye, but instead we averaged all Zernike surface coefficients for the anterior and posterior corneal surfaces for every visit, i.e. pre-op and all post-op visits. We then imported the averaged Zernike surfaces into the corneal models. For each visit we created a model and evaluated the aberrations at a 6mm entrance pupil diameter.

The output of the analysis was converted to the OSA standard Zernike coefficients [19]. We can directly compare the corneal aberrations presented here to the aberrations measured with the aberrometer that will be presented in the next chapter.

Figure 76 shows total corneal aberration for a 6 mm pupil diameter. The most important aberrations plotted here are spherical aberration and the RSS higher order non-spherical aberrations. The RSS higher-order non-spherical aberrations are the root sum squared of all Zernike coefficients starting at coma and trefoil and leaving all spherical aberration coefficients out. Spherical aberration experiences the largest increase after surgery and coma is the aberration with the second largest increase after surgery. The chart shows that most of the increase in higher order aberrations is due to an increase in coma. All other aberrations that are plotted stay constant, increase or even decrease slightly. Statistical analysis of these data is not possible because each data point is based on one Zemax simulation. Therefore, the data points are plotted without error bars.
Figure 76: Total corneal aberration for a 6 mm pupil diameter.

Figure 77 and Figure 78 show spherical aberration and RSS higher order aberrations for the entire cornea and for the anterior and posterior corneal surfaces separately. They show an increase in aberrations for both surfaces separately. The temporary changes in spherical and higher order aberrations at the 6 months visit are due to changes to the anterior corneal surface. There are no notable changes in the aberration structure of the posterior corneal surface during wound healing.
Figure 77: Spherical aberration plotted over time, showing the total spherical aberration for the cornea and for anterior and posterior cornea separately.

Figure 78: Root-sum-squared (RSS) of the higher order non-spherical aberration plotted over time, showing the total aberration for the cornea and for anterior and posterior cornea separately.
Figure 79: Spot diagram of the corneal model pre-op at a 6mm pupil diameter. Scale bar in microns.

Figure 80: Spot diagram of the corneal model 12 months post-op at a 6mm pupil diameter. Scale bar in microns.
Figure 79 and Figure 80 show the spot diagrams of the best-corrected pre-op and 12 months post-op corneal model. The increase in spherical aberration is clearly visible, resulting in the halo-like structure around the central spot. The size of the central spot is also increased at the 12 months model. This is due to the increase in higher order aberrations.

Based on the corneal topography, we found that corneal aberrations increase as a result of surgery, but stay mainly unchanged during wound healing. Spherical aberration and coma experience the largest increase. An increase can be observed in both the anterior and posterior aberrations.
Changes in Conic Constant

Another common way to characterize optical surfaces is the use of a conic constant $K$. The conic constant describes the deviation of the surface from a sphere and is defined by the sag equation of a conic surface [16].

$$z = r - \sqrt{r^2 - (K+1) \cdot s^2}$$

In this equation, $z$ is the sagitta, $r$ is the radius of curvature at the apex and $s$ is calculated from the coordinates $x$ and $y$ by $s^2 = x^2 + y^2$ and is not normalized. Table 16 lists different surfaces and their conic constants.

<table>
<thead>
<tr>
<th>$K$</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K &gt; 0$</td>
<td>Oblate ellipsoid (ellipsoid rotated about minor axis)</td>
</tr>
<tr>
<td>$K = 0$</td>
<td>Sphere</td>
</tr>
<tr>
<td>-1 &lt; $K$ &lt; 0</td>
<td>Prolate ellipsoid (ellipsoid rotated about major axis)</td>
</tr>
<tr>
<td>$K = -1$</td>
<td>Paraboloid</td>
</tr>
<tr>
<td>$K &lt; -1$</td>
<td>Hyperboloid</td>
</tr>
</tbody>
</table>

Table 16: Different surfaces and their conic constants [16].

Figure 81 shows the conic constant for the anterior and posterior corneal surfaces of the eyes in the Whitaker study. The average conic constant for the anterior corneal surface changes from -0.13 pre-op to +0.30 12 months post-op. The average conic constant for the posterior cornea changes from -0.74 pre-op to -1.18 12 months post-op. The changes between the pre-op and the 1 week visits are statistically significant for both
anterior and posterior corneal surfaces (p < 0.001). Another significant change occurs between the 1 week and 1 month visits for both surfaces (p < 0.05). No significant changes in the conic constant for both surfaces occur during wound healing after 1 month.

![Conic Constant Graph](image)

Figure 81: Conic constant for the anterior and posterior corneal surfaces plotted over time.

In order to evaluate the influence of the pre-op manifest refraction on the conic constants, we plotted the scattergram for the pre-op and 12 months post-op conic constants over the pre-op manifest refraction (spherical equivalent power). Figure 82 and Figure 83 show the distribution of the conic constants of the anterior corneal surface before and 12 months after surgery. Figure 84 and Figure 85 show the conic constants of the posterior corneal surface pre-op and 12 months post-op. Note that the scales of all the above scattergram have the same range.
Figure 82: Conic constant of the anterior corneal surface pre-op plotted over the pre-op spherical equivalent power.

Figure 83: Conic constant of the anterior corneal surface 12 months post-op plotted over the pre-op spherical equivalent power.
Conic Constant of the Posterior Corneal Surface

Pre-op

Conic Constant of the Posterior Corneal Surface

12 months Post-op

Figure 84: Conic constant of the posterior corneal surface pre-op plotted over the pre-op spherical equivalent power.

Figure 85: Conic constant of the posterior corneal surface 1 week post-op plotted over the pre-op spherical equivalent power.
The distributions in Figure 82 and Figure 83 show that the pre-op conic constant of the anterior corneal surface is not dependent on the pre-op spherical equivalent power. The 12 months post-op data are more widely scattered than the pre-op data and a slight dependence on pre-op manifest refraction (spherical equivalent power) can be seen.

The distributions in Figure 84 and Figure 85 show that the conic constants of the posterior corneal surface both pre-op and 12 months post-op are weakly dependent on the pre-op spherical equivalent power. We can also see that in the pre-op data, the conic constant decreases in magnitude for increasing spherical equivalent power. The distribution of the conic constant of the posterior corneal surface is very wide for both the pre-op and post-op data.

We calculated the difference between the pre-op and 12 months post-op conic constants for every individual eye in the study. The scattergrams in Figure 86 and Figure 87 show the changes in the conic constants between the pre-op and 12 months post-op visits for the anterior and posterior corneal surface respectively. These scattergrams show the dependence of the change in the conic constants plotted over the pre-op spherical equivalent power. The change in conic constant of the anterior corneal surface is positive and slightly increases with higher pre-op myopia. The change in conic constant of the posterior corneal surface is negative and the absolute change also slightly increases with higher pre-op myopia.
Change in Conic Constant of the Anterior Corneal Surface
Pre-op vs. 12 months Post-op

![Graph showing change in conic constant of the anterior corneal surface.]

Figure 86: Change in conic constant of the anterior corneal surface (pre-op vs. 12 months post-op) plotted over the pre-op spherical equivalent power.

Change in Conic Constant of the Posterior Corneal Surface
Pre-op vs. 12 months Post-op

![Graph showing change in conic constant of the posterior corneal surface.]

Figure 87: Change in conic constant of the posterior corneal surface (pre-op vs. 12 months post-op) plotted over the pre-op spherical equivalent power.
Refractive surgery changes the conic constants of both the anterior and posterior corneal surfaces. Significant changes occur during the surgery and between 1 week and 1 month post-op. After 1 month, the conic constants do not change. The pre-op conic constant of the anterior corneal surface is not related to the pre-op spherical equivalent power. The conic constant of the posterior corneal surface depends weakly on the pre-op spherical equivalent power.

The changes in conic constants between the pre-op and 12 months post-op visits are widely distributed, but they clearly depend on the pre-op manifest refraction and therefore to the amount of correction achieved by refractive surgery. Holladay et al. [27] have reported a change in the conic constant of the anterior corneal surface that confirms our results.
Aberrations

In the first chapters of this dissertation, we described the design and testing of a Shack-Hartmann aberrometer to objectively measure aberrations in the human eye. We determined accuracy, reliability, and repeatability of our instrument and discussed problems with induced aberrations. In this chapter, we present the aberrations in the population of the Whitaker study that we have measured with the aberrometer before and at several visits after surgery.

During the course of the Whitaker study, we disassembled and rebuilt the entire Shack-Hartmann aberrometer. We added an interface for a second wavefront sensor to be used parallel to the Shack-Hartmann wavefront sensor. We also changed the lenses in the optical relay system from 100mm to 120mm achromats to increase the eye relief for the patient by 20mm, and exchanged the CCD camera that is used to capture the Shack-Hartmann grid image with a smaller and lighter model. The aberrometer was rebuilt in February 2002. Unfortunately, almost all of the 6 months exams were taken before and almost all of the 12 months exams were taken after this rebuilding of the aberrometer. While every effort was made to calibrate the new system with the same accuracy as the original system, we cannot be completely certain that the change in the instrument does not induce systematic errors. Possible error sources are the distance between the lenslet array and the aspect ratio of the pixels on the CCD camera sensor. Both aberrometers have been calibrated by measuring defocus and astigmatism in the range of ±20 D sphere and +8 D cylinder.
The Shack-Hartmann aberrometer measures the total wavefront error of the human eye at the natural dark-adapted pupil size. The standard Zernike set was used to fit the wavefront error [19]. The advantage of using Zernike polynomials is that the single terms are orthogonal, which means that we can analyze the single terms independently. The Zernike coefficients are dependent on the pupil size, so that we can only compare two exams with the same pupil diameter. In order to compare aberrations for all of our measurements, we have to recalculate the Zernike coefficients for discrete pupil sizes. For this analysis, we calculated the Zernike coefficients for all pupil sizes between 4.0 and 7.0 mm in increments of 0.5 mm [24]. For each individual exam, we calculated the Zernike coefficients for all discrete pupil sizes smaller than the natural dark-adapted pupil size. This resulted in a larger number of data points for smaller pupil sizes and a lower number of data points for larger pupil sizes. For example, for an eye with a dark-adapted pupil size of 4.8 mm, we calculate the Zernike coefficients for a pupil size of 4.0 and 4.5 mm. For an eye with a dark-adapted pupil size of 6.8 mm, we calculate the Zernike coefficients for the pupil sizes of 4.0, 4.5, 5.0, 5.5, 6.0, and 6.5 mm. This was done for all available eyes.

The aberrations are calculated from the Zernike coefficients. In order to calculate aberrations from Zernike coefficients, we compute the root-sum-squared (RSS) of the coefficients $a_{m,n}$ or $Z_n$. The RSS corresponds to the wavefront error caused by these terms. In some papers, the authors report the RMS (root-mean-squared) wavefront error which is defined mathematically similar to the RSS. The RMS equals the RSS divided by the square root of the number of coefficients $n$. Some authors also report what they call $RMS$
wavefront error, but actually calculate the RSS. These differences in the definition of RMS wavefront error by different authors have to be taken into account when comparing absolute values for the aberrations reported. It has less influence on any trends or changes in aberrations reported.

\[ RSS = \sqrt{\sum a_{m,n}^2} \]  

(17)

\[ RMS = \sqrt{\frac{1}{n} \sum a_{m,n}^2} \]  

(18)

The aberrations presented in this chapter were calculated using the RSS formula. There are different ways to divide the total aberrations based on the Zernike terms. The first division is between lower order and higher order aberrations. This separation places defocus and astigmatism in the group of lower order and all other aberrations in the group of higher order aberrations. The lower order aberrations are the refractive errors in the eye that can be corrected by spectacles or contact lenses and that were corrected with laser refractive surgery in the Whitaker study. The higher order aberrations can be separated into individual aberrations like spherical aberration, coma, etc, that have a relation to the Seidel aberration coefficients widely used in lens design. Another separation is to divide the aberrations in groups of the same radial Zernike order. The higher order aberrations are then separated into third, fourth, fifth, and sixth order aberrations. In the Whitaker study, we analyze the ocular aberrations before and after laser refractive surgery (LASIK). Analyzing lower order aberrations gives us insight in the results of the surgery, i.e. the correction of defocus and astigmatism. A side-effect of
current surgery is the introduction of large amounts of spherical aberration. We therefore analyze spherical aberration separately when we present different groups of higher order aberrations.

<table>
<thead>
<tr>
<th>Aberrations</th>
<th>Zernike Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower Order Aberrations</td>
<td>$Z_3, Z_4, Z_5$ or $a_{2,-2}, a_{2,0}, a_{2,2}$</td>
</tr>
<tr>
<td>Higher Order Aberrations</td>
<td>$Z_6$ to $Z_{27}$ or $a_{3,-3}$ to $a_{6,6}$</td>
</tr>
<tr>
<td>Higher Order Non-Spherical Aberrations</td>
<td>$Z_6$ to $Z_{27}$, excluding $Z_{12}$ and $Z_{24}$ $a_{3,-3}$ to $a_{6,6}$ excluding $a_{4,0}$ and $a_{6,0}$</td>
</tr>
<tr>
<td>Spherical Aberration</td>
<td>$Z_{12}, Z_{24}$ or $a_{4,0}, a_{6,0}$</td>
</tr>
<tr>
<td>Coma</td>
<td>$Z_7, Z_9$ or $a_{3,-1}, a_{3,1}$</td>
</tr>
<tr>
<td>Trefoil</td>
<td>$Z_6, Z_9$ or $a_{3,-3}, a_{3,3}$</td>
</tr>
<tr>
<td>Fourth Order Astigmatism</td>
<td>$Z_{11}, Z_{13}$ or $a_{4,-2}, a_{4,2}$</td>
</tr>
<tr>
<td>Quadrafoil</td>
<td>$Z_{10}, Z_{14}$ or $a_{4,-4}, a_{4,4}$</td>
</tr>
<tr>
<td>Third Order</td>
<td>$Z_6$ to $Z_9$ or $a_{3,\pm n}$</td>
</tr>
<tr>
<td>Fourth Order Non-Spherical</td>
<td>$Z_{10}$ to $Z_{14}$ excluding $Z_{12}$ $a_{4,\pm n}$ excluding $a_{4,0}$</td>
</tr>
<tr>
<td>Fifth Order</td>
<td>$Z_{15}$ to $Z_{20}$ or $a_{5,\pm n}$</td>
</tr>
<tr>
<td>Sixth Order Non-Spherical</td>
<td>$Z_{21}$ to $Z_{27}$ excluding $Z_{24}$ $a_{6,\pm n}$ excluding $a_{6,0}$</td>
</tr>
</tbody>
</table>

Table 17: Aberrations and the Zernike coefficients used to calculate them.

Table 17 shows the aberrations and the coefficients that were used to calculate the aberration. For example, the spherical aberration term was calculated using the $a_{4,0}$ and $a_{6,0}$ terms: $\text{Spherical Aberration} = \sqrt{a_{4,0}^2 + a_{6,0}^2}$. The other aberrations were calculated accordingly.
The amount of spherical aberration after surgery is much larger than any other higher order aberration. We therefore added the group of higher order non-spherical aberrations. This group combines all higher order aberrations except spherical aberration. By doing this we can divide the higher order aberrations into spherical aberration and all other higher order aberrations.

Most of the charts in this chapter show the aberration coefficients plotted over the pupil diameter. Different curves represent different visits. These charts show the dependence of the aberrations on pupil diameter and the development of the aberrations with time during surgery and wound healing. For these charts, it is important to note the number of eyes that were used to calculate each point in the chart. Figure 88 shows the number of eyes available for every diameter at every exam.

There are two general trends that can be seen in these numbers.

1. The number of eyes decreases with increasing pupil diameter. Therefore, the average and standard deviations of aberrations for smaller pupil diameters are based on larger numbers of measurements.
2. Due to the increase in pupil size after surgery, we have more eyes available at the 1 week post-op visit for larger pupil diameters. Accordingly, the numbers for the pre-op, 6 and 12 months post-op exams at large pupil diameters are lower.
Figure 88: Number of eyes in the analysis of different pupil diameters for the pre-op and follow-up exams. The same colors for the different visits will be used for all charts in this chapter.

The analysis of aberrations in this chapter is divided into the following sections:

- **Changes in lower order aberrations**: We present lower order aberrations and their correlation to manifest refraction and corneal power.

- **Changes in spherical aberration and higher order non-spherical aberrations** due to surgery and during wound healing.

- **Statistical analysis of changes during wound healing**.

- **Higher order aberrations, pupil diameter, and contrast sensitivity**: Correlating changes in higher order aberration and pupil diameter with changes in contrast sensitivity due to surgery and during wound healing.

- **Changes in coma, trefoil, fourth order astigmatism, and quadrafoil** due to surgery and during wound healing.

- **Changes in third, fourth, fifth and sixth order aberrations** due to surgery and during wound healing.
- **Total and corneal aberrations**: Correlating changes in total aberrations measured with the aberrometer with corneal aberrations calculated on corneal topography data.

In the following plots of aberrations in human eyes, we use the standard deviation of the population in the Whitaker study as error bars and plot the error bars for the pre-op, 1 week post-op, and 12 months post-op data. The magnitude of the standard deviation for all post-op exams is about the same. The charts for all higher order aberrations or aberration groups were plotted on the same scale to give an idea about their magnitude relative to each other. For selected aberrations, we conducted a two-tailed Student T-test to compare the aberrations at different visits.
Changes in Lower Order Aberrations

We start our analysis of ocular aberrations with lower order aberrations. These aberrations are defocus and astigmatism. Figure 89 shows the lower order aberrations for the pre-op and post-op exams plotted over increasing pupil diameter.

Figure 89: Lower order aberrations plotted over different pupil sizes for the pre-op and follow-up visits.

Figure 89 shows that overall refractive surgery corrects the pre-op lower order aberrations. The post-op data show some fluctuation between the different visits. Due to surgery, the lower order aberrations have decreased at the 1 week post-op visit and then stay constant or increase slightly until the 3 months visit. The lower order aberrations at the 6 months visit are even lower than at the 1 week visit. At the 12 months visit, they
have increased back to higher values. Figure 90 shows lower order aberrations plotted over time for a 6mm pupil size. The curve shows the behavior that we have just described. The pre-op value of about 4 microns for lower order aberrations is not shown in this chart, only wound healing is shown. During wound healing, there is a slight increase in lower order aberrations between the 1 week and 3 months visits, a sudden, temporary decrease at the 6 months visit, and an increase to even higher values at the 12 months visit.

Figure 90: Lower order aberrations plotted over time during wound healing.

The temporary change in lower order aberrations at the 6 months follow-up visit looks very familiar. We had encountered the same behavior when we were analyzing the total corneal power (Figure 66). We can see the same behavior with time in both measurements of the refraction of the eye based on lower order aberrations and based on corneal topography.
The plots in Figure 90 and Figure 66 show that there is a general regression in refraction, i.e. a myopic shift, with time after surgery. This trend was also visible in the analysis of manifest refraction. Our data show a temporary relapse in the regression at the 6 months visit. We do not currently have an explanation for this phenomenon. While we see this relapse at the 6 months visit in the lower order aberrations and corneal power plots, it is not visible in the manifest refraction data.

The plots for lower order aberrations and corneal power do not seem to level out after some time after surgery. This might be a serious problem with LASIK refractive surgery. There is a chance that the regression continues with time.

Figure 91: Changes in refraction, calculated from lower order aberrations plotted over the pre-op manifest refraction.
Figure 91 shows the changes in refraction due to surgery plotted over the pre-op manifest spherical equivalent power. The data were calculated from the measurement of lower order aberrations (i.e. sphere and cylinder). This chart corresponds to the data presented in Figure 53, where we plotted the same changes in refraction measured as manifest refraction. The measurements of lower order aberrations correspond to the measurements of manifest refraction. Bland-Altman analysis of the data shows a bias of 0.05 D and a 95% confidence interval of 1.30 D. If we take into account the bias of 0.29 D determined when comparing aberrometer measurements with manifest refraction, we achieve a bias of 0.34 D which matches the bias of 0.35 D measured with manifest refraction. The confidence interval is in the same order as the confidence interval of the measurement of manifest refraction of 1.16 D. This again indicates that our measurements of lower order aberrations are both accurate and reliable.
Changes in Spherical and Higher Order Non-Spherical Aberrations

Figure 92 shows the spherical aberration for the different visits plotted over time. The spherical aberration pre-op increases with pupil diameter. The dependence on pupil diameter becomes even more emphasized in the post-op exams where we encounter grossly elevated spherical aberration. The amount of spherical aberration for different post-op exams is almost constant. Only at the 6 months visit, we see a temporary decrease in spherical aberration. This behavior at 6 months corresponds to the behavior seen in the lower order aberrations.

Figure 92: Spherical aberration plotted over different pupil sizes for the pre-op and follow-up visits.

In order to verify that the decrease in spherical aberration at the 6 months visit is not an artifact caused by our sampling, we limited the data that were used in this analysis to
eyes that had been examined at all consecutive visits. We also included the eyes of a subject that was examined at all visits up to 3 months and then dropped out. On the other hand, we did not include the eyes of a subject that, for example, missed the 3 and 6 months follow-up visits but returned for the 12 months visit.

Figure 93: Higher order non-spherical aberrations plotted over different pupil sizes for the pre-op and follow-up visits.

Figure 93 shows the higher order non-spherical aberrations calculated for different pupil diameters at the different post-op visits. In general, we can see the same trend as in the previous charts for lower order aberrations and spherical aberration. The amount of aberrations increases with surgery and is highest at the 1 week post-op visit. It then decreases until, at the 6 months visit, it reaches values even below the pre-op values. It then increases again for the 12 months visit.
Figure 94 shows spherical aberration and higher order non-spherical aberrations for a 6 mm pupil diameter plotted over time. Refractive surgery causes an increase in both spherical and higher order aberrations. During wound healing, we can see a trend of decreasing aberrations with time, reaching its low point at the 6 months visit. Between the 6 and the 12 months visits, the aberrations increase again, reaching values even higher than the 1 week post-op values.

![Graph showing spherical and higher order non-spherical aberrations](image)

Figure 94: Spherical aberration and higher order non-spherical aberrations for a 6mm pupil plotted over time.

The change in spherical and non-spherical aberrations between the pre-op and the 1 week post-op visits are statistically significant ($p < 0.001$, 6mm pupil). While the changes between the 1 week and the 12 months visits are not significant for both spherical and non-spherical aberrations, the change between the 3 months and 6 months as well as the change between the 6 months and 12 months visits are statistically significant ($p < 0.001$). All other changes between consecutive visits are not significant.
Change in Aberrations for a 6mm Pupil  
**Pre-op vs. 1 week Post-op**

- **Spherical Aberration**
- **Higher Order Non-Spherical**

Figure 95: Changes in spherical aberration and higher order non-spherical aberrations plotted over pre-op spherical equivalent power.

Figure 95 shows the changes in aberrations due to surgery measured at a 6mm pupil. The solid lines are the linear fit for spherical aberration (blue) and higher order non-spherical aberration (red). The change in spherical aberration is dependent on the pre-op spherical equivalent power. The average change is positive, indicating that the laser refractive surgery increases the amount of spherical aberration. The amount of spherical aberration is larger for larger corrections. The amount of increase of spherical aberration is proportional to the amount of correction. This dependence of increased spherical aberration confirms findings of other studies [33], [34] and will be discussed in more detail later. For higher order non-spherical aberrations, we cannot find a dependence on refractive correction.
In Figure 95, both spherical aberration and higher order non-spherical aberrations are widely scattered. This scatter can be caused by measurement uncertainties or by actual fluctuations in the aberration structure of the human eye. When we analyzed the changes in aberration measurements in the time period after surgery, we found the same wide scatter in the changes. Because this scatter could be due to actual changes in the eyes due to wound healing as well as due to measurement uncertainties, we cannot conclude what is the cause for the wide scatter of aberration measurements. The scatter in the aberrations measured with the aberrometer is smaller than the scatter in corneal aberrations calculated based on measurements of corneal topography.
Statistical Analysis of Changes During Wound Healing

In the previous two sections, we have found indications of changes in lower and higher order aberrations during wound healing between 1 week and 12 months post-op. To analyze these changes more thoroughly, we performed a statistical analysis of the changes between the 1 week and the 6 months post-op visits and between the 6 months and the 12 months visits for both lower and higher order aberrations. We calculated lower and higher order aberrations for a single eye of every subject that was examined at 1 week, 6 months, and 12 months post-op. Aberrations were calculated for a 5.5mm pupil diameter. The limitations to one eye per subject, the pupil diameter, and the requirement that we have exams for all three visits left us with 28 eyes (24 OD, 4 OS) that are included in the analysis. Lower order aberrations and higher order aberrations were calculated according to Table 17, i.e. lower order aberrations contain defocus and astigmatism; higher order aberrations contain all aberrations of 3rd through 6th Zernike order.

**Lower Order Aberrations**

Between 1 week and 6 months post-op, the lower order aberrations in this group of eyes decreased by -0.158 ± 0.288 microns. A paired, two-tailed T-test showed statistical significance with p = 0.0097. The sign test showed that 58% of the changes were negative. Figure 96 shows a histogram of the changes in lower order aberrations between 1 week and 6 months post-op.
Lower Order Aberrations
1 week vs. 6 months Post-op

Figure 96: Histogram of changes in lower order aberrations between 1 week and 6 months post-op.

Between 6 months and 12 months post-op, the lower order aberrations increase by $0.232 \pm 0.220$ microns ($p = 0.0007$). The sign test showed that 77% of the changes were positive. Figure 97 shows the histogram of the changes in lower order aberrations between 6 and 12 months post-op.

Figure 97: Histogram of changes in lower order aberrations between 6 and 12 months post-op.
Higher Order Aberrations

Between 1 week and 6 months post-op, the higher order aberrations in this group of eyes decreased by \(-0.143 \pm 0.132\) microns. A paired, two-tailed T-test showed statistical significance with \(p < 10^{-5}\). The sign test showed that 88\% of the changes were negative. Figure 98 shows the histogram of the changes in higher order aberrations between 1 week and 6 months post-op.

![Histogram of changes in higher order aberrations between 1 week and 6 months post-op.](image)

Between 6 months and 12 months post-op, the higher order aberrations increase by 0.122 \(\pm 0.125\) microns \((p < 10^{-5})\). The sign test showed that 92\% of the changes were positive. Figure 99 shows the histogram of the changes in higher order aberrations between 6 and 12 months post-op.

The statistical analysis verifies that significant changes in both lower and higher order aberrations occur during wound healing. The aberrations decrease until they reach a low
point at 6 months after surgery. Between 6 and 12 months post-op, the amount of aberrations increases. Since we see significant changes in aberration structure between 6 and 12 months post-op, it is possible that such variations could continue beyond 1 year post-operatively. Longer follow-up studies are needed to determine when and if the eye stabilizes. Further investigation will have to be conducted to determine the changes in aberrations for longer time periods after laser refractive surgery.

![Changes in Higher Order Aberrations](change_aberrations.png)

**Figure 99:** Histogram of changes in higher order aberrations between 6 and 12 months post-op.

At this point, we have to note again that the aberrometer was rebuilt between the 6 and 12 months follow-up visits like we have explained earlier. Therefore, there is a possibility that systematic errors in the measurements with the aberrometer were introduced by this change in instruments during the course of the study. Further research would therefore also verify results obtained in this study.
Higher Order Aberrations, Pupil Diameter, and Contrast Sensitivity

In the chapter about pupil diameter, we started to correlate the development of contrast sensitivity after surgery with the changes in pupil diameter in the same time frame. Aberrations have a direct impact on contrast sensitivity. The more aberrations present, the lower the contrast sensitivity. For a given corneal shape, the aberrations are larger for larger pupil diameters as could be seen in Figure 92 and Figure 93. For the purpose of illustrating the changes occurring with time, we plot the $RSS$ of all higher order aberrations over their pupil size for the pre-op, as well as the 1 week, 6 months, and 12 months post-op visits, i.e. the visits where we had found statistically significant changes to occur.

![Higher Order Aberrations](image)

Figure 100: Higher order aberrations and the aberrations at the different visits for the average pupil diameter. The markers indicate the higher order aberrations of the average eye in our study at the average pupil diameter for that visit.
Aberrations are functions of the shape of the optical surface and of the pupil diameter. In our study, we noticed that the shape of the anterior and posterior corneal surfaces change due to surgery and during wound healing. Every single curve in Figure 100 corresponds to a different shape (at different visits). Aberrations are also strongly dependent on pupil size as was shown in the previous charts.

Figure 100 indicates the aberrations of the average eye in the Whitaker study for different visits. The aberrations for the average pupil diameter are indicated for every visit. Before surgery, the average eye in our study had a pupil diameter of 5.75 mm and contained 0.375 microns of higher order aberrations (pre-op marker on the blue curve). Surgery induces aberrations into the cornea and the pupil size of the eye increases as a response to surgery. The average eye now has a pupil diameter of 6.35 mm and contains 0.845 microns of higher order aberrations (1 week marker on the red curve). This is more than twice the pre-op value. At the 6 months visit, the pupil diameter has decreased back to 5.75 mm and the higher order aberrations have decreased back to pre-op values (6 months marker on the pink curve). Between the 6 and 12 months exams, the shape of the cornea changes again and we now have elevated aberrations of 0.560 microns at a pupil diameter of 5.75 mm (12 months marker on the green curve).

The changes in higher order aberrations can be correlated to the changes in contrast sensitivity as plotted in Figure 55. The increase of average higher order aberrations between the pre-op and the 1 week post-op exams corresponds to the strong drop in contrast sensitivity at the 1 week post-op exams. The return to pre-op aberrations level at
the 6 months visit corresponds to the return to pre-op contrast sensitivity, and the drop at the 12 months visit can also be seen in both increased higher order aberrations and contrast sensitivity. The correlation between the decrease in contrast sensitivity and the increase in ocular aberrations agrees with findings by Seiler et al. [30].

We have shown in two independent measurements, i.e. aberrometry and contrast sensitivity that a temporary change happens at 6 months post-op. Plotting the changes in contrast sensitivity versus the changes in total higher order aberrations does not show a linear correlation. This is due to the fact that there is no linear relationship between aberrations and contrast sensitivity. Another problem with presenting the aberrations as one single number is that the wavefront error consists of different aberrations like spherical aberration, coma, etc. that have a different impact on the modulation transfer function (MTF) of the eye and therefore on the contrast sensitivity.
Changes in Coma, Trefoil, Fourth Order Astigmatism, and Quadrafoil

In this chapter, we present the charts of coma, fourth order astigmatism, and quadrafoil plotted over different pupil sizes for the different visits. All charts are plotted on the same scale.

Figure 101 shows coma. The amount of coma increases after surgery and then drops until it reaches the lowest amount at the 6 months visit. It then increases for the 12 months visit. This is the same behavior as seen in Figure 93 for higher order nonspherical aberration.

Figure 102 shows trefoil. There is no significant change in the amount of trefoil during wound healing. Figure 103 shows fourth order astigmatism. Fourth order astigmatism shows the same behavior during wound healing as coma.

Figure 104 shows quadrafoil. Quadrafoil also shows the behavior that we could observe for coma and fourth order astigmatism. The amount of aberrations is largest for coma and about the same for trefoil, fourth order astigmatism and quadrafoil.

After spherical aberration, coma is the aberration that shows the largest increase after surgery. Mrochen et al. [46] have found that subclinical decentration of less than 1 mm can induce the amounts of coma we see in our patient group. In our analysis, we can also see large changes in coma during wound healing.
Coma

Figure 101: Coma plotted over different pupil sizes for the pre-op and follow-up visits.

Trefoil

Figure 102: Trefoil plotted over different pupil sizes for the pre-op and follow-up visits.
Fourth Order Astigmatism

Figure 103: Fourth order astigmatism plotted over different pupil sizes for the pre-op and follow-up visits.

Quadrafoil

Figure 104: Quadrafoil plotted over different pupil sizes for the pre-op and follow-up visits.
Changes in Third, Fourth, Fifth, and Sixth Order Aberrations

In this chapter, we present the aberrations in groups of their radial order. Figure 105 shows the third order aberrations, i.e. coma and trefoil. The behavior of the third order aberrations is similar to the behavior of higher order non-spherical aberrations presented earlier.

Figure 106 shows the fourth order non-spherical aberrations. In this group, we again see the same behavior, but on a much smaller scale. Figure 107 shows the fifth order aberrations and Figure 108 the sixth order non-spherical aberrations. In both groups, we cannot see any significant changes due to surgery or during wound healing. The amount of aberrations is very small compared to the confidence interval of ±0.011 microns for higher order aberrations coefficients. The changes in aberrations during surgery and wound healing decrease with increasing order.

Based on the charts of higher order aberrations presented here and taking into account the very low amounts of aberrations present in the groups of fifth and sixth order aberrations, we can conclude that the representation of the wavefront error of the human eye with Zernike polynomials up to 6th order are sufficiently accurate. Adding higher order terms will not increase the accuracy of the representation.
Third Order Aberrations

Figure 105: Third order aberrations plotted over different pupil sizes for the pre-op and follow-up visits.

Fourth Order Non-Spherical Aberrations

Figure 106: Fourth order non-spherical aberrations plotted over different pupil sizes for the pre-op and follow-up visits.
Figure 107: Fifth order aberrations plotted over different pupil sizes for the pre-op and follow-up visits.

Figure 108: Sixth order non-spherical aberrations plotted over different pupil sizes for the pre-op and follow-up visits.
Total and Corneal Aberrations

The aberrometer measures the total aberrations of the human eye. Based on topography maps of the anterior and posterior corneal surfaces, we have previously calculated corneal aberrations. With both measurements, we had found that laser refractive surgery increases the aberration contents of the eye. We can now compare the two measurements directly in order to see if both measurements quantitatively show the same changes in aberration due to surgery and wound healing.

Figure 109: Change in aberrations between pre-op and 12 months post-op. Total aberrations were measured with the aberrometer, corneal aberrations were calculated based on topography measurements. The error bars for the change in total aberrations are the standard deviation of the aberrometer measurements 12 months post-op.

Figure 109 shows the increase in aberrations between pre-op and 12 months post-op measured with the aberrometer (total aberrations) and topographer (corneal aberrations).
The increase in aberrations measured with the two independent instruments show very similar results. The differences that can be seen are still less than one standard deviation of the aberrometer measurement. No error bars for the corneal aberrations are available. The two measurements show a very close correlation when comparing the pre-op to the 12 months post-op aberration contents of the eye.

In Figure 109, we have compared changes in aberrations. We now look at the absolute amount of aberrations measured with the aberrometer and the topographer before and at all follow-up visits. The total aberrations of the human eye are the sum of the aberrations introduced at every optical interface in the human eye. There are four interfaces: the anterior and posterior corneal surfaces and the anterior and posterior surfaces of the crystalline lens. We can calculate the aberrations of the crystalline lens by subtracting the corneal aberrations from the total aberrations [47], [48], and [49]. This can be done for individual aberrations or groups of aberrations. We chose to compare spherical aberration and coma as individual aberrations and the total higher order aberrations as a group of aberrations. The following figures show charts of both corneal and total aberrations plotted over time. The difference between the two curves can be associated to aberrations in the crystalline lens. Error bars are plotted for the measurements of total aberrations with the aberrometer. No error bars are available for the measurements of corneal aberrations. Previous results had shown a large scatter for measurements based on corneal topography. We therefore expect the error bars for the corneal aberrations to be larger than for the total aberrations.
Figure 110: Spherical aberration plotted over time measured with the aberrometer (total) and calculated from corneal topography (cornea).

Figure 110 shows spherical aberration measured with the aberrometer and calculated from corneal topography. Both curves show an increase in spherical aberration as a result of surgery. The difference between total and corneal aberrations is constant for most of the post-op measurements. At the 6 months follow-up visit, we see a decrease in total spherical aberration that is not shown in the corneal spherical aberration. Unlike with the lower order aberrations, we cannot confirm with certainty that the two independent measurements show the same trend during wound healing.

The values for the corneal spherical aberration are always higher than for the total spherical aberration, indicating that the crystalline lens contains negative spherical aberration. This is consistent with reports by Artal et al. [47] and Marcos et al. [48]
Figure 111: Coma plotted over time measured with the aberrometer (total) and calculated from corneal topography (cornea).

Figure 111 shows the total and corneal coma plotted over time. The overall behavior of the two curves is quite similar during wound healing. The amount of coma for both measurements decreases during wound healing, reaching the lowest amount at the 6 months follow-up visit. After that, the amount of coma increases again. The corneal coma is within the range of the error bars of the aberrometer measurements.

Figure 112 shows the total and corneal higher order aberrations. The higher order aberrations contain spherical aberration. The behavior of higher order aberrations is dominated by the changes in spherical aberration. While the corneal higher order aberrations level out after the 1 month visit, we see a decrease in total higher order aberrations up to the 6 months visit and an increase thereafter.
Figure 112: Higher order aberrations plotted over time measured with the aberrometer (total) and calculated from corneal topography (cornea).

Figure 113: Higher order non-spherical aberrations plotted over time measured with the aberrometer (total) and calculated from corneal topography (cornea).
Figure 113 shows higher order non-spherical aberrations plotted over time. We can see that the measurements of corneal aberrations are in the range of the error bars of the aberrometer measurement. We can conclude that both measurements agree nicely with the measurements of higher order non-spherical aberrations.

Comparing the total aberrations measured with the aberrometer with the corneal aberrations that were calculated based on corneal topography measurements, we find that the overall changes measured with both instruments achieve similar results. The corneal aberrations are higher than the total aberrations both before surgery and during the wound healing period. This indicates that the crystalline lens contains negative spherical aberration. A strong increase in spherical aberration directly after surgery is seen. The temporary decrease in spherical and higher order aberration at the 6 months visit that is apparent in the measurements of spherical aberration with the aberrometer cannot be seen in the measurements of corneal spherical aberration, indicating that the measurement of corneal aberrations is not sensitive enough to detect these changes. The amounts of coma and higher order non-spherical aberrations are very similar for both measurements. The fluctuations of the measurements with time lie within the measurement uncertainty.
Discussion

We have analyzed the impact of laser refractive surgery (LASIK) on the ocular aberration structure of the eye. In the following we will review a number of studies that have reported similar results. The studies include aberration studies in the normal population, post-LASIK eyes and post-PRK eyes.

PRK (Photorefractive keratectomy) uses the same techniques for correcting refractive errors as LASIK, only that no flap is cut, and the tissue is ablated at the front surface of the anterior cornea, instead of inside the stroma. Pallikaris et al. [21] have reported that the cutting of the flap introduces higher order aberrations by an average of 0.1 microns. Main aberrations introduced by the flap-cutting were spherical aberration and coma. Schwiegerling et al. [53] have found a subtle change in the corneal shape due to the cutting of the flap. On the other hand, LASIK is supposed to have higher refraction stability after surgery than PRK. Based on these differences, only limited comparisons between results of PRK and LASIK can be conducted.

Aberrations in Normal Eyes

Thibos et al. [29] reported on the aberration structure of a normal population of healthy eyes. In accordance with their results, we found in our pre-op data that the average of the individual Zernike coefficients for all eyes was almost zero with a large variability between eyes. Our results also agree in the fact that the only non-zero Zernike coefficient is \( a_{8,0} \) for spherical aberration with 0.1 microns at a 6 mm pupil. In our analysis of aberrations, we had not looked at individual Zernike coefficients, but instead
we had looked at individual aberrations or groups of aberrations. When combining different Zernike coefficients using the RSS calculation, we get a better indicator for the wavefront error present in the eye because we now analyze the magnitude of the aberration instead of two orthogonal components. For example, the impact of 1 micron of coma on vision will be the same, no matter at what angle the coma is present. Magnitude and angle of coma is determined by the Zernike coefficients $a_{3,-1}$ and $a_{3,1}$. If we calculate the coefficients at a large number of randomized angles and then average the coefficients, we will find the average for both coefficients to be zero, although the average magnitude of coma is 1 micron. Thibos et al. found large variations in the aberration contents between individual eyes in the population, but no significant variations were found in five consecutive days. The large variations in the aberrations between individual eyes are confirmed by the large scatter that we have found in almost every scattergram that we have analyzed and by the large standard deviations we determined for our measurements of aberrations. The temporal changes in the aberration structure of normal eyes that the authors reported were only tested in three individuals over five days which gives very limited reliability of the results. Thibos, one of the co-authors of the above papers, reports in another paper [32] a large temporal variation in aberrations of individual eyes. More research will have to be conducted to find out how large the variations in aberrations in individual eyes are on a short and long-term scale.

Porter et al. [36] conducted a large scale study to measure the monochromatic aberrations of normal human eyes. Their results in aberrations agree with our pre-op aberration contents in both average and standard deviation.
Cheng et al. [31] related the monochromatic aberrations of normal eyes to the eye’s refractive error. They measured 124 eyes with a Shack-Hartmann aberrometer and found that the amount of wavefront aberration in these eyes is not correlated to the refractive error. Our measurements confirm these findings. We find the same large scatter and the same range of values as reported in their paper. Figure 114 shows the scattergram of higher order aberrations plotted over the pre-op spherical equivalent power in our study.

Figure 114: Higher order aberrations plotted over the pre-op spherical equivalent power. The aberrations included are 3rd through 6th Zernike order.

The studies quoted above confirm that our Shack-Hartmann wavefront sensor is working with the required accuracy and repeatability. They also confirm our findings that the main higher order aberration present in normal eyes is positive spherical aberration. We also find confirmation for our finding that the aberrations are very widely scattered. Some further investigations might still be necessary to determine what fraction of the
scatter is due to measurement uncertainties and what fraction is due to variability of aberrations in a large population of human eyes.

**Aberrations Induced by PRK**

Seiler et al. [30] found an increase in higher order aberrations following PRK. They generally show the same trend of increasing aberrations with increasing pupil diameter both before and after surgery. Their absolute values for 6 and 7mm pupils are lower than our average values for the pre-op and higher for the post-op but, are within our error margins. We have to keep in mind that they were analyzing a different surgery. Also, their study included only 15 eyes which can further explain the differences.

**Aberrations Induced by LASIK**

Boxer Wachler et al. [33] analyzed the change in spherical aberration in 76 eyes pre-op and 3 months after LASIK surgery. Their calculations are based on topography measurements of the anterior corneal surface. They found an increase in spherical aberrations after refractive surgery. They also found the increase to be larger for larger corrections. While we had found the same increase in corneal aberrations post-op, we did not find a functional dependence on pre-op manifest refraction, or attempted correction (see Figure 75). Our measurements of corneal aberrations based on topography measurements have a very large variability that might cover any functional dependence of induced aberrations for the number of measurements that we have analyzed. On the other hand, we did find a functional dependence of the spherical and non-spherical higher
order aberrations on the attempted correction when measured with the aberrometer. An improved algorithm to determine corneal aberrations of both the anterior and posterior corneal surfaces might decrease the variability of our measurements and reveal the dependency of corneal aberrations on refractive correction.

Oshika et al. [34] analyzed the amount of spherical aberrations in 100 eyes pre-op and 1 month post-LASIK. Their results were based on corneal topography and agreed with the ones mentioned above. It should be noted here that the in the study reported by Oshika [34] the same laser system was used as in our Whitaker study.

Moreno-Barriuso et al. [35] evaluated the total aberrations in 22 eyes 2 months post-LASIK and found a statistically significant increase in spherical aberration. The numbers reported in this study agree with the numbers found in our study. They also found a strong functional dependence of induced spherical aberrations on pre-op manifest refraction.

**Summary**

The differences between the above mentioned studies that evaluated aberrations post LASIK and the Whitaker study are that we have analyzed at larger numbers of eyes and that we have evaluated the changes in aberrations during wound healing between 1 week and 12 months post-op. While the increase in spherical aberration and higher order aberrations in our study agrees with the above mentioned studies, this is the first study that analyzed aberrations during a 12 months follow up period. We have not found
reports of the changes in aberrations similar to what we saw during the 12 months following surgery in our population.

While we could statistically confirm the decrease in average aberrations at the 6 months post-op, we cannot confirm increase in aberrations between the 6 and 12 months follow-up visit. While the data show a statistically significant change, part of it might be due to the fact that we have rebuilt the aberrometer between the 6 and 12 months follow-up visits. An argument that supports our findings of continued changes throughout wound healing is that we found the same temporary change at 6 months in the independent measurements of contrast sensitivity, ocular aberrations, and corneal power.
Summary

The Whitaker study assessed visual performance of about 150 eyes before and after laser refractive surgery (LASIK). A number of measurements were taken at every follow-up visit. These measurements quantify the changes that occur due to surgery and during wound healing. 48 subjects were female, 41 subjects male. The pre-op manifest refraction range was up to -9.25 D myopia, averaging at -4.65 ± 1.79 D spherical power. Cylinder power was up to +3.25 D, averaging at 0.79 ± 0.72 D cylinder power.

Analyzing visual acuity after surgery, we found that the uncorrected visual acuity directly after surgery was lower than the best-corrected visual acuity before surgery. During wound healing, the visual acuity improved slightly. No changes to visual acuity occurred after 6 months. Laser refractive surgery eliminates the need for corrective glasses, but the uncorrected visual acuity after surgery is slightly worse than the best spectacle corrected visual acuity before surgery.

Uncorrected visual acuity after surgery improved up to the 3 months follow-up visit and stayed constant after 6 months. The average visual acuity after 12 months was 0.07 logMAR or about 20/25.

Average manifest refraction before surgery was -4.47 D sphere and 0.80 D cylinder. The correction achieved at 12 months was -0.61 D sphere and 0.41 D cylinder. A slight undercorrection of -0.5 D was attempted. Bland-Altman analysis of the achieved correction compared to the pre-op manifest refraction found a bias of -0.35 D and a 95%
confidence interval of 1.16 D. A slight regression of refraction during wound healing was found that was higher for higher pre-op myopia. The accuracy of the measurements of manifest refraction is limited by the presentation of the prescription in positive cylinder notation, which only has an accuracy of a quarter diopter.

Contrast sensitivity decreased as a result of surgery. After surgery, contrast sensitivity reaches the lowest levels and slowly increases until it reaches almost pre-op values at the 6 months post-op exam. A decrease in contrast sensitivity occurred between the 6 months and the 12 months follow-up visits. The eyes with high myopia of less than –5 D spherical equivalent power generally had lower contrast sensitivity than the eyes with mild myopia of up to -5 D spherical equivalent power.

Pupil diameter increased significantly due to surgery. In the first 3 months after surgery, the pupil diameter slowly decreased. The pupil diameter returned to pre-op values between 3 and 6 months after surgery.

Pachymetry measurements showed that the center corneal thickness increased during wound healing. The increase leveled out after about 6 months post-op. The increase in center corneal thickness was greater for eyes with high myopia and less for eyes with mild myopia. The largest increase occurred in the first three months.

The radius of curvature of the anterior and posterior corneal surfaces changed due to surgery. As a result of surgery, the anterior corneal surface after surgery was flatter, while there was a steepening of the posterior corneal surface. No statistically significant
changes to the anterior radius of curvature during wound healing were found, but the posterior corneal surface flattened significantly between 1 week and 1 month post-op.

Changes in corneal power calculated from the topography measurements correlated to the changes in manifest refraction. A general regression during wound healing of about 0.4 D at the 12 months follow-up visit was found. We also found a temporary relapse in corneal power based on the topography measurements at the 6 months post-op visit. This temporary improvement was not visible in the measurements of manifest refraction. The analysis of changes in corneal power due to surgery based on corneal topography showed a wider scatter, and therefore a higher uncertainty than the analysis of the changes based on measurements of manifest refraction.

Corneal aberrations, calculated based on the topography measurements, showed an increase in spherical and higher order aberrations after surgery for both the anterior and posterior corneal surfaces. After 1 month post-op, the aberrations did not change. Corneal aberrations were calculated based on the averaged topographies. Therefore, a statistical analysis of the changes was not possible. Analysis of aberrations of the anterior corneal surface showed a large scatter of the measurements of individual eyes.

The conic constant of both anterior and posterior corneal surfaces changed due to surgery and stayed constant after 1 month post-op. The average anterior corneal surface changed from a prolate to an oblate ellipsoid. The posterior corneal surface changed from a prolate ellipsoid to a hyperboloid. The changes in conic constant due to surgery and
wound healing were dependent on the pre-op manifest refraction. The higher the prescription before surgery, the larger the changes in conic constant.

Laser refractive surgery decreased the amount of lower order aberrations because it corrected defocus and astigmatism. Changes in lower order aberrations measured with the aberrometer were correlated to changes in lower order aberrations measured with corneal topography. The analysis of the changes in refractive error due to surgery with the aberrometer determined the same accuracy and repeatability as measurements of manifest refraction. During wound healing, the amount of lower order aberrations decreases significantly until 6 months after surgery. Between the 6 and 12 months post-op visits, the amount of lower order aberration increases again.

Laser refractive surgery introduced higher order aberrations, mainly spherical aberration and coma. The increase in higher order aberrations due to surgery is statistically significant. We noticed a temporary decrease in higher order aberrations between the 3 and 6 months post-op visits and an increase in higher order aberrations between 6 and 12 months after surgery. This temporary change was statistically significant. Changes in contrast sensitivity due to surgery and during wound healing could be explained by changes in higher order aberrations and pupil diameter.
CHAPTER 6

CUSTOMIZED EYE MODEL

Customized Refractive Surgery

In the previous chapter, we have presented the changes to the ocular aberration structure due to surgery and during wound healing. New laser systems have become available that will allow customized refractive surgery for every individual eye [42], [43], [44], and [54]. Two different approaches have been proposed to create customized ablation patterns based either on wavefront measurements (aberrometry) or on corneal topography [54]. While aberrometry measures the total aberrations of the eye, including aberrations from the cornea and the lens, corneal topography measures only the aberrations of the cornea and not of the crystalline lens. Because of aberration balancing between the cornea and the crystalline lens in the normal eye [47], [48], [49], the corneal aberrations alone are not sufficient to determine the level of correction that is necessary.

Aberrometry, on the other hand, provides measurements of the aberrations of the entire eye. This means that we can measure the total aberrations and provide correction for them. While this has been done successfully in astronomical telescopes by introducing deformable mirrors that contain the corrections, creating the corrective pattern directly on the cornea has not yet been successful. One of the reasons why current customized refractive surgery does not achieve the desired results is a biomechanical
corneal change due to surgery that is currently not completely understood or predictable [55]. Another problem specific to LASIK is the cutting of the flap. It has been shown that cutting the flap induces aberrations [21] and changes to the corneal structure [53]. From an optical engineering point of view, another reason might be that the eye is a complex optical system, and we cannot just change the curvature of one or two surfaces and expect the aberration balancing in the system to remain unchanged.

Laser refractive surgery also has to take into account the changes to the aberration structure due to accommodation. Recent studies have shown that the aberration content of the crystalline lens changes during accommodation. Ninomiya et al. [38] have measured aberrations in 33 eyes of 33 young adults during 3 diopters of accommodation and found that the amount of spherical aberrations for a 6mm pupil decreases from 0.11 ± 0.10 microns non-accommodated to 0.00 ± 0.16 microns accommodated. Their results suggest that during accommodation, the crystalline lens induces negative spherical aberrations. Krueger et al. [45] have also found accommodation to induce negative spherical aberrations. Artal et al. [52] found that both coma and spherical aberration change with accommodation. Based on these results, it might not be advisable to correct all spherical aberrations in the non-accommodated human eye.

A solution for these issues is the creation of a Customized Eye Model that contains both measurements of corneal topography and aberrometry. With such a model, we can characterize corneal, lenticular and total aberrations, and use optical design software to calculate the ideal anterior corneal shape for best optical performance. This model can be
extended to include different states of accommodation. In the following sections, we will present and evaluate Customized Eye Models that include both pre- and post-op measurements. While this analysis might not be suitable for refractive surgery because we analyze eyes that already underwent surgery, this method provides us with a large number of measurements of the same eyes in different states. We can use these measurements to validate the Customized Eye Model.

One of the results of the Whitaker study was that significant changes to the biomechanical structure of the eye are induced by surgery. If we build a Customized Eye Model based on pre-op and post-op measurements, we can determine an ablation pattern that corrects for residual higher order aberrations and takes into account the biomechanical changes due to surgery.
The Arizona Eye Model

The design of the customized eye model was based on the Arizona Eye Model [26]. Figure 115 shows a drawing of the Arizona Eye Model. The Arizona Eye Model consists of five surfaces, anterior and posterior corneal surface, anterior and posterior lenticular surface, and retina. The stop (pupil) is located at the anterior lenticular surface.

![Figure 115: The Arizona Eye Model [26].](image)

Table 18 lists the parameters of the Arizona Eye Model as they were entered into the optical design program (Zemax).

<table>
<thead>
<tr>
<th>Surface</th>
<th>Radius of Curvature (mm)</th>
<th>Conic Constant</th>
<th>Thickness (mm)</th>
<th>Refractive Index / Abbe Number</th>
<th>Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior Cornea</td>
<td>7.80</td>
<td>-0.25</td>
<td>0.55</td>
<td>1.3771 56.7067</td>
<td>Stroma</td>
</tr>
<tr>
<td>Posterior Corneal</td>
<td>6.50</td>
<td>-0.25</td>
<td>3.05</td>
<td>1.3374 49.6176</td>
<td>Aqueous</td>
</tr>
<tr>
<td>Anterior Lens</td>
<td>11.03</td>
<td>-4.3</td>
<td>4.0</td>
<td>1.4200 48.0000</td>
<td>Lens</td>
</tr>
<tr>
<td>Posterior Lens</td>
<td>-5.72</td>
<td>-1.17</td>
<td>16.5</td>
<td>1.3360 50.9091</td>
<td>Vitreous</td>
</tr>
<tr>
<td>Retina</td>
<td>-13.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 18: Prescription of the Arizona Eye Model [26].
Tolerancing the Arizona Eye Model

In the chapter about the Whitaker study, we have presented measurements of corneal topography. We have noticed that the measurements are very widely scattered. We have not yet determined whether this scatter is due to variations between individual eyes or due to uncertainties in the measurement. Further research will have to be conducted to determine the accuracy and repeatability of the topography measurements and the Zernike surface presentation, as well as the calculations of the conic constant.

To determine the necessary accuracy of the measurements, we performed a tolerance analysis of the Arizona Eye Model. We analyzed the impact of measurement errors in radius of curvature and conic constant of the anterior and posterior corneal surfaces, corneal thickness, and anterior chamber depth. We were mainly interested in tolerances for the radii of curvature and the conic constants. We did not therefore vary the anterior chamber depth and axial length. We did not analyze tolerances for the crystalline lens because we do not have measurements of the lens.

We first performed an “inverse sensitivity” test. For this test, we define the entities that will be tolerated and define the maximum variation of the given criteria that we can accept. The analysis returns the maximum variation in the selected entities that would create the defined error. We chose the RMS wavefront error as our criteria. For the Arizona Eye Model at a 6mm pupil diameter and 780nm wavelength, the RMS wavefront error is 0.242 microns. This number is slightly lower than our clinical measurements for higher order aberrations, but still shows that the Arizona Eye Model agrees with actual
measurements of human eyes. In the tolerance analysis, we defined a compensator. This compensator is a free parameter that the algorithm can use to minimize aberrations for every configuration that it creates. We chose the distance between the posterior surface of the crystalline lens and the retina as our compensator. We chose to restrict the compensation to a ±0.25 D change in total refraction of the eye. The “inverse sensitivity” algorithm constricted the tolerances of all entities to meet the chosen criteria, which was set at a 10% increase in RMS wavefront error. The resulting tolerances are for a 10% increase in residual RMS wavefront error after correcting paraxial focus in a ±0.25 D range. Table 19 lists the tolerances for radii of curvature and conic constants. The tolerances listed here correspond to the required accuracy of the measurements if we want to build an eye model based on topography measurements. The tolerances for the radius of curvature and the conic constant of the anterior corneal surface are tighter than for the posterior corneal surface.

<table>
<thead>
<tr>
<th></th>
<th>Nominal</th>
<th>Tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radius of Curvature</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior Cornea</td>
<td>7.80</td>
<td>±0.05 mm</td>
</tr>
<tr>
<td>Posterior Cornea</td>
<td>6.50</td>
<td>±0.35 mm</td>
</tr>
<tr>
<td><strong>Conic Constant</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior Cornea</td>
<td>-0.25</td>
<td>-0.23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+0.004</td>
</tr>
<tr>
<td>Posterior Cornea</td>
<td>-0.25</td>
<td>±0.20</td>
</tr>
</tbody>
</table>

Table 19: Tolerances for the Arizona Eye Model for a ±0.25 D refractive error and a 10% increase in RMS wavefront error.

After determining the tolerances in Table 19, a Monte Carlo simulation of 500 eyes was performed. The simulation picked a value for each entity with a normal distribution
inside the tolerance interval. The resulting average RMS wavefront error for the above listed tolerances was 0.256 ± 0.146 microns, i.e. 6% higher than the RMS wavefront error of the nominal Arizona Eye Model. This indicated that we might actually be able to tolerate slightly looser tolerances.

In conclusion, the Arizona Eye Model is most sensitive to errors in the following entities (in order of decreasing influence):

1. Conic constant of the anterior corneal surface.
2. Radius of curvature of the anterior corneal surface.
3. Radius of curvature of the posterior corneal surface.
4. Conic constant of the posterior corneal surface.
Design of the Customized Eye Model

The Customized Eye Model was designed based on the Arizona Eye Model and used measurement data from the Whitaker study presented in the previous chapter. It incorporated all available measurements of optical components in the human eye. We used measurements of the anterior and posterior corneal surface, the central corneal thickness, the anterior chamber depth, and the axial length of the eye.

Measurements of the crystalline lens were not available, but instead we had measurements of the aberrations of the entire eye. Because the total aberrations of the eye are the sum of the corneal aberrations and the aberrations of the crystalline lens, we can calculate, or reverse engineer, the aberrations of the crystalline lens using lens design software.

\[
\text{Total Aberrations} = \text{Corneal Aberrations} + \text{Lens Aberrations} \quad (19)
\]

\[
\text{Lens Aberrations} = \text{Total Aberrations} - \text{Corneal Aberrations} \quad (20)
\]

\[
\text{Corneal Aberrations} + \text{Lens Aberrations} - \text{Total Aberrations} = 0 \quad (21)
\]

The last equation is used in the Customized Eye Model. The corneal aberrations were calculated based on corneal topography, total aberrations were measured with the aberrometer, and we used the lens design software’s default optimization algorithm to calculate the lens aberrations. In the model, we entered the corneal surfaces representing the measurements of corneal topography, and added a phase plate in front of the eye representing the wavefront error of the eye.
To get a more reliable result for the crystalline lens, we incorporated models for the same eye, based on all measurements pre-op and post-op. While refractive surgery and wound healing change the corneal structure, the lens should remain unchanged. We can therefore use the different measurements of the eye and calculate a lens that matches all configurations.

In this analysis, we used the wavefront measurements for a 5.5mm pupil diameter. This is slightly less than the average of 5.7mm pupil diameter in our group of subjects. The entrance pupil diameter in our model was set to 5.4mm. Choosing a slightly smaller entrance pupil diameter than the diameter of the aberration measurements ensures that we do not encounter problems at the edges of the pupil when using non-standard Zernike surfaces in the optical design program.

Our Customized Eye Model is simplified due to the fact that it does not incorporate astigmatism or coma. The model is a rotationally symmetric and contains only defocus and spherical aberrations. The surfaces are described by the radius of curvature and the conic constant, two entities that have been calculated from the corneal topography measurements. The wavefront error contains only defocus and spherical aberration. We first evaluated this model for the averaged data of all eyes in our study and then for a number of individual eyes.

In the Customized Eye Model, we use the basic lens description from the Arizona Eye Model and add a 4th and 6th order asphere to the anterior lens surface to provide variables for the spherical aberration introduced by the lens. If all our measurements were
error-free, we would find a lens that creates zero aberrations with all configurations for an individual eye at the same time. Because of errors in our measurements, the sum of total, corneal, and lens aberrations might not be zero for all configurations simultaneously. We needed a metric to quantify this residual error. Because this error should ideally be very small, the metric that proved useful was the Strehl ratio. The Strehl ratio is defined as the ratio between the height of the diffraction limited point spread function (PSF) and the PSF of the aberrated optical system. The Strehl ratio is reported in percent, 100% being the best possible performance. The Strehl ratio, $SR$, relates to the RMS wavefront error $W(x,y)$ by the following equation.

$$SR = e^{-\left(\frac{2\pi W(x,y)}{\lambda}\right)^2}$$

(22)

Another metric that is useful in this analysis is the peak-to-valley (PV) wavefront error. Different criteria exist to determine what wavefront error is acceptable for the specific application. The Rayleigh criteria is based on how much wavefront error can be tolerated in an imaging system before its effects on image quality are noticeable. The limit determined by Lord Rayleigh was 0.25 waves peak-to-valley. This corresponds to a Strehl Ratio of 80%. In terms of RMS wavefront error we can use the Marechal criteria that states that an RMS wavefront error of $1/14$ of a wave or 0.070 waves can be considered diffraction limited. All three criteria (Rayleigh, Strehl, and Marechal) are practically equivalent [61].
Customized Eye Model for the Average Eye

The Customized Eye Model consisted of conic surfaces for the anterior and posterior corneal surfaces. We created configurations of all six visits, i.e. pre-op, 1 week post-op, 1 month, 3, 6, and 12 months post-op. Adding all measurements from the visits to one model slightly increased the residual error of the individual models sharing the same lens, but showed the validity of the model. Table 20 lists the Strehl ratio, the RMS wavefront error and the peak-to-valley wavefront error for the individual configuration of the customized eye model consisting of the averaged corneal curvatures and the averaged conic constants. While most of the individual configurations achieve very high Strehl ratios of over 96%, the pre-op and the 6 months post-op models do not fit as nicely. The reason for the poorer fit of the lens in the 6 months post-op eye model is the mismatch in measurements of spherical aberration between corneal topography and aberrometry that was shown in the chapter about the Whitaker study.

<table>
<thead>
<tr>
<th></th>
<th>Pre-op</th>
<th>1 week</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SR (%)</strong></td>
<td>89</td>
<td>97</td>
<td>98</td>
<td>98</td>
<td>78</td>
<td>99</td>
</tr>
<tr>
<td><strong>RMS (waves)</strong></td>
<td>0.054</td>
<td>0.029</td>
<td>0.025</td>
<td>0.024</td>
<td>0.079</td>
<td>0.051</td>
</tr>
<tr>
<td><strong>PV (waves)</strong></td>
<td>0.250</td>
<td>0.146</td>
<td>0.116</td>
<td>0.108</td>
<td>0.310</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Table 20: Strehl ratio (SR), RMS wavefront error (RMS), and peak-to-valley (PV) wavefront error for the best fit lens for all six configurations. SR in %, RMS and PV in waves (780nm)

By removing the total wavefront error from the eye model, we created a Customized Eye Model that represented the average eye at each pre-op and post-op visit.
Figure 116: OPD wavefan plots for pre-op, 1 week, and 1 month post-op.
Figure 117: OPD wavefan plots for 3, 6, and 12 months post-op.
Figure 116 and Figure 117 show the optical path difference (OPD) wavefan plots for the six different configurations corresponding to the different follow-up visits. All six Customized Eye Models use the same model lens. All plots except the pre-op plot have the same scale of ±1.5 waves (wavelength of 780nm, i.e. ±1.17 microns). The pre-op plot shows mainly defocus, which is caused by the refractive error of the eye. The post-op plots show some residual defocus and large amounts of spherical aberration.

We see an increase in spherical aberration at the 6 months visit. This does not match the findings of the Whitaker study that had determined a decrease in spherical aberration at the 6 months post-op visit. This is again due to a mismatch of the measurements of spherical aberration based on topography and with the aberrometer, while the measurements for the other visits agreed closely. At the 12 months post-op visit, the defocus has increased and is now more dominant than the spherical aberration.

The above analysis resulted in a model for the crystalline lens that best fits all configurations. In the next step, we isolate the lens by replacing the optics of the cornea with an aberration free paraxial lens of 23.2 mm focal length. The residual aberrations in the model are now the aberrations of the crystalline lens model. Because we had limited this model to conic surfaces and our wavefront error to defocus and spherical aberration, the only aberration in the crystalline lens is spherical aberration. We found an amount of -0.187 microns of spherical aberration in our model lens. This is in the range of the -0.10 microns reported by Ninomiya [38] and the -0.2 microns reported by Artal [52].
This analysis of the Customized Eye Model has shown that it is possible to calculate the crystalline lens to acceptable accuracy based on the averaged measurements of corneal curvature and conic constants. When incorporating several eye models in one analysis and determining a crystalline lens model that fits all configurations, we get a more reliable result for the crystalline lens.
Customized Eye Model for Individual Eyes

One of the conclusions of the Whitaker study was that the average measurements based on corneal topography give us reasonable results, but the individual measurements are very widely scattered. We have created customized eye models for individual eyes based on their measurements of corneal curvature, conic constant, and wavefront error. For simplicity, we have used only the pre-op and 1 week post-op configurations. We first evaluated the individual Customized Eye Model when using the model lens that we have calculated based on the averaged data in the previous section. We then used the Customized Eye Model to calculate a custom lens for each eye.

<table>
<thead>
<tr>
<th>Eye</th>
<th>Pre-op SEP (D)</th>
<th>SR pre-op (%)</th>
<th>SR post-op (%)</th>
<th>SR pre-op (%)</th>
<th>SR post-op (%)</th>
<th>Spherical Aberration (microns)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>-4.07</td>
<td>89</td>
<td>97</td>
<td>94</td>
<td>95</td>
<td>-0.187</td>
</tr>
<tr>
<td>W0004OD</td>
<td>-2.75</td>
<td>67</td>
<td>48</td>
<td>93</td>
<td>95</td>
<td>-0.112</td>
</tr>
<tr>
<td>W0006OD</td>
<td>-2.875</td>
<td>88</td>
<td>77</td>
<td>97</td>
<td>97</td>
<td>-0.261</td>
</tr>
<tr>
<td>W0011OD</td>
<td>-4.5</td>
<td>26</td>
<td>-</td>
<td>91</td>
<td>91</td>
<td>-0.367</td>
</tr>
<tr>
<td>W0014OD</td>
<td>-4.5</td>
<td>64</td>
<td>16.5</td>
<td>82</td>
<td>82</td>
<td>-0.089</td>
</tr>
<tr>
<td>W0017OD</td>
<td>-3.5</td>
<td>-</td>
<td>35.1</td>
<td>20</td>
<td>20</td>
<td>-0.177</td>
</tr>
<tr>
<td>W0018OD</td>
<td>-2.625</td>
<td>16</td>
<td>64</td>
<td>89</td>
<td>89</td>
<td>-0.080</td>
</tr>
<tr>
<td>W0020OD</td>
<td>-5.75</td>
<td>70</td>
<td>74</td>
<td>76</td>
<td>75</td>
<td>-0.229</td>
</tr>
<tr>
<td>W0025OD</td>
<td>-3.5</td>
<td>96</td>
<td>34</td>
<td>73</td>
<td>73</td>
<td>-0.260</td>
</tr>
<tr>
<td>W0026OD</td>
<td>-2.25</td>
<td>55</td>
<td>21</td>
<td>94</td>
<td>94</td>
<td>-0.076</td>
</tr>
<tr>
<td>W0035OD</td>
<td>-0.875</td>
<td>98</td>
<td>-</td>
<td>50</td>
<td>50</td>
<td>-0.085</td>
</tr>
</tbody>
</table>

Table 21: Strehl ratio (SR) of the average and several individual eye models when using the average lens and when calculating a custom lens.
Table 21 lists the Strehl ratio of the Customized Eye Model for the averaged data, as well as for a custom lens calculated for each individual eye. While the average lens achieves high Strehl ratios with the average eye, it does not work well with individual eyes. The Strehl ratios are very low and these models would not be acceptable. If instead, we calculated a custom lens based on the data in the individual Customized Eye Model, we achieved acceptable Strehl ratios. To verify the validity of the respective custom lenses, we analyzed the spherical aberration of each individual custom lens. The individual results are widely scattered, but are in a reasonable range.

This analysis shows that it is not possible with our current measurements to create a Customized Eye Model for individual eyes when using the averaged lens. When calculating the custom lens based on the pre-op and post-op measurements, we achieve acceptable and reasonable results.

For the design of customized ablation patterns, it causes a problem if we can create the model only based on pre- and post-op data. We would like to be able to create a reliable Customized Eye Model based on pre-op measurements alone. To analyze if this is possible with the eyes listed above, we removed the post-op configuration from the models and calculated the optimum custom lens based on pre-op values. The main characteristic of the lens in this basic model using conic surfaces is spherical aberration. Table 22 lists the spherical aberration of the model lens when calculated based on pre- and post-op data and based on pre-op data alone. The spherical aberration of the
individual model lens varies greatly, while the results for the two different model lenses appear to be close.

<table>
<thead>
<tr>
<th>Eye</th>
<th>Pre-op SEP (D)</th>
<th>Based on pre-op and post-op (microns)</th>
<th>Based on pre-op (microns)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>-4.07</td>
<td>-0.187</td>
<td>-0.175</td>
</tr>
<tr>
<td>W0004OD</td>
<td>-2.75</td>
<td>-0.112</td>
<td>-0.130</td>
</tr>
<tr>
<td>W0006OD</td>
<td>-2.875</td>
<td>-0.261</td>
<td>-0.234</td>
</tr>
<tr>
<td>W0011OD</td>
<td>-4.5</td>
<td>-0.367</td>
<td>-0.348</td>
</tr>
<tr>
<td>W0014OD</td>
<td>-4.5</td>
<td>-0.089</td>
<td>-0.14</td>
</tr>
<tr>
<td>W0017OD</td>
<td>-3.5</td>
<td>-0.177</td>
<td>-0.023</td>
</tr>
<tr>
<td>W0018OD</td>
<td>-2.625</td>
<td>-0.080</td>
<td>-0.039</td>
</tr>
<tr>
<td>W0020OD</td>
<td>-5.75</td>
<td>-0.229</td>
<td>-0.208</td>
</tr>
<tr>
<td>W0025OD</td>
<td>-3.5</td>
<td>-0.260</td>
<td>-0.201</td>
</tr>
<tr>
<td>W0026OD</td>
<td>-2.25</td>
<td>-0.076</td>
<td>-0.107</td>
</tr>
<tr>
<td>W0035OD</td>
<td>-0.875</td>
<td>-0.085</td>
<td>-0.190</td>
</tr>
</tbody>
</table>

Table 22: Spherical aberration of the crystalline lens, calculated based on two configurations (pre-op and post-op) and based on one configuration (pre-op).

The Bland-Altman plot in Figure 118 analyzes the difference in spherical aberration between the two lenses over the mean spherical aberration. The bias, i.e. the average difference, is 0.011 microns; the 95% confidence interval is 0.133 microns. For comparison, the spherical aberration in the average lens was about -0.180 microns. While the bias is acceptable, indicating an error of less than 10%, the confidence interval is too large for our purposes. Further research is necessary to find if refined measurement and analysis techniques for the corneal topography can improve the confidence.
The above analysis can be summarized in the following results:

- It is not possible to use an average model lens to create individual Customized Eye Models; the variations between individual crystalline lenses are large.

- We can create a Customized Eye Model based on individual pre- and post-op measurements and calculate an individual model lens for each eye. In our small sample, we achieved satisfactory results with a Strehl ratio greater than 75% for 8 out of 10 eyes.

- We can calculate a model lens based only on pre-op measurements. The lens that we obtain this way matches the lens that is obtained when using pre- and post-op measurements.
• The Customized Eye Model is highly dependent on the accuracy and repeatability of the measurements of radius of curvature and conic constant of the anterior and posterior corneal surfaces.

• The crystalline lens of the human eye in the non-accommodated state contains negative spherical aberration. The average in our group of eyes was -0.187 microns. The amount of spherical aberration varies greatly between individual eyes, ranging from -0.06 to -0.36 microns.
CHAPTER 7

CUSTOMIZED ABLATION PATTERNS FOR LASER REFRACTIVE SURGERY

In the previous chapter, we have shown that Customized Eye Models can be created based on measurements of topography and aberrations for every individual eye. In this chapter, we use the Customized Eye Model to design Customized Ablation Patterns that can correct for higher order aberrations in the human eye. We first discuss different strategies of customized refractive surgery based on the Customized Eye Model and then show an example Customized Ablation Pattern calculated based on the average measurements from the Whitaker study.

When creating the Customized Eye Model, we have to calculate a model crystalline lens based on corneal topography and aberrometry. This can be done for individual eyes based on pre-op measurements only or based on pre- and post-op measurements. Based on these two different approaches for the Customized Eye Model, there are two different possible approaches for the design of Customized Ablation Patterns.

The first approach is a one-step correction. For this, we build the Customized Eye Model based on the pre-op data. Because we have only one state of the eye, it will be advantageous to collect measurements of the eye at several pre-op visits to make sure that the model is reliable. Based on this model, we can calculate the optimum anterior corneal surface for best visual performance. In general, this approach does not exactly account
for biomechanical changes to the eye, but we can take some average biomechanical changes to the cornea into account by adjusting the radius of curvature and conic constant of the posterior corneal surface. This approach cannot account for changes to the cornea due to the cutting of the flap. Because the biomechanical response of the eye to surgery varies strongly between eyes, we do not expect this approach to be very successful.

The second approach is a two-step correction where we perform two refractive surgeries. The first surgery is a traditional refractive surgery that corrects for the lower order aberrations, i.e. defocus and astigmatism. Large changes to the biomechanical structure of the eye occur based on the strong changes to the cornea due to the cutting of the flap and due to the actual ablation. We assess corneal topography and aberrations before and after surgery and build a Customized Eye Model based on these data. Based on the post-op data, we can then calculate the optimum anterior corneal surface for best visual performance. A second surgery is performed to correct the residual or induced lower and higher order aberrations. The advantage of this approach is that it takes into account the actual biomechanical changes due to the cutting of the flap and due to the ablation. The impact of the second surgery will be much less than the impact of the first surgery and accordingly we expect only minimal biomechanical changes. The next section presents the procedure for a Customized Ablation Pattern in the two-step method.
**Customized Ablation Pattern**

In this section, we present the calculation of a Customized Ablation Pattern based on the Customized Eye Model with conic corneal surfaces. Here, we have calculated and analyzed the Customized Ablation Pattern for the data of the average eye in the Whitaker study, but the same algorithm can be used for individual eyes as well.

Once we have created the Customized Eye Model, we can use the post-op model and optimize the anterior corneal surface to eliminate defocus and spherical aberrations. In this simplified model, the result will be a different conic constant. We also add some higher order aspheric terms, assuming that we can create whichever surface we would like. For the optimization, we used the default merit function and optimization routine provided by the lens design software (Zemax).

Table 23 lists the radius of curvature (ROC), conic constant (CC) and the aspheric coefficients $A_4$ and $A_6$ for the pre-op eye model as well as the real and the ideal post-op eye model. For the post-op eye model, we have chosen the 1 week post-op exam and will ignore changes during wound healing for now.

<table>
<thead>
<tr>
<th>Eye Model</th>
<th>ROC (mm)</th>
<th>CC</th>
<th>$A_4$</th>
<th>$A_6$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-op</td>
<td>7.62</td>
<td>-0.12</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>REAL post-op</td>
<td>8.14</td>
<td>0.20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IDEAL post-op</td>
<td>8.14</td>
<td>-0.43</td>
<td>1.71 $\times 10^{-4}$</td>
<td>-8.00 $\times 10^{-6}$</td>
</tr>
</tbody>
</table>

Table 23: Radius of curvature (ROC), conic constant (CC), and 4th and 6th order asphere coefficients for the pre-op eye model, the real post-op eye model, and the ideal post-op eye model.
The formula for the sagitta of conic surfaces has been described earlier. When adding aspheric terms, the formula for the sagitta $z$ is

$$z = \frac{r - \sqrt{r^2 - (K + 1) s^2}}{K + 1} + A_4 s^4 + A_6 s^6 + ...$$ (23)

where $A_4$ and $A_6$ are the aspheric coefficients and $s$ is the non-normalized radius.

We can now compare the pre-op anterior corneal surface to the post-op surface and determine the height changes in the cornea due to surgery, i.e. the real ablation pattern, averaged in our group of eyes. We can also compare the pre-op anterior corneal surface to the ideal post-op corneal surface and determine the ideal ablation pattern. The difference between the real and the ideal ablation pattern gives us an indication of necessary alterations to current ablation patterns.

Several reports have been published about the changes in spherical aberration in the crystalline lens during accommodation [38], [45], [52]. They all agree that the crystalline lens induces more negative spherical aberration when accommodating for near vision. If we would correct all spherical aberration in the human eye for far vision, the eye would suffer from spherical aberration during near vision. It might therefore be useful to leave the eye with its natural pre-op amount of positive spherical aberration. In order to demonstrate that our Customized Eye Model is capable of doing this, we have also calculated the ideal ablation pattern for natural spherical aberration (SA). Figure 119 shows the ablation depth for the real and the two ideal ablation patterns. Correcting all
spherical aberration requires a larger increase in ablation depth than correcting the spherical aberration to their pre-op amount.

Figure 119: Ablation depth of the real ablation pattern, for the ideal ablation pattern for aberration free correction and for an ideal ablation that leaves the eye with an amount of spherical aberration of 0.1 microns that was found in the average pre-op population.

Figure 120: Difference between the real ablation depth and the ablation depth for an aberration free eye (Real vs. Ideal), and difference between real ablation depth and ablation depth that achieves an eye with the average natural spherical aberration.
Figure 120 shows a plot of the differences in ablation depth between the real ablation pattern and the ideal or the ideal-natural-spherical-aberration pattern. This ablation pattern raises the question if the laser delivery system will be capable of ablating the desired ablation pattern. Current laser systems use pulsed excimer laser light focused to a small spot. The beam profile in the focus is usually Gaussian. The diameter of the focus spot limits the lateral resolution of the ablation pattern. Spot sizes in the range of about 1 mm have been reported. This size might actually not provide a good enough lateral resolution to create the desired ablation pattern. The lateral resolution can be improved by overlapping individual ablation spots. The depth resolution of the ablation pattern is limited by the amount of tissue removed with each laser pulse. The ablation rate is in the order of 0.220 µm/pulse at the fluence of 160 mJ/cm². For comparison, the difference in ablation depth between the center of the ablation and the maximum at about ±2 mm radius in Figure 120 is only 0.286 microns for the blue ablation pattern. This is only slightly more than the ablation depth of one pulse. It remains to be proven if we can actually ablate the cornea with this accuracy.
Discussion

In the previous section, we have demonstrated the use of the Customized Eye Model with the default optimization algorithm of lens design software (Zemax) to calculate a Customized Ablation Pattern for a second refractive surgery, correcting residual and induced lower and higher order aberrations after standard LASIK laser refractive surgery. We have discussed the question, if current refractive surgery system can provide enough accuracy to ablate the desired pattern.

Some other issues about customized corneal ablation are still unresolved and need further investigation. These issues include chromatic aberrations and accommodation. Our measurements and calculations of aberrations before and after laser refractive surgery were conducted for one wavelength in the near infrared. This was the wavelength of our choice in the Shack-Hartmann aberrometer and was discussed earlier.

Llorente et al. [37] have measured aberrations in human eyes in the visible and the near infrared. The only difference that they have found was in defocus, i.e. chromatic aberration. No higher order chromatic aberrations like sphero-chromatism were found in normal eyes.

During accommodation, the amount of aberrations in the crystalline lens of the eye changes. These changes are mainly in spherical aberration, although changes in coma also occur. It might therefore not be advisable to correct the eye to be aberration-free at far vision, but rather to aim for an eye that contains the same amount of higher order
aberrations after surgery than before surgery. Because of changes to the curvatures and conic constant of both anterior and posterior cornea, the actual shape of the cornea that provides the same amount of aberrations after surgery as before will be different than the shape before surgery. We have demonstrated how to add any desired amount of aberration to the Customized Eye Model before performing the optimization that results in the desired ideal post-op anterior corneal surface.

In our simplified model, we did not account for astigmatism and coma. Coma is induced to the eye by decentered ablation. An extension of our Customized Eye Model including coma and astigmatism requires further research.

The biomechanical changes to the cornea due to surgery and wound healing cannot be predicted accurately. Therefore, we propose to perform surgery in two steps. The first surgery will correct defocus and astigmatism in the eye using traditional refractive surgery. After the cornea has stabilized, be build our Customized Eye Model based on the individual pre- and post-op measurements, thereby taking the biomechanical changes into account. A second surgery can then be performed correcting for residual or surgery-induced aberrations.

Customized refractive correction of higher order aberrations in the second step will only be successful if the eye stabilizes after the first surgery. Based on our results in the Whitaker study, it remains questionable at what time after initial surgery we reach this point. It might not even be sure if the eye ever stops changing after LASIK.
CHAPTER 8

CONCLUSIONS AND FUTURE WORK

Shack-Hartmann Aberrometer

We designed and tested a Shack-Hartmann wavefront sensor for the human eye suited for clinical use. The accuracy of the sensor was tested using an optical model eye and human eyes, testing spherical and cylindrical refractive error and spherical aberration. Accuracy, repeatability, and reliability were tested and found suitable for the measurement of optical aberrations in human eyes both pre-op and post-op refractive surgery. When used as an autorefractor, the accuracy and repeatability of the aberrometer was comparable to current state-of-the-art autorefractors.

The limitations of the current aberrometer design were found to be vignetting and induced aberrations by the relay optics. The size of the optical elements used in our design limits the measurement range of the aberrometer to a -15 D to +10 D range. In the current clinical setup, we use a spatial filter to improve contrast in the measurement images which further limits our measurement range to about ±6 D. When imaging highly aberrated wavefronts with the optical relay system, i.e. when testing eyes with large refractive errors, we induce spherical aberration into the test wavefront. When decentering the measurements, we induce defocus, astigmatism, and coma. These systematic errors can be accounted for analytically. The measured wavefronts can also be
traced back through the relay system to find the original aberrated wavefront.

Decentrations of less than 1 mm have no noticeable impact on the measurement.
Whitaker Study

A clinical study was performed assessing visual performance before and after laser refractive surgery (LASIK). The purpose of the study was to gain insight in the changes to ocular aberrations and visual performance as a result of both laser refractive surgery and wound healing. The Whitaker study included 158 eyes of 89 subjects and tested them before surgery and at 1 week, 1 month, 3 months, 6 months, and 12 months post-op. Seventy four subjects (132 eyes, 83.5%) returned for the 12 months follow-up. At every visit, we measured visual acuity, manifest refraction, contrast sensitivity, corneal topography and aberrations. At the pre-op visit, we also measured axial length and anterior chamber depth, as well as photopic and scotopic pupil diameter.

The results in manifest refraction and visual acuity in the Whitaker study match the results of LASIK refractive surgery reported by other research groups. A slight regression in refraction was seen in our group of subjects up to the 12 months visit. Long term studies on the regression in refraction after LASIK will have to show if the refraction is stable or continues to regress after 12 months post-op.

Contrast sensitivity drops dramatically directly after surgery, but slowly recovers in the first 6 months post-op. Other researchers have reported similar results.

We have further found an increase in pupil diameter as a result of surgery. Between 3 and 6 months after surgery, the pupil diameter returns back to the pre-op size.
The analysis of corneal topography revealed systematic changes in the posterior corneal surface that impact both the corneal power and corneal aberrations. While the anterior corneal surface flattens after surgery, we found a steepening of the posterior corneal surface in a biomechanical response to surgery. Future research will have to analyze a biomechanical model of the eye that can predict these changes in the posterior corneal surface.

The measurements of corneal power and corneal aberrations based on topography measurements in our population are very widely scattered. Further research will have to be conducted to determine whether this scatter is due to variability in the population or due to measurement uncertainties. The analysis of corneal aberrations, quantified by Zernike surface coefficients and conic constants indicate a systematic change in the aberration structure of both the anterior and posterior corneal surfaces. While the aberrations of the anterior corneal surface can be controlled by altered ablation patterns, we have no access to changing the posterior corneal surface. The changes in the posterior corneal surfaces are biomechanical responses to surgery and require further investigation.

Our measurements of total ocular aberrations with the Shack-Hartmann wavefront sensor or aberrometer are similar to the results of other studies in that we found the main impact of refractive surgery to be the introduction of spherical aberration and coma. Furthermore, we found significant changes in the aberration structure during wound healing. To our knowledge, these results have not previously been reported. These changes occur for both lower and higher order aberrations. Future research is necessary to
determine if the aberration structure of the eye continues to change after 12 months post-LASIK.

We attempted to verify the continued changes in aberrations during wound healing with two independent measurements: contrast sensitivity and corneal topography. We found that the change in aberrations and pupil diameter correlate to the changes in contrast sensitivity. The combination of increased pupil diameter and increased ocular aberrations explain the strong drop in contrast sensitivity directly after surgery. Changes in aberrations and pupil diameter also correspond to the progression of contrast sensitivity throughout wound healing.

The changes in corneal power correlate with the changes in lower order aberrations (defocus and astigmatism) during wound healing, both showing a temporary decrease at the 6 months visit. The fact that we found two independent measurements showing the same changes indicates that these changes are due to wound healing and are not artifacts of statistical analysis. Measurements of manifest refraction did not confirm this temporary change in refraction during wound healing, but this may be due to the lack of sensitivity of this measurement. An overall regression in refraction was noted in all three measurements of corneal power, lower order aberrations, and manifest refraction. These changes are not clinically significant because the changes are below the quarter diopter that can be corrected with eye glasses or contact lenses.

We were not able to show the changes in higher order aberrations during wound healing that we had found with the aberrometer when calculating the aberrations from
corneal topography. The reason for this is the larger measurement uncertainty in corneal
topography when compared to the aberrometer. Further investigation will have to show if
the accuracy of corneal higher order aberrations measurements can be improved and if
we will then be able to correlate the changes in corneal aberrations during wound healing
to the measurements with the aberrometer.

In summary, the most important conclusions of the Whitaker study are:

- Laser refractive surgery (LASIK) is an effective tool to correct myopia and
  astigmatism. The uncorrected visual acuity 12 months after surgery is slightly lower
  than the best spectacle correct visual acuity.
- A slight regression in manifest refraction is noted during the 12 months after
  surgery.
- Laser refractive surgery introduces large amounts of higher order aberrations,
  mainly spherical aberrations and coma.
- Significant changes in lower and higher order aberrations occur during wound
  healing. The amount of aberrations reaches a low point at 6 months post-op.
  Between 6 and 12 months post-op, the amount of lower and higher order
  aberrations increases again.
- The pupil diameter increases temporarily after surgery. It slowly decreases and
  reaches pre-op values at the 6 months post-op visit.
- Changes in pupil diameter together with changes in higher order aberrations
  correlate to changes in contrast sensitivity.
• Changes in the posterior corneal surface are significant. A systematic steepening of the posterior cornea occurs as a biomechanical response to surgery.

• Corneal aberrations are induced by changes in both the anterior and posterior corneal surface.

• While we saw very clear and statistically significant trends in our data analysis, we encounter a very large scatter in almost all data that we have assessed.

The results of the Whitaker study raised the following questions that require further investigation:

• The most important question is if the regression in refraction and aberrations that we have found in the study continue after the 12 months post-op, or at what time period after laser refractive surgery the eye can be considered stable.

• A biomechanical model of the cornea will have to be developed that can predict the corneal changes due to surgery and wound healing.

• The accuracy and repeatability of topography measurements before and after LASIK surgery will have to be assessed.

• The Whitaker study did not include a control group of eyes that did not undergo refractive surgery and were followed over the same time period. Natural fluctuations in human eyes over short and long time periods will have to be assessed. The analysis should include corneal topography and aberration measurements.
• Although many of the results of the Whitaker study were found to be statistically significant, the question remains as to where these changes are also clinically significant. Subtle changes in manifest refraction might be notable in the analysis, but changes below 0.25 D cannot be corrected with standard eye glasses or contact lenses, and are not considered notable to the subject.
Customized Eye Model and Customized Ablation Patterns

We have designed and tested a Customized Eye Model based on measurements of radius of curvature and conic constant of both corneal surfaces, pachymetry and anterior chamber depth. This model is rotationally symmetric and is suited for representing defocus and spherical aberration. We used this model of the eye together with aberrometer measurements to calculate the spherical aberration of the crystalline lens in this eye. When combining measurements of the pre-op and the post-op eye, we achieved higher accuracy for the calculation of the crystalline lens.

We proposed customized refractive surgery to be performed in two steps. The first step is traditional refractive surgery that corrects for defocus and astigmatism. We measure the eye before and after surgery and build a Customized Eye Model based on these measurements. The post-op eye model contains the biomechanical changes to the cornea due to surgery and wound healing. In the second step, we calculate the optimum anterior corneal surface to achieve the desired correction of aberrations in the post-op eye.

Future work will include the integration of astigmatism and coma in the Customized Eye Model. Because the Customized Eye Model is based on measurements of corneal topography, we will have to assess the accuracy and repeatability of these measurements and compare them to the required tolerances for the eye model. Once reliable and accurate measurements of corneal topography are available, they can be used to model the eye and its aberrations more accurately and improve the Customized Eye Model.
REFERENCES


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