Microfluctuations of wavefront aberrations
of the eye

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Keywords

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Abstract

The human eye suffers various optical aberrations that degrade the retinal image. These aberrations include defocus and astigmatism, as well as the higher order aberrations that also play an important role in our vision. The optics of the eye are not static, but are continuously fluctuating. The work reported in this thesis has studied the nature of the microfluctuations of the wavefront aberrations of the eye and has investigated factors that influence the microfluctuations.

The fluctuations in the ocular surface of the eye were investigated using high speed videokeratoscopy which measures the dynamics of the ocular surface topography. Ocular surface height difference maps were computed to illustrate the changes in the tear film in the inter-blink interval. The videokeratoscopy data was used to derive the ocular surface wavefront aberrations up to the 4th radial order of the Zernike polynomial expansion. We examined the ocular surface dynamics and temporal changes in the ocular surface wavefront aberrations in the inter-blink interval. During the first 0.5 sec following a blink, the tear thickness at the upper edge of the topography map appeared to thicken by about 2 microns. The influence of pulse and instantaneous pulse rate on the microfluctuations in the corneal wavefront aberrations was also investigated. The fluctuations in ocular surface wavefront aberrations were found to be uncorrelated with the pulse and instantaneous heart rates. In the clinical measurement of the ocular surface topography using videokeratoscopy, capturing images 2 to 3 seconds after a blink will result in more consistent results.
To investigate fluctuations in the wavefront aberrations of the eye and their relation to pulse and respiration frequencies we used a wavefront sensor to measure the dynamics of the aberrations up to the Zernike polynomial 4th radial order. Simultaneously, the subject’s pulse rate was measured, from which the instantaneous heart rate was derived. An auto-regressive process was used to derive the power spectra of the Zernike aberration signals, as well as pulse and instantaneous heart rate signals. Linear regression analysis was performed between the frequency components of Zernike aberrations and the pulse and instantaneous heart rate frequencies. Cross spectrum density and coherence analyses were also applied to investigate the relation between fluctuations of wavefront aberrations and pulse and instantaneous heart rate. The correlations between fluctuations of individual Zernike aberrations were also determined. A frequency component of all Zernike aberrations up to the 4th radial order was found to be significantly correlated with the pulse frequency (all $R^2 \geq 0.51$, $p<0.02$), and a frequency component of 9 out of 12 Zernike aberrations was also significantly correlated with instantaneous heart rate frequency (all $R^2 \geq 0.46$, $p<0.05$). The major correlations among Zernike aberrations occurred between second order and fourth order aberrations with the same angular frequencies. Higher order aberrations appear to be related to the cardiopulmonary system in a similar way to that reported for the accommodation signal and pupil fluctuations.

A wavefront sensor and high speed videokeratoscopy were used to investigate the contribution of the ocular surface, the effect of stimulus vergence, and refractive error on the microfluctuations of the wavefront aberrations of the eye. The fluctuations of the Zernike wavefront aberrations were quantified by their variations around the mean and using power spectrum analysis. Integrated power was determined in two regions: 0.1 Hz
— 0.7 Hz (low frequencies) and 0.8 Hz — 1.8 Hz (high frequencies). Changes in the ocular surface topography were measured using high speed videokeratoscopy and variations in the ocular wavefront aberrations were calculated. The microfluctuations of wavefront aberrations in the ocular surface were found to be small compared with the microfluctuations of the wavefront aberrations in the total eye. The variations in defocus while viewing a closer target at 2 D and 4 D stimulus vergence were found to be significantly greater than variations in defocus when viewing a far target. This increase in defocus fluctuations occurred in both the low and high frequency regions (all $p \leq 0.001$) of the power spectra. The microfluctuations in astigmatism and most of the 3rd order and 4th order Zernike wavefront aberrations of the total eye were found to significantly increase with the magnitude of myopia.

The experiments reported in this thesis have demonstrated the characteristics of the microfluctuations of the wavefront aberrations of the eye and have shown some of the factors that can influence the fluctuations. Major fluctuation frequencies of the eye’s wavefront aberrations were shown to be significantly correlated with the pulse and instantaneous heart rate frequencies. Fluctuations in the ocular surface wavefront aberrations made a small contribution to those of the total eye. Changing stimulus vergence primarily affected the fluctuations of defocus in both low and high frequency components. Variations in astigmatism and most 3rd and 4th order aberrations were associated with refractive error magnitude. These findings will aid our fundamental understanding of the complex visual optics of the human eye and may allow the opportunity for better dynamic correction of the aberrations with adaptive optics.
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“The work contained in this thesis has not been previously submitted for a degree or diploma at any other higher education institution. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made.”

Signed: ........................................

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Signed: __________________________

Date: 29.12.2005
Chapter 1

Introduction

The optical performance of the human eye is not ideal. It has long been recognised that it approaches a diffraction limited system only for relatively small pupil diameters. For larger diameter pupils the monochromatic aberrations of the eye’s optics contribute significantly to the eye’s visual performance.

1.1 Aberrations of the eye

There are three common representations of aberrations of an optical system (Figure 1.1). Wave aberration is defined as the departure of the wavefront from the ideal waveform, as measured at the exit pupil. Transverse aberration is the departure of a ray from its ideal position at the image plane and longitudinal aberration is the departure of the intersection of a ray with a reference axis (i.e. the pupil ray) from its ideal intersection.

Figure 1.1: Three common representations of aberrations of an optical system.
Redrawn from Atchison and Smith (2000)
1.2 Wave aberration theory

Figure 1.2 shows the real ray $ABB'$ produced by point source $A$. For an ideal optical system, it should cross the optical axis $AC$ and the image plane $B'A'$ at the point $A'$. But for an aberrated system, this ray can only cross the image plane at point $B'$, and its ray path crosses the optical axis at the point $C$. Then the aberration of this optical system can be quantified in three ways:

Longitudinal aberration: $A'C$;

Transverse aberration: $B'A'$

Wave aberration: $OPD$.

Here $OPD$ stands for optical path difference. For the following diagram,

$$OPD = [ABB'] - [AOA'] = (AB + BB'' \times n') - (AO + OA'' \times n')$$

In this equation, the square brackets refer to optical path lengths and it is the geometric path multiplied by the refractive indices. For an eye, the OPD is the difference in optical path length between the reference ray and any ray from the same point source.

Figure 1.2: Three ways of quantifying the aberrations of a ray: wave, transverse and longitudinal.
Chapter 1

The wave aberration function is the most widely used way to quantify the aberrations of the eye in vision research. There are three common ways of representing the wave aberration.

1.2.1 Taylor power series

Using Taylor polynomials, the wavefront aberrations can be expressed with the following formula (Howland and Howland 1977):

\[ W(x, y) = a + bx + cy + dx^2 + exy + fy^2 + gx^3 + hx^2y + ixy^2 + jy^3 + kx^4 + lx^3y + mx^2y^2 + nxy^3 + oy^4 + \text{higher order aberrations} \]

In this equation, the first three terms \( a + bx + cy \) represent the piston and tilt (prism) terms, \( dx^2 + exy + fy^2 \) are defocus and astigmatism, \( gx^3 + hx^2y + ixy^2 + jy^3 \) are third-order aberrations, and \( kx^4 + lx^3y + mx^2y^2 + nxy^3 + oy^4 \) are fourth-order aberration terms.

1.2.2 Seidel aberrations

A Seidel expression of wavefront aberrations (Mouroulis and Macdonald 1997; Kidger 2002; Freeman and Hull 2003) is:

\[ W(x, y) = w_1x + w_2y + w_3(x^2 + y^2) + w_4(x^2 + 3y^3) + w_5y(x^2 + y^2) + w_6(x^2 + y^2)^2 \]

The Seidel representation is used to quantify the optical aberrations for a rotationally symmetric system, but practically the eye’s optics are not rotationally symmetric.

1.2.3 Zernike aberrations

Zernike polynomials are most widely used to describe the shape of the wavefront due to their mathematical properties for representing a circular pupil and their orthogonality.
**Single indexing**

The wavefront aberrations \( W(\rho, \theta) \) at a radial distance \( \rho \) and angle \( \theta \) can be modelled by a sum of scaled Zernike polynomials:

\[
W(\rho, \theta) = \sum_{i=1}^{N} a_i Z_i(\rho, \theta)
\]

where \( a_i, i = 1, 2, \ldots, N \) are the Zernike coefficients and \( Z_i(\rho, \theta) \) are the Zernike polynomials in a single index scheme, and \( N \) is a mode number.

Zernike polynomials are a set of functions that are orthogonal over the unit circle. In the single index scheme, they are defined as follows (Noll 1976):

\[
Z_{i(even)}(\rho, \theta) = \sqrt{n+1} R_n^m(\rho) \sqrt{2} \cos m\theta, \quad m \neq 0
\]

\[
Z_{i(odd)}(\rho, \theta) = \sqrt{n+1} R_n^m(\rho) \sqrt{2} \sin m\theta, \quad m \neq 0
\]

\[
Z_i(\rho, \theta) = \sqrt{n+1} R_n^0(\rho), \quad m = 0
\]

where

\[
R_n^m(\rho) = \sum_{s=0}^{(n-m)/2} \frac{(-1)^s (n-s)!}{s! [0.5(n+m)/2-s] ![0.5(n-m)/2-s] !} \rho^{n-2s}
\]

are the radial polynomials. Here, \( m \) is the azimuthal frequency and \( n \) is the radial order, the value of \( m, n \) and \( i \) are integers, and \( m \leq n, n - |m| = \text{even} \).

A useful aspect of this Zernike analysis is that the wavefront can be broken into independent components, which represent specific aberrations (Table1) (Thibos et al. 2000). Then each of these Zernike terms or components may be analysed separately or collectively. An example of wavefront maps for 2nd, 3rd and 4th order Zernike aberrations is presented in Figure 1.3.
Table 1.1: Zernike polynomials up to the 4th radial order.

<table>
<thead>
<tr>
<th>Mode Number $i$</th>
<th>Zernikes</th>
<th>Frequency $m$</th>
<th>Order $n$</th>
<th>$Z_n^m(\rho, \theta)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Piston</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Prism (Horizontal)</td>
<td>-1</td>
<td>1</td>
<td>$\rho \sin \theta$</td>
</tr>
<tr>
<td>3</td>
<td>Prism (vertical)</td>
<td>1</td>
<td>1</td>
<td>$\rho \cos \theta$</td>
</tr>
<tr>
<td>4</td>
<td>Astigmatism (45 degree)</td>
<td>-2</td>
<td>2</td>
<td>$\rho^2 \sin 2\theta$</td>
</tr>
<tr>
<td>5</td>
<td>Defocus</td>
<td>0</td>
<td>2</td>
<td>$2\rho^2 - 1$</td>
</tr>
<tr>
<td>6</td>
<td>Astigmatism (Horizontal)</td>
<td>2</td>
<td>2</td>
<td>$\rho^2 \cos 2\theta$</td>
</tr>
<tr>
<td>7</td>
<td>Trefoil (Y axis)</td>
<td>-3</td>
<td>3</td>
<td>$\rho^3 \sin 3\theta$</td>
</tr>
<tr>
<td>8</td>
<td>Coma (Horizontal)</td>
<td>-1</td>
<td>3</td>
<td>$(3\rho^3 - 2\rho)\sin \theta$</td>
</tr>
<tr>
<td>9</td>
<td>Coma (Vertical)</td>
<td>1</td>
<td>3</td>
<td>$(3\rho^3 - 2\rho)\cos \theta$</td>
</tr>
<tr>
<td>10</td>
<td>Trefoil (X axis)</td>
<td>3</td>
<td>3</td>
<td>$\rho^3 \cos 3\theta$</td>
</tr>
<tr>
<td>11</td>
<td>Tetrafoil (22.5 degree)</td>
<td>-4</td>
<td>4</td>
<td>$\rho^4 \sin 4\theta$</td>
</tr>
<tr>
<td>12</td>
<td>Secondary Astigmatism (45 degree)</td>
<td>-2</td>
<td>4</td>
<td>$(4\rho^3 - 3\rho^2)\sin 2\theta$</td>
</tr>
<tr>
<td>13</td>
<td>Spherical Aberration</td>
<td>0</td>
<td>4</td>
<td>$6\rho^4 - 6\rho^2 - 1$</td>
</tr>
<tr>
<td>14</td>
<td>Secondary Astigmatism (Horizontal)</td>
<td>2</td>
<td>4</td>
<td>$(4\rho^3 - 3\rho^2)\cos 2\theta$</td>
</tr>
<tr>
<td>15</td>
<td>Tetrafoil (Horizontal)</td>
<td>4</td>
<td>4</td>
<td>$\rho^4 \cos 4\theta$</td>
</tr>
</tbody>
</table>
Figure 1.3: Wavefront maps for the 2nd, 3rd and 4th order Zernike aberrations.
Double indexing

In the double indexing scheme of the Zernike polynomials, the Zernike polynomials are defined by the following formula (Applegate et al. 2000):

\[
Z_n^m (\rho, \theta) = \begin{cases} 
N_n^m & \text{if } m \geq 0 \\
-N_n^m & \text{if } m < 0
\end{cases} \right. 
\]

\[
N_n^m = \frac{2(n+1)}{1 + \delta};
\]

\(\delta\) is the Kronecker's symbol.

(1) a normalisation factor

(2) a radial dependent component

\[
R_n^m (\rho) = \frac{(-1)^s (n-s)!}{s! [0.5(n+|m|-s)] [0.5(n-|m|-s)]} \rho^{n-2s};
\]

(3) and an azimuthal component \(\cos m\theta\) or \(\sin m\theta\).

Single index \(j\) and double index \(n, m\) can be converted by the following formula (Thibos 2000):

\[
j = \frac{n(n+2) + m}{2};
\]

\[
n = \text{roundup} \left[ \frac{-3 + \sqrt{9 + 8j}}{2} \right];
\]

\[
m = 2j - n(n+2).
\]
1.3 Measuring aberrations

The aberrations of the eye are usually measured in object space as they can not be easily measured on the image side of the eye’s optical system. They can be measured by a variety of techniques either subjectively or objectively. The subjective methods were the first to be used for measuring the eye aberrations.

1.3.1 Subjective methods

Howland and Howland (1977) developed a subjective aberroscope based on the principle of Tscherning’s aberroscope, to investigate and characterise the monochromatic aberrations. The subjects were asked to view the grid produced by a crossed cylinder aberroscope and then draw the grid. This drawing was later analysed to quantitatively determine the aberrations of the eye. Taylor polynomials and Zernike polynomials were used to fit the wave aberrations up to the 4th radial order. This was the first time that the comatic aberrations of the eye were measured rather than being estimated.

The spatially resolved refractometer has also been extensively used in recent years as a psychophysical technique to measure wavefront aberrations (He et al. 1998; Marcos et al. 1999; He et al. 2000; Marcos and Burns 2000; Marcos et al. 2001; McLellan et al. 2001; Prieto et al. 2002). The subjects’ task is to align the test beam to a reference beam to measure the aberrations at various positions in the pupil. This technique has practical advantages for measuring wavefront aberrations in subjects for whom the objective techniques may not work well, such as patients with ocular opacities and very high levels of aberrations. The spatially resolved refractometer has also been modified to function as an objective technique (Pallikaris et al. 2001).
The psychophysical spatially resolved refractometer was used to measure the monochromatic wavefront aberrations up to the 7th radial order to investigate the influence of the accommodation (He et al. 2000) and refractive error magnitude (He et al. 2002). It has been also used to measure age-related changes in monochromatic wavefront aberrations (McLellan et al. 2001). The disadvantages of the technique are the subjective nature of the measurements and the time involved.

1.3.2 Objective methods

Many objective methods for eye aberration measurement have been developed more recently. They have important advantages over the subjective methods because of their speed and ability to make repeated measures in a short period of time.

Based on the subjective cross-cylinder aberroscope, Walsh et al. (1984) improved this technique by applying a beam splitter and a camera that recorded the retinal image of the distorted aberroscope grid. They measured the ocular aberrations for up to the 4th radial order from direct measurements of the grid distortion. The comparison of the results of the objective method with the one from the previous subjective cross-cylinder aberroscope with the same subjects showed significantly reduced variance in the estimates of the wave aberration’s polynomial coefficients (Walsh et al. 1984). Therefore the objective technique had better precision than the subjective technique.

More recently, the Hartman-Shack wavefront sensor has been developed for measuring the wavefront aberrations of the eye. It has a capacity of making rapid, repeated measurements of the wavefront aberration of eye at a user defined sampling frequencies (Thibos 2000).
Based on the Scheiner principle, a Hartmann screen was firstly used to construct objective aberrometer to measure aberrations in 1900. Shack and Platt (1971) developed the Hartmann-Shack aberrometer by filling each hole of Hartman screen with a tiny lenslet that focuses lights into an array of spots.

In 1994, Liang and co-workers were the first to demonstrate a new technique to measure the eye’s aberrations based on a Hartmann-Shack principle. They used a Hartmann-Shack wavefront sensor to measure the local slope of the wavefront, then they used those data to estimate and reconstruct the actual wavefront from the Zernike polynomials for up to the 4th radial order. The lenslets of the lens array of the Hartmann-Shack they used had a focal length of 170 mm and the dimensions of $1 \text{ mm} \times 1 \text{ mm}$ (Liang et al. 1994). Liang and Williams (1997) constructed a wavefront sensor with lenslet aperture of 0.5 mm lenslet focal length of 97 mm and was able to measure the wave aberration up to the tenth order aberrations for more complete description of the eye aberrations.

The Hartmann-Shack wavefront sensor has become the most widely used technique for objective measurement of the eye aberrations. Hartmann-Shack wavefront sensors have been used to measure the wave aberrations for various research purposes, such as description of the eye aberrations in large populations (Porter et al. 2001; Cagigal and Canales 2002), myopic eyes (up to-9.25 D) (Paquin et al. 1998), an assessing optical benefits of eye aberrations correction (Hong et al. 2001; Guirao et al. 2002; Yoon and Williams 2002; Yoon et al. 2004).

Thibos and Hong (1999) used a Hartmann-Shack aberrometer to explore the optical imperfections of dry eye, corneal disease (keratoconus), corneal refractive surgery
(LASIK), and lenticular cataract (nuclear sclerosis). Results showed in each of these cases that it is possible to obtain at least a partial map of the aberrations of the patient’s eyes, but severe losses of data integrity can occur due to high level of aberrations or loss of transparency of the eye’s media (Thibos and Hong 1999). In another study, it has been demonstrated that the tear film break-up has an impact on the measurement of the higher order aberrations by Hartman-Shack wavefront sensor (Koh et al. 2002). It has also been suggested that Hartman-Shack aberrometer may be useful to measure the deterioration of image quality objectively in eyes with mild cataract (Kuroda et al. 2002a).

**Double-pass point spread function technique**

The double-pass technique is based on recording images of a point source projected on the retina after retinal reflection and double-pass through the ocular media. From the point spread function, the ocular wave aberrations can be estimated (Iglesias et al. 1998). This technique has been applied for research on retinal image quality & age (Artal et al. 1993; Guirao et al. 1999), retinal image quality & accommodation (Lopez-Gil et al. 1998) and, off-axis image quality for geometrical aberrations across the visual field (Navarro and Losada 1997; Navarro et al. 1998).

**Comparison of aberration measurement techniques**

Numerous experiments have been carried to compare the performance of Hartmann-Shack sensor with other techniques. Liang and Williams (1997) compared the results measured by Hartmann-Shack wavefront sensor with those results measured by other techniques and showed that the Hartmann-Shack wavefront sensor can provide repeatable and accurate measurement of the eye’s wavefront error.
It has been reported that the Hartmann-Shack wavefront sensor produced better estimates of the retinal image quality than the double-pass method for measuring the aberrations of the human eye (Prieto et al. 2000). The Hartmann-Shack wavefront sensor provided higher estimates of the Modulation Transfer Function (MTF) compared with double-pass method at the best focus (Prieto et al. 1998).

Another study showed agreement of the wavefront aberrations measured by laser ray tracing and Hartmann-Shack sensor (double pass) (Moreno-Barriuso and Navarro 2000; Rodriguez et al. 2004). Comparison of the spatially resolved refractometer (psychophysical method), laser ray tracing, and Hartmann-Shack sensor again showed a close match between the Zernike coefficients (Moreno-Barriuso et al. 2001).

1.3.3 Magnitudes of monochromatic aberrations

Population & age

All studies have found that monochromatic aberrations vary from subject to subject (Howland and Howland 1977; Walsh et al. 1984; Liang and Williams 1997; He et al. 1998; Navarro et al. 1998; Marcos et al. 2001; Porter et al. 2001). Most aberrations have also been found to be correlated between the left eye and right eyes (Liang and Williams 1997; Porter et al. 2001; Castejon-Mochon et al. 2002; Thibos et al. 2002b).

The magnitude of aberrations increases with the pupil size (Liang and Williams 1997; Castejon-Mochon et al. 2002; Thibos et al. 2002b) and with the eccentricity of measurement angle (Navarro et al. 1998). As radial order increases, the contribution of the aberrations of this order to the total wavefront aberrations generally decreases (Castejon-Mochon et al. 2002; Thibos et al. 2002b). Wavefront aberrations in adults eyes
have been found to increase with age (McLellan et al. 2001; Kuroda et al. 2002b; Marcos 2002; Brunette et al. 2003).

**Effect of accommodation**

Using a psychophysical method third and higher order spherical aberration and coma were measured at various accommodative levels and were found to change significantly with accommodation (Lu et al. 1993). However, no clear relationship between aberrations and accommodation was found in this study.

Atchison et al. (1995) used the Howland aberroscope to investigate the effect of accommodation on monochromatic ocular aberrations. The wave aberration data did not show a clear trend with change in accommodation level (0 D, 1.5 D and 3 D), however they found that the longitudinal spherical aberration decreased (increase of negative spherical aberration) as accommodation increased.

Lopez-Gil et al. (1998) studied the changes in the retinal image quality with accommodation using a double pass technique and found the shape of the retinal images clearly changed with accommodation, indicating that ocular aberrations altered with accommodation.

Monochromatic aberrations of the human eye were studied by using a spatially resolved refractometer with accommodative stimuli ranging from 0 D to 6 D (He et al. 2000). Monochromatic wavefront aberrations were found to generally increase when the eye accommodates at closer stimuli, but with substantial individual variations. The high order aberration (5th to 7th order) appeared to decrease as the eye accommodated for
accommodation stimulus from 0 D to -2 D and increased for -2 D to -6 D. On average the spherical aberration decreased (from positive values to negative dioptric values) with increasing accommodation and this showed good agreement with the previous study by Atchison et al. (1995). The change in individual spherical aberration varied between subjects including decreases of larger positive values to low positive values and increases of low negative values toward high negative values.

A real-time Hartman-Shack wavefront sensor was used to measure the optical aberrations during accommodation in normal eyes (Artal et al. 2002b). Wavefront aberrations maps were shown to vary for different stimulus vergence and some aberrations were found to change with accommodation.

Changes in wave aberrations with accommodation were examined with a Hartman-Shack wavefront sensor in a large young adult population for accommodation stimulus up to 6 D and up to 6th order (Cheng et al. 2004a). Average RMS of all aberrations measured (excluding defocus) was not found to change with accommodation for accommodative levels up to 3 D. Spherical aberration appeared to have the greatest change with accommodation and change was towards increasing negative dioptric values. Coma and astigmatism also showed some variable change with accommodation.

**Refractive error**

Several studies have been carried out to investigate the relationship between monochromatic aberrations of the eye and refractive error using different techniques. Collins et al. (1995b) reported significantly lower 4th order monochromatic aberrations in myopia than in emmetropia. He et al. (2002) found that mean root mean square (RMS)
value of wavefront aberrations was greater in myopic subjects than in emmetropic subjects. Positive levels of spherical aberration were shown to be significantly less in low myopia (range -0.5 D to -3.0 D) than in high myopia, emmetropia and hyperopia (Carkeet et al. 2002). Llorente et al. (2004) reported significantly higher RMS of 3rd order aberrations for the hyperopic eye. However, in another recent study on the relationship between monochromatic aberrations of the eye and refractive error, no correlation was discovered between RMS of 3rd, 4th and total higher order (3rd to 10th) aberrations and refractive error (Cheng et al. 2003).

**Stiles and Crawford effect**

Stiles and Crawford discovered that the luminous efficiency of a beam of light entering the eye and incident on the fovea depends on the entry point in the pupil (Stiles and Crawford 1933). The further the entry point is away from the centre of the pupil, the less effective it will be in eliciting a response from the retinal photoreceptors. The Stiles Crawford effect has little impact on spatial visual performance in the case of centred pupils (Atchison et al. 1998). It has been shown that Stiles Crawford effect slightly improves the image quality by providing compensation for aberrations induced by pupil decenteration (Atchison et al. 2001).
1.4 Contribution of the Cornea to the Optics of the Eye

1.4.1 Tear film

As the outermost surface of the eye, the tear contributes to the optical properties of the eye. Normal tear film is about 7-10 $\mu m$ thick and composed of an outer lipid layer (0.1 $\mu m$ thick), an intermediate aqueous phase (7 $\mu m$), and an inner mucus layer (1 $\mu m$) (Wolff 1946; Holly 1973). Tears from lacrimal glands are spread by blinking and then drained through the lacrimal punctum (Tsubota 1998). Stable pre-corneal tear film between blinks is essential for maintaining clear vision.

An early study by Brown and Dervichian (1969) has shown a two-step response of the tear film to blinking and motion of the upper eyelid. Tears move up rapidly with the upper eyelid after a blink and within one second post blink tear spreading velocity decreases to minimum (Owens and Phillips 2001). Changes over time in the tear film thickness have also been observed in the blink intervals using fluorophotometry and were found to be dependent on the location of the tear film on the cornea (Benedetto et al. 1984). It has been suggested that thinner lipid layer in the superior cornea immediately after a blink causes a high surface tension which results in upward drift of the tear film and then leads to a thicker tear film in the upper cornea (Benedetto et al. 1984; King-Smith et al. 2004).

1.4.2 Anterior Cornea

Corneal shape

The refractive power of the cornea is primarily determined by its two surface topographies and its refractive index. The corneal refractive power is normally about 43
Diopter, providing approximately 2/3 of the eye's focusing power when the eye is not accommodated (Atchison and Smith 2000).

The cornea is approximately 12 mm in diameter and is usually vertically smaller than horizontally. The average central radius of curvature for the normal adult cornea is 7.83 mm, with a range from about 7.4 to 8.6 mm (Mandell 1996).

Corneas are usually steeper centrally and flatter in the periphery. The profile of the cornea along a meridian can be considered as approximating an ellipse. The aspheric normal cornea can be mathematically represented by a conic equation (Kiely et al. 1982):

\[ X^2 + Y^2 + (1 + Q)Z^2 - 2ZR = 0, \]

where Z is the optical axis, R is the vertex radius of curvature and Q is the surface asphericity (Figure 1.4).

The following values of Q denote different types of conic sections:

Q< -1, hyperboloid,
Q= -1, paraboloid,
-1<Q<0, prolate ellipsoid,
Q= 0, sphere,
Q> 0, oblate ellipsoid.
The flattening of the peripheral cornea reduces positive spherical aberration, but the amount of the asphericity in the average cornea is insufficient to eliminate spherical aberration. It has been calculated that the asphericity value needs to be $Q = -0.528$ for zero spherical aberration of the cornea (Kiely et al. 1982). Generally, the normal cornea’s asphericity value is about $Q = -0.26 \pm 0.18$ (Kiely et al. 1982). Table 1.2 Lists some Q-values and examples.

<table>
<thead>
<tr>
<th>Asphericity</th>
<th>Shape</th>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Q &gt; 0$</td>
<td>Oblate</td>
<td>Peripheral steepening</td>
<td>Refractive surgery</td>
</tr>
<tr>
<td>$Q = 0$</td>
<td>Sphere</td>
<td>Uniform curvature</td>
<td>Steel calibration ball</td>
</tr>
<tr>
<td>$Q = -0.26$</td>
<td>Prolate</td>
<td>Peripheral flattening</td>
<td>Most normal corneas</td>
</tr>
<tr>
<td>$Q &lt; -0.5$</td>
<td>Prolate</td>
<td>Marked peripheral flattening</td>
<td>Keratoconus</td>
</tr>
</tbody>
</table>

Table 1.2: Corneal asphericity ($Q$) and examples (Corbett et al. 1999).
Bogan et al. (1990) conducted corneal topography evaluation on 399 normal corneas and described five topography patterns: round (22.6%), oval (20.8%), symmetric bow tie (17.5%), asymmetric bow tie (32.1%) and irregular (7.1%). The round shape pattern represents a cornea with no astigmatism or asymmetry. The symmetric bow tie indicates “regular astigmatism” while the asymmetric bow tie indicates “irregular astigmatism”, representing radial asymmetry in the rate of change of the radius of the curvature from centre to periphery.

**Astigmatism**

Often the anterior corneal surface exhibits toricity, leading to corneal astigmatism. The average difference between the refractive powers of the major and minor meridians is mostly between 0.5 D and 1 D (Corbett et al. 1999). Normal young corneas are typically steeper in the vertical meridian than horizontal meridian (with-the-rule astigmatism) (Grosvenor 1976; Hayashi et al. 1995). When the cornea is less curved in the vertical meridian than the horizontal meridian, it is termed against-the-rule astigmatism. Hayashi et al. (1995) demonstrated that the normal cornea shifted from with-the-rule astigmatism in young subjects to little corneal astigmatism for subjects in their 60s, and then to against-the-rule astigmatism for subjects in their 70s to 80s.

**Corneal optics**

The cornea plays an important role in determining the overall image quality of the eye. Corneal aberrations mostly arise from anterior surface of the human cornea, although the posterior corneal surface also contributes some aberrations to the eye in the normal cornea. The posterior corneal surface has a radius of curvature of about 6.7 mm and a
negative power of $-6\ \text{D}$ (Corbett et al. 1999). Barbero et al. (2002) have shown that the contribution of the posterior corneal surface to the corneal aberrations is up to 2% at most.

The major aberration of the corneal surface is typically spherical aberration and the calculated longitudinal spherical aberration can reach up to 1.5 D at ray height of 3.5 mm for a normal cornea ($Q = -0.26$) (Kiely et al. 1982). The spherical aberration is positive in sign and it is partly corrected in the young unaccommodated eye by the negative spherical aberration of the lens.

Astigmatism and coma also typically contribute to the total corneal aberrations. It was reported that in the central cornea the difference in radius of curvature between steepest and flattest meridian is about 0.15 mm and this would contribute approximately 0.9 D of corneal astigmatism (Guillon et al. 1986). For large pupils (above 5 mm), substantial peripheral corneal asymmetries cause large amounts of coma-like aberrations (Hemenger et al. 1996; Oshika et al. 1999). The magnitude of coma-like aberrations of the cornea is partially compensated by the internal optics of the eye (Artal et al. 2001).

Corneal surface height data can be decomposed into Zernike polynomials to compute corneal aberrations (Schwiegerling et al. 1995; Schwiegerling and Greivenkamp 1997). The Zernike polynomials provide a numerically stable expansion of corneal height data and contain terms representative of fundamental corneal shapes such as sphere and cylinder. Removing the lower order Zernike terms from the height data helps display the higher order terms. This methodology has provided a convenient approach for corneal aberration studies.
Effects of age

In the investigation of the corneal aberrations and its relation with age, Oshika et al. (1999) reported a significant increase of the coma-like aberrations of the cornea with ageing but no age-related changes in spherical aberration of the cornea. It was suggested that the cornea becomes less symmetric with aging (Oshika et al. 1999). However, Guirao et al. (2000) found that corneas became more spherical with age and the average corneal radius decreased. They explained that this change leads to significantly higher positive spherical aberration in middle-aged and older corneas (Guirao et al. 2000). It was also reported that the corneal aberrations were higher than the total eye aberrations for younger subjects and the opposite for the older subjects (Artal et al. 2002a). They inferred that for younger subjects the corneal aberrations were compensated by the internal ocular aberrations.

Stability of corneal topography

Corneal shape and accommodation

There have been conflicting findings on the question of whether accommodation induces any changes in corneal shape. Some studies have found that accommodation does not have a significant effect on corneal shape (Fairmaid 1959; Mandell and St. Helen 1968). Other experiments have shown that accommodation may have some effect on the corneal shape. Lopping and Weale (1964) reported a statistically significant increase in the horizontal radius of curvature following convergence. Pierscionek et al. (2001) have shown when focus was changed between a distant (6 m) and a near (11 cm) target, most of the subjects had about 0.4 D difference in the central corneal curvature in at least one principal meridian. More recently, Buehren et al. (2003b) have found that corneal shape
change during the accommodation is not due to a real change of corneal shape but is due to a small cyclotorsion of the eyes during accommodation which changes the relative orientation of the topography with respect to the instrument.

*Tear stability and topography*

The precorneal tear film provides a smooth, regular anterior surface of the eye. It is not stable over time, evaporating and finally breaking-up. Current techniques for corneal topography such as keratometry and videokeratoscopy use the tear film as a convex mirror to view the first Purkinje image, so the stability of the corneal tear film plays an important role in corneal topography assessment. It has been reported that corneal curvature measured by topography becomes steeper when the local tear film gets thinner and finally breaks up (Chen and Wang 1999). A significant increase in corneal topography irregularity (surface regularity index) was discovered during even a short pause in blinking, but no significant changes in the values for corneal refractive power or astigmatism were noted (Nemeth et al. 2000). Tear film disruption causes degradation of the retinal image and the optical quality during periods of non-blinking (Thibos and Hong 1999; Tutt et al. 2000). Topographic images acquired with tear instability may influence both accuracy and reproducibility of videokeratoscope corneal topography measurements.

*Lid force and topography*

Wilson et al. (1982) has shown that lifting the eyelid in corneas with more than 1 D of with-the-rule astigmatism causes systematic changes in the corneal toricity towards less with-the-rule astigmatism. The effect of the eyelid on corneal topography has also been examined by looking at the corneal topography changes after blinking (Nemeth et al. 2000; Buehren et al. 2001). Buehren et al. (2001) found a statistically significant
variability of topography at the upper and lower edges of an 8 mm diameter of the corneal topography map. It was suggested that this change might be related to the effects of the eyelid pressure (Buehren et al. 2001). Buehren et al. (2003a) presented data showing significant changes in corneal topography and optics after reading for one hour and these changes showed a clear association with the eye-lid position, especially the upper eyelid. Ford et al. (1997) also found corneal changes associated with close work, near the position of eyelids. It is evident that the force of the eyelid can slightly alter the shape of the cornea (Ford et al. 1997).

Videokeratoscopes

Keratometry measures the curvature of the central cornea and is both accurate and reproducible for regular sphero-cylindrical surfaces. The computer-assisted videokeratoscope provides detailed quantitative information about the corneal contour. In Placido disk videokeratoscopes, the mire image reflected from the corneal surface is captured by a CCD video camera. The data in this image can then be analysed to derive the axial, tangential and refractive power of the cornea as well as the corneal height. Videokeratoscopes measure power of spherical test objects with an accuracy of about 0.25 D. Because of rotationally symmetric videokeratoscope mires and the spherical biased reconstruction algorithms, accuracy can be better for rotationally symmetric surfaces than for the asymmetric surfaces such as most real corneas. Videokeratoscopes measure the real cornea more accurately in the central cornea, with accuracy as high as 0.15 D (Corbett et al. 1999; Corbett 2000). In the peripheral cornea, the accuracy can be reduced to as low as several diopters (Mandell 1996). Videokeratoscope measures the cornea with the precision of less than $\pm 0.5\,\text{D}$ in the central 4 to 5 mm and $\pm 1\,\text{D}$ in the peripheral cornea (Buehren et al. 2001).
The natural dynamics of the eye and ocular anterior surface cause variations between measurements and decrease the repeatability (Buehren et al. 2002). Factors such as the stability of the tear film, the lid force, normal pulsation of blood with heartbeat and micro-movements of the eye can induce changes in the corneal topographic measurement from videokeratoscopes (Chen and Wang 1999; Buehren et al. 2002). Potential sources of inaccuracy in videokeratoscope operation are mainly associated with misalignment due to lack of appropriate corneal reference position, fixation error and focusing error.
1.5 Contribution of the crystalline lens to the optics of the eye

1.5.1 Structure of the crystalline lens

The crystalline lens is contained within an elastic capsule (Figure 1.5). It has an equatorial diameter of approximately 9 mm and the central lens is about 3.6 mm thick when in a relaxed state (Bennett and Rabbetts 1989). Both surfaces of the crystalline lens are prolate and the radius of curvature increases from centre to periphery for both surfaces (i.e. prolate ellipsoid). The anterior surface radius is flatter than the posterior surface by about 1.7 times.

![Figure 1.5: Cross-section of the crystalline lens.](image)

The refractive index within the crystalline lens is not constant, being higher in the centre (nucleus) and lower in the periphery (cortex). In the nucleus (inner 2/3) of the lens, the refractive index is relatively constant while in the cortical region there is an index gradient (Pierscionek 1997). At the centre of the lens, the refractive index reaches the
maximum value of about 1.406 and reduces to 1.386 at the edge of the lens (Atchison and Smith 2000).

In the relaxed state, the crystalline lens has negative spherical aberration and there are three factors that contribute to this spherical aberration: the anterior surface asphericity, posterior surface asphericity and the refractive index gradient within the crystalline lens (Smith et al. 2001). This negative spherical aberration of the relaxed lens is only slightly less than the positive spherical aberration of the anterior corneal surface, leaving the eye as whole with relatively low levels of positive spherical aberration (Smith et al. 2001).

The crystalline lens shape changes over time, becoming more convex with age. It has been calculated that the front surface asphericity (Q value) of the lens decreases with age, while the back surface asphericity increases with age (Smith and Atchison 2001). Brown (1974) found a linear decrease of the central anterior lens radius of curvature from about 15 mm at the age of 20 years to around 8.5 mm at the age of 80 years. There was less decrease of posterior lens radius of curvature from about 8.6 mm at the age of 20 years to approximately 7.5 mm at the age of 80 years. Apart from the increasing thickness and surface curvature of the lens with the age, the equatorial diameter of the unaccommodated lens increases by approximately 0.9 mm from age 15 to age 85 years.

The refractive index of the crystalline lens also alters with ageing. Pierscionek (1997) found that in general the refractive index in the peripheral region of the equatorial plane increases with age. This could account for increasing positive spherical aberrations found in older eyes.
1.5.2 Crystalline lens and accommodation

Accommodation is the process of changing the focus of the eye across various object distances. The amplitude of accommodation is normally defined as the difference between the vergences of the far and near points of the eye. For a ‘relaxed eye’, the accommodation level is zero, and the power of the crystalline lens is approximately 19 D (Atchison and Smith 2000). When the eye accommodates to a point 10 cm away from the anterior cornea, the power of the crystalline lens increases to about 29 D with an accommodation level of 10 D.

The crystalline lens is suspended inside the eye by the zonules that are attached to the ciliary body. These structures all play an important role in the accommodation process. When the ciliary body contracts, the zonules relax, the natural elasticity of the lens and its capsule causes the lens to become thicker and this increases its dioptric power for near vision (see Figure 1.6). When the ciliary body relaxes, the zonules contract, the lens becomes thinner and this reduces the lens’ power for distance vision.

Accommodation reduces in both amplitude and speed with age. This might be due to the lens losing elastic force of the capsule with age and more compacted lens fibres in the nucleus causing increased difficulty of lens deformation (Fisher 1988). Objectively measured amplitude of accommodation generally reduces almost linearly with age at a rate of approximately 0.3 D per year and reaches zero at about age of 50 (Charman 1989). The static accommodation responses (in dioptres) to stimuli ranging between 0.5 D to 5.0 D were found to reduce with age (Kalsi et al. 2001). Phase lag of accommodation response was also found to increase with age for targets oscillating sinusoidally at a frequency of 1.0 Hz (Heron et al. 2002).
1.5.3 Accommodation stimulus and response

Accommodation response is influenced by various target characteristics such as contrast, colour, spatial content and luminance. For a low vergence stimulus, the typical accommodation response exceeds accommodation stimulus and shows a “lead” of accommodation (Figure 1.7). For a high vergence stimulus, accommodation falls below the accommodation stimulus and shows a “lag” of accommodation (Figure 1.7). The “cross-over point” is the point where the accommodation stimulus/response curve intersects a one-to-one slope and where the accommodation response is equal to the accommodation stimulus. This point is normally located between 1 D and 2.5 D for young adults (Ward and Charman 1985; Bennett and Rabbetts 1989).
Figure 1.7: Accommodation stimulus-response. The dashed line is the ideal 1:1 slope.

**Tonic accommodation**

Resting-state accommodation is also called tonic accommodation. In the absence of any objects or contours in the visual field (when looking into an empty space or in the dark), the accommodation mechanism of the eye adopts a level known as the resting state (Barlow and Mollon 1982; Ward and Charman 1985).

**Proximal accommodation**

Proximal accommodation is also called psychological accommodation. Proximally induced accommodation is the change in accommodation response resulting from the
awareness of nearness (Rosenfield et al. 1990). Proximal vergence is also an important factor that contributes significantly to the vergence response (Joubert and Bedell 1990). The magnitudes of proximally induced accommodation and vergence were found to be linearly related to target distance (Rosenfield et al. 1991). The proximally induced accommodation response / accommodative stimulus ratio was observed to be 0.60 D/D (Rosenfield and Gilmartin 1990).

**Stimulus spatial frequency and form**

Charman and Tucker (1977, 1978) studied the monocular accommodation response to sinusoidal grating targets of various spatial frequencies and found that monocular steady-state accommodation response is dependent on the spatial frequency spectrum of the object. They reported that the response was more accurate at higher frequencies but often substantially in error at very low frequencies.

A study by Ward (1987a) showed that accommodation response to mid spatial frequencies (15 cycle/degree (c/d) sinusoidal grating) was less accurate than the lower spatial frequencies of 1.67 and 5 c/d. He suggested that intermediate stimulus spatial frequencies around 5 c/d were the most important for accommodation.

It has been found that accommodation responses to square-wave grating stimuli were more accurate than those to sine-wave grating stimuli at low spatial frequencies (≤ 2 c/d), but similar responses occurred for both stimuli types at the higher spatial frequencies (Tucker and Charman 1987).
It has also been suggested that accuracy and stability of the accommodation response may be adversely affected by low-frequency flickering stimuli, but are little affected by the flicker at high frequencies (≥ 40 Hz) (Chauhan and Charman 1996).

**Stimulus colour**

Studies have indicated that accommodation responses to steady or moving targets are more accurate in white or broad wavelengths than in monochromatic light, possibly due to the presence of the longitudinal chromatic aberration which facilitates accommodation (Stone et al. 1993; Aggarwala et al. 1995). Doubling the longitudinal chromatic aberration has been shown to have little effect on accommodation accuracy, but correcting or reversing the longitudinal chromatic aberrations leads to poorer accommodation response (Stone et al. 1993; Aggarwala et al. 1995).

**Stimulus contrast**

For stimuli composed of a single spatial frequency objects under supra-threshold contrast conditions, lower object contrast causes greater accommodative error (Charman and Tucker 1978). For more complex objects, lower object contrast may cause some high-frequency components in the image to fall below threshold, leading to even larger errors in accommodation (Charman and Tucker 1978).

It has been suggested that the accommodation system has only a small dependence on stimulus contrast for both edge and simple sine-wave targets (Ward 1987b). The magnitude of accommodation responses to edge targets were accurate until contrast dropped to around 20% stimulus contrast, and to approximately 15% for sinusoidal gratings with 5 c/d spatial frequency.
**Stimulus luminance**

Accommodation response varies little with luminance for single spatial frequency targets and natural pupils (Charman and Tucker 1978). For targets of wide spatial bandwidth, accommodative response of the visual system becomes less accurate as luminance decreases from photopic to scotopic levels (Tucker and Charman 1986).

**Effect of pupil size**

Ward and Charman (1985) demonstrated that in the near vision region (2.5 to 5 D vergence) of the accommodation stimulus/response curve, the magnitude of the slope (accommodation gain) decreases with pupil size for pupil diameters below 3 mm.

**Accommodation response and moving stimuli**

Campbell and Westheimer (1960) investigated the nature of the accommodation response for monocular viewing of a variety of moving stimuli and found accommodation response to step stimuli (instantaneous displacement of a target from one optical viewing distance to another) followed the responding stimulus after reaction time of approximately 0.37 s. Heron *et al.* (2002) reported that reaction and response for step stimuli did not change with age.

Campbell and Westheimer (1960) also recorded the amplitude of accommodation response when a focused (within 0.6 D) target oscillated sinusoidally at different frequencies. The accommodation response was found to decrease when the target oscillation frequency increased (Campbell and Westheimer 1960).
1.5.4 Accommodation microfluctuations

Collins (1937) first noticed rapid fluctuations around the mean level of accommodation using an infra-red electronic refractometer. It has been found that microfluctuations in steady-viewing accommodation have an amplitude of about a quarter diopter and a frequency spectrum extending up to a few Hz. In studies of what causes and influences accommodation microfluctuations, the power spectrum analysis is often used to indicate the dominant frequencies in the microfluctuations of accommodation (Pugh et al. 1987).

Campbell et al. (1959) were the first who used an objective recording technique to investigate the characteristics of the accommodation of the eye. The continuous recording was achieved by using an infra-red optometer and showed that refractive power of the eye constantly undergoes microfluctuations while viewing a stationary target. They noticed that the microfluctuations had dominant frequency components in the 0-0.5 Hz region, and with larger pupils a strong frequency peak near 2 Hz (Campbell et al. 1959).

The accommodation microfluctuation during steady-state accommodation can be influenced by various viewing conditions, such as pupil diameter, target vergence, target form, target luminance and target contrast.

Pupil diameter

The influence of the pupil diameter on the microfluctuations of the accommodation has attracted many researchers’ interest. Campbell and his coworkers’ experiment on one subject showed a marked high frequency component present in the power spectrum of the
accommodation microfluctuations for a large pupil (7 mm), but absence of the high frequency component using a small pupil (1 mm) (Campbell et al. 1959). However, Ward and Charman (1985) have theoretically shown that microfluctuations in accommodation should decrease in magnitude with larger pupil sizes if microfluctuations of accommodation are actively controlled to produce constant changes in modulation transfer.

A later study by Gray et al. (1993a) explored this issue more extensively. The power of the low frequency component of accommodation microfluctuations was found to decrease with increasing pupil diameter for pupil diameters smaller than 3 mm and to be relatively constant for the pupil diameters greater than 3 mm (Gray et al. 1993a). This result showed general agreement with the prediction by Ward and Charman (1985). Gray et al. (1993a) also reported that the high frequency components of the accommodation microfluctuations did not show systematic change with varying pupil diameter.

Similar results were reported by Stark and Atchison (1997) and they found that low frequency components of accommodation microfluctuations increased with smaller pupils, while the high frequency components were independent of the pupil size.

**Target vergence**

The dependence of accommodation microfluctuations on target vergence was first systematically studied by Alpern (1958) who found an increase in accommodation microfluctuation magnitude when subjects viewed closer objects. Denieul (1982) also reported that increasing target vergence resulted in an increase of the mean spectrum magnitude of accommodation microfluctuations.
Kotulak and Schor (1986b) demonstrated a statistically significant positive correlation between the standard deviation (or variance) of the accommodative response and the mean level of accommodation response (1 D to 4 D). They also showed that the amplitude of the 2 Hz component of accommodation increased linearly with the mean level of accommodation response. The microfluctuations of accommodation over a large dioptric range (+3 D to −9 D) were explored by Miege and Denieul (1988). They found that both the magnitudes of accommodation microfluctuations and the 2 Hz relative activity increased with target vergence up to −3 D and then decreased with closer targets.

Toshida et al. (1998) investigated the effects of the accommodative stimulus on accommodative microfluctuations in young subjects at various accommodative stimulus vergence levels (0 D to −12 D). The integrated power of the high frequency component, chosen as (1.3 Hz − 2.2 Hz), in accommodation was found to be minimum with the accommodative stimulus at the far point, to increase with accommodative stimulus until reaching a peak at −5 D, and then to gradually decrease with closer stimuli. The integrated power of the low frequency component (<0.5 Hz), was found to be at a minimum at the far point, to increase for stimuli closer than the far point, and to stabilise for stimuli closer than the near point. Recently Strang et al. (2004) found that the magnitude of microfluctuations in accommodation significantly increased with target vergence in both myopes and emmetropes due to an increase in the power at the low frequency region.

Variation of the high frequency components of accommodative microfluctuations with accommodative stimulus was suggested to be associated with factors such as lens
elasticity, zonular tension, ciliary muscle pulse and intraocular pressure (Kotulak and Schor 1986b). It has also been suggested that the increase of the total value of accommodative microfluctuations as stimulus vergence increases might be due to increased activity of the low frequency components which are thought to be used in the control of the blur-driven accommodative response (Miege and Denieul 1988).

**Target luminance**

Changes of target luminance cause variations in the accommodation level and changes in the accommodation microfluctuations power spectrum. Charman and Heron (1988) first studied the effect of target luminance on the frequency components of the power spectrum of accommodation microfluctuations. They reported frequency changes in the low frequency components of accommodation microfluctuations when the target luminance is reduced from 70 cd/m\(^2\) to 0.07 cd/m\(^2\) (Charman and Heron 1988).

A study by Gray et al. (1993b) extended Charman’s research. They examined nine different but equal logarithmic stepped, luminance levels on the microfluctuations of accommodation. Their experimental results suggested a general power decrease in the low frequency components when the target luminance increased and no systematic variation of the high frequency components with the increase of target luminance.

**Ageing**

Heron and Schor (1995) investigated the effect of ageing on the microfluctuations of accommodation and found that the spatial power spectrum of accommodation microfluctuations generally reduces with age. Their experimental data showed that power of the accommodation microfluctuations increased for increasing response levels (target
vergences) with larger magnitudes for younger subjects than the elder subjects in both low and high frequency components.

Toshida et al. (1998) examined the integrated power of accommodation microfluctuations at the higher frequency region for subjects groups between 20 and 50 years of age. The integrated power at higher frequency region of the subjects in their 40s showed almost no changes for accommodative stimulus range between 0 D to -6 D and was significantly smaller than that of the subjects in their 20s and 30s for accommodative stimulus range between -2 D to -6 D. A similar experimental result was reported by Mordi and Ciuffreda (2004) on the accommodation microfluctuations activity with age. In this study, a shift in frequency components towards the lower frequency range was noticed for the older subjects.

**Cardiopulmonary system effects on accommodation microfluctuations**

A significant correlation between the higher frequency components (range between 0.9-2 Hz) and arterial pulse was first demonstrated by Winn et al. (1990a). Their results showed a positive correlation between arterial pulse frequency and the dominant high frequency component of accommodation microfluctuations. This correlation was maintained during the recovery phase of an exercise-induced increase in pulse rate. They also reported the absence of the high frequency component in an aphakic eye. Based on these results they proposed three possible mechanisms through which the ocular pulse could be associated with high frequency accommodation microfluctuations:

1. Pulsatile blood flow in the ciliary body affecting the ciliary ring diameter;
2. Intraocular pressure pulse displacing the crystalline lens; or
3. Reduced resistance to lens elasticity with each cyclic reduction in intraocular pressure.
Collins et al. (1995a) also investigated the relationship between variations in steady-state accommodation (microfluctuations) and rhythmic cycles in the cardiopulmonary system. Respiration and an associated cycle in the instantaneous pulse rate showed a correlation with a low frequency component of the accommodation microfluctuations power spectra. This apparent coherence between respiration frequency and an accommodation microfluctuations low frequency component was maintained during rapid breathing and was evident at the expected frequency during regulated breathing patterns (Collins et al. 1995a). One possible mechanism through which the respiration could influence accommodation fluctuations is through respiration’s modulation of instantaneous pulse rate or intraocular pulse. This modulation causes the heart rate to slightly increase during inhalation and reduce during exhalation and is termed respiratory sinus arrhythmia.

**Possible roles of accommodation microfluctuations in accommodation control**

The accommodation control system of the eye might be influenced by out-of-focus targets by over- or under-accommodation response (Campbell and Westheimer 1959). The accommodation fluctuation can either improve the out-of-focus image by changing towards to the right response direction or worsen the image by going in the other direction. The accommodation response system might use an error detector in the feedback-control system to elicit the required direction of response. Accommodation microfluctuations could derive odd-error (directional) cues from an even-error (non-directional) source (the defocused retinal image) to optimise the initial accommodation response (Alpern 1958). A recent study has also suggested that even-order aberrations could provide odd-error cues for accommodation control (Wilson et al. 2002).
Experimental results have shown that accommodation response can be provoked by a dioptric stimuli as low as 0.1 D (Ludlam et al. 1968). This is less than the ocular perceptual depth of focus and also less than the RMS of natural accommodation microfluctuations.

Kotulak and Schor (1986b) found high frequency microfluctuations at 2 Hz ranged between 0.02 D to 0.1 D (mean to peak for stimulus vergence level between –1 D and –4 D). They proposed that the accommodation error detector could use these 2 Hz oscillations to provide some information on the error signal (e.g. magnitude or direction) (Kotulak and Schor 1986b). They also demonstrated that an accommodation response could be detected with the stimulus oscillation as low as 0.12 D, while blur perception threshold for a defocus oscillation was as high as 0.18 D (Kotulak and Schor 1986a).

Winn et al. (1989) examined the possibility of the accommodation microfluctuations providing perceptual sign information for accommodation control. They found that RMS values of accommodation microfluctuations were similar to the threshold for perception of blur. They showed that a proportion of accommodation microfluctuations were larger than depth of focus and could therefore provide information for the accommodation control system without the need for a subthreshold mechanism.

Charman and Heron (1988) suggested that the high frequency components of accommodation microfluctuations were not likely to play a role to actively control the steady-state accommodation while the low frequency components seemed to be more likely to be used to maintain accommodation response. The low frequency component of accommodation microfluctuations has been found to vary in magnitude as a function of
pupil size and in frequency as a function of target luminance (Gray et al. 1993a; Gray et al. 1993b). The high frequency component is highly correlated with the arterial pulse (Winn et al. 1990a; Collins et al. 1995a) and doesn’t seem to show much systematic change with varying stimuli conditions such as pupil diameter or target luminance.

In summary, accommodation microfluctuations probably produce detectable changes in the retinal image that could provide the steady state accommodation control system with cues to maintain optimal state of focus for the eye.
1.6 Correction of the eye’s aberrations

Conventional spectacles and contact lenses can normally be used to correct two basic types of lower order aberrations: defocus and astigmatism. Now researchers are looking at other techniques for correcting the higher order aberrations through the use of customised refractive surgery (Mrochen et al. 2001) and customised contact lenses (Guirao et al. 2001). The impact of higher order aberrations on the retinal image and the visual benefit of correcting higher order aberrations of the eye have been studied by Williams et al. (2000). Significant improvements in MTFs was reported when both lower order and higher order aberrations are corrected compared with only defocus and astigmatism corrected. The visual benefit (contrast improvement) of correcting of the higher order aberrations on 109 normal subjects was predicted to be a factor of 3 (Williams et al. 2000). Guirao et al. (2002) has reported a 2.5 visual benefit for a group of normal eyes for a 5.7 mm pupil at 16 (c/deg) spatial frequency and a 12 times visual benefit for a keratoconic patients group after correcting the higher order aberrations.

Three main kinds of adaptive optics techniques have been developed and applied for wavefront correction. They are liquid-crystal spatial light modulator, phase plates and adaptive mirrors. The liquid-crystal spatial light modulator has the advantage of low cost, but its performances are limited in terms of speed for dynamic correction of the aberrations in human eyes and magnitude and the range of higher order aberration correction (Thibos and Bradley 1997; Vargas-Martin et al. 1998).

Because of the fluctuations of the eye aberrations, the dynamic correction of the eye’s aberrations is necessary for applications such as high-resolution retinal imaging. The deformable mirrors are now the most popular devices for adaptive optics. They can
provide real-time dynamic corrections, which significantly improve the retinal image, but have the disadvantage of high cost.

Liang et al. (1997) first developed adaptive optics to measure and correct the higher order (up to 10th order) monochromatic wave aberrations of the eye. The RMS wavefront errors for four subjects before and after compensation with adaptive optics were shown to be significantly reduced. They also noted that correcting of high-order aberrations with a deformable mirror or a custom contact lens would provide more visual benefit for larger pupils (Liang et al. 1997).

Improvement has been measured in retinal image quality following correction of the temporal variations in the eye's wave aberration with a closed-loop adaptive optics system (Hofer et al. 2001b). The system provided dynamic correction of fluctuations in Zernike modes up to the 5th radial order with temporal frequency components up to 0.8 Hz. Correction of the temporal variation in the eye's wave aberration increased the Strehl ratio of the point spread function nearly 3 times, and increased the contrast of images of cone photoreceptors by 33% compared with images taken with only static correction of the eye's higher order aberrations.

Fernandez et al. (2001) developed a prototype apparatus for real time closed–loop measurement and correction of eye aberrations. They corrected the defocus by a motorised optometer and the higher order aberrations by a deformable mirror. They were able to measure the aberrations at 25 Hz and correct them at 5 Hz. The improvement of the retinal images (Point Spread Function) was demonstrated in real time with the closed-loop correction activated.
Yoon and Williams (2002) measured the wave aberrations with a Hartmann-Shack wavefront sensor and corrected the eye’s higher-order aberrations with a deformable mirror. In their experiments for a 6 mm pupil and low illuminance level, the improvement of visual acuity for seven subjects was an average of 1.4 lines (logMAR) after correcting the monochromatic aberrations, and a factor of 1.6 after correcting both the monochromatic aberrations and the chromatic aberrations (Yoon and Williams 2002).

Yoon et al. (2004) measured aberrations in three normal subjects’ eyes for a pupil size of 6 mm using a Shack-Hartmann wavefront sensor and corrected the high order aberrations with phase plates. Results showed that the wavefront error RMS reduced by more than 50% with the phase plates. Retinal image quality (modulation transfer function) was improved by a factor of 1.8 with the phase plates compared with sphero-cylinder correction. Visual acuity was also demonstrated to be improved for both high and low contrast letters.
1.7 Rationale

The human eye suffers various optical aberrations that affect retinal image quality. These aberrations include defocus and astigmatism, as well as the higher order aberrations that also play an important role in our vision. The optics of the eye are not static, but are continuously fluctuating. The microfluctuations of accommodation have been previously studied, however there have been few studies on the microfluctuations of monochromatic aberrations, in particular high order wave aberrations. The relative contributions of the ocular surface and internal optics of eye to microfluctuations of wave aberrations of the whole eye are also unknown. These issues were addressed in the following series of experiments, described in the following chapters, where the microfluctuations of wavefront aberrations and factors that influence the fluctuations were investigated.

The ocular surface is one of many components that may contribute to the dynamics of the eye optics. Most previous studies on the changes of the ocular surface in the inter-blink period were limited because only static measurements of the topography were performed. With the new technology of high speed videokeratoscopy, the dynamics of the ocular surface were studied at a sampling frequency of 50 Hz (Chapter 2). Using a program written in MATLAB (Mathworks, Inc.) developed for this study, it was possible to visualise the changes in tear film flow and tear film thickness changes during inter blink intervals.

Previous research has examined the characteristics of microfluctuations in accommodation and the magnitude of monochromatic aberrations as accommodation varies. The characteristics of microfluctuations of the individual components of the monochromatic aberrations and the sources of these microfluctuations remain unknown.
In Chapter 3, the microfluctuations of the wavefront aberrations of the eye up to the 4th order were measured using a COAS wavefront sensor and their relation to the pulse and instantaneous heart rate were investigated. A power spectrum analysis based on autoregressive processes was developed for this study.

Many previous studies have investigated the relative contributions of the ocular surface and the internal optics to the monochromatic aberrations of the whole eye. However, there have been no studies on the contributions of the ocular surface and the internal optics to the microfluctuations of monochromatic aberrations of the eye. Microfluctuations of accommodation with stimulus vergence have been extensively studied, but little is known about the microfluctuations of the monochromatic aberrations and stimulus vergence. Chapter 4 describes the ocular factors that influence these microfluctuations of wavefront aberrations in the human eye, including the contribution of the ocular surface, accommodation, and refractive error magnitude. This study provided details on the contribution of the ocular surface and internal optics to the microfluctuations of the total eye’s wavefront aberrations.

The findings of these studies are important for understanding the optical quality of the eye and the sources that cause the fluctuations of the eye’s wavefront aberrations. This will aid in the development of techniques for more accurate measurement of the eye aberrations that take account of fluctuations and may aid correcting the eye’s aberrations to potentially allow better vision and visualisation of the retina.
Chapter 2

Dynamics of Ocular Surface Topography

2.1 Introduction

The cornea plays an important role in determining the overall image quality of the eye. The pre-corneal tear film provides a smooth, regular anterior surface of the eye. Tear film builds up after a blink and becomes unstable over time, finally breaking-up (Benedetto et al. 1984; Nemeth et al. 2002; Montes-Mico et al. 2004a). Local changes in the tear film or tear irregularity can introduce additional aberrations into the optics of the eye, hence instability of the tear film will cause microfluctuations in the optical quality of the eye. Corneal topography techniques based on the Placido disk principle use the tear film as a convex mirror to view the first Purkinje image, therefore they measure the pre-corneal tear film surface and not the corneal surface. The most outer surface of the tear film is therefore the actual ocular surface that is measured. If the tear film is stable, continuous and has constant radial thickness, then we can assume that the Placido technique is closely approximating the corneal surface.

There have been numerous studies of the changes in the topography of the ocular surface in the inter-blink period using videokeratoscopy. Nemeth et al. (2000) measured the ocular surface topography with a videokeratoscopy in the interval between 5 and 10 seconds after a complete blink and showed significant differences in ocular surface topography (in terms of surface regularity index) while the ocular surface refractive power remained unaltered. A significant
increase in both total and ocular surface aberrations 10 and 20 seconds after blink have been reported for larger pupil sizes (>3.5 mm) by Montes-Mico et al. (2004b) and they suggested that these optical changes were caused by increasing irregularity in the tear film with time, which affected the entire optics of the eye. In another study, the changes of higher order ocular surface wavefront aberrations were investigated with a time resolution of one second for 15 seconds after a blink (Montes-Mico et al. 2004a). The higher order aberrations were found to first decrease immediately after a blink, reaching a minimum 6 seconds post blink, and then increase steadily (Montes-Mico et al. 2004a). However, these studies were limited because only a single topography image was captured at a time.

With the emerging technology of high-speed videokeratoscopy, it is possible to acquire information on the dynamic changes of the ocular surface. High speed videokeratoscopy was developed to automatically capture consecutive ocular surface topography and hence this technique can be used to examine the tear film dynamics. In the investigation of tear film stability, this technique was introduced as a non-invasive and objective method for the clinical assessment of tear film stability (Goto et al. 2003; Goto and Zheng 2004; Kojima et al. 2004). Nemeth et al. (2002) used it to measure the tear film build-up time based on the changes in the surface regularity and asymmetry indices and found that tear film was most stable three to ten seconds after blink. However, the limitations of the surface regularity and asymmetry indices as an assessment of the stability of the tear film by high speed videokeratoscopy were recently reported by Iskander et al. (2005). They proposed a technique for estimating the tear film build up time based on the RMS of the error of the parametric model fit to the ocular surface which is independent of the micro-movements of the eye or the pupil displacement.
2.2 Aims

The aim of this study was to examine the ocular surface dynamics in the inter-blink interval and investigate the tear stabilization time. Changes in the tears will influence ocular surface topography measurements along with measurements of the total optics of the eye. This study will help in our understanding of the relationship between the changes in the tear film and the variations in the ocular surface wavefront aberrations.

2.3 Methods

2.3.1 Data acquisition

Ocular surface topography was obtained by using a high speed videokeratoscopy system (Medmont Studio version 3.7 Medmont Pty Ltd, Australia). The main components of this system are shown in Figure 2.1 and have been described in Iskander et al. (2005).

The ocular surface topography of the left eye was measured at a sampling frequency of 50 Hz and for each recording we collected a 40 second continuous record (i.e. 2000 images). The subjects did not wear contact lenses or spectacles and were instructed to focus on the instrument’s internal fixation target. The right eye (untested) had a free view past the instrument. Subjects were instructed to have natural blinks whenever necessary and to breathe at 0.5 Hz, guided by an electronic metronome. A breathing rate of 0.5 Hz was chosen for ease of identification of this frequency component, since higher and lower frequency components (i.e. >0.8 Hz or <0.2 Hz) are typically present in accommodation power spectrum (Winn et al. 1990a; Collins et al. 1995a). When two similar frequencies arise in power spectra, discrimination of two separate peaks can be difficult. Subjects were also instructed not to
deliberately open their eyes wide, but to look naturally at the fixation target. By instructing subjects to blink naturally and not deliberately widen their eyelid aperture, we assessed ocular surface dynamics in a relatively natural state.

![Figure 2.1: Main components of the high speed videokeratoscopy used in our study.](image)

The pulse signal of the subject was simultaneously collected by a MacLab/4s and Bio Amp (ADInstruments Pty Ltd, Australia) which is designed to record the electrocardiogram (ECG) using electrodes connected to both wrists and the right ankle of the subject. The pulse signal was measured at a sampling frequency of 40 Hz for a duration of 40 seconds. The frequency range of primary interest is normally less than 2 Hz, so the sampling rates of both instruments were well above the Nyquist frequency. The acquired pulse signal was used to derive the instantaneous heart rate (Friesen et al. 1990). Instantaneous heart rate is the cyclic fluctuation in the time delay between each heart beat (heart rate increases slightly during inspiration and reduce during expiration), whereas pulse rate is simply the number of heart beats per minute. The configuration of the instruments used in the experiment is depicted in Figure 2.2.
Figure 2.2: Experiment setup. A high speed videokeratoscopy is used for the dynamic ocular surface topography measurement. Three electrodes from the MacLab system were attached to subjects’ wrists and left ankles to acquire the pulse signal.

A group of ten young subjects participated in this study with mean ages of 24.8 years (range between 21 to 30 years). Informed consent was obtained from all participants and the experiment conformed to a protocol approved by a Human Research Ethics Committee of the university. Seven subjects were emmetropes and three were myopes ($<-5$ D). All subjects had normal, healthy eyes and none had dry eye symptoms. Three simultaneous recordings of pulse signals and ocular surface topography data were collected for each of the subjects. During the data analysis of changes in the inter-blink interval, there were only nine subjects with consistent inter-blink intervals of at least 4.5 seconds.
2.3.2 Data analysis

Surface characteristics

The high speed videokeratoscopy data were used to calculate the ocular surface height maps that depict the relative height from the apex of ocular surface. Ocular surface height maps were centred on the videokeratoscope axis (vertex normal). Ocular surface height difference maps were derived by subtracting a baseline ocular surface height map from a series of sequential maps to reveal and highlight the changes in the tear film. The height difference map provides two-dimensional information and reflects the changes in the thickness of tear film that covers the ocular surface provided that the underlying ocular surface topography is stable and does not change in the time interval of the measurements. To study the tear dynamics in the inter-blink interval we normally chose as the baseline map the first available videokeratography directly after a blink that had complete information and a good quality ring pattern (defined as t=0). All the subsequent ocular surface images leading up to the next blink were subtracted from this baseline map (i.e. surface difference maps) to investigate the tear dynamics such as tear flow and tear distribution. In this study, our subjects were instructed to focus on the target naturally without widening their aperture purposely, therefore the location of the eyelids was normally 3 to 4 mm from the centre of the pupil. Hence the surface height maps were generally 6-8 mm wide vertically and 9-11 mm wide horizontally.

Zernike Analysis

Each videokeratography was also used to estimate the ocular surface wavefront aberrations for a 5 mm pupil diameter by a ray tracing technique (Guirao and Artal 2000). The principal axis of the wavefront was chosen to be at the centre of the entrance pupil that was located in the raw
videokeratoscopy digital image. Compared with the height difference maps, the Zernike wavefront aberrations analysis has the advantage of providing a mathematical analysis of shape changes in the surface of the tear film. The wavefront aberrations were decomposed into a set of Zernike polynomials up to the 4th radial order. The time-varying ocular surface wavefront aberrations, $w(\rho, \theta; t)$ are mathematically modelled.

$$w(\rho, \theta; t) = \sum_{i=1}^{15} a_i(t)Z_i(\rho, \theta) + \varepsilon(\rho, \theta; t)$$

where $a_i(t)$, $i=1,2,\ldots,15$, are the time-varying Zernike coefficient signals and $Z_i(\rho, \theta)$ are the orthogonal Zernike polynomials (Thibos et al. 2002a). Note that in the above equation the wavefront is a function of the radial distance $\rho$ and angle $\theta$ as well as the time $t$. The instrument and modelling noise is denoted by $\varepsilon(\rho, \theta; t)$.

An example of ocular surface Zernike aberration coefficients signals derived from 40 seconds continuous recording for subject DF’s ocular surface topography is shown in Figure 2.3. To remove the blink artefacts from the ocular surface wavefront Zernike aberration coefficients signals, we used a third order polynomial global interpolation technique (i.e. using the full data set except those data points where the blinks occurred). Specifically, an algorithm was applied to the ocular surface wavefront signals to find the locations of the blinks where the ocular surface wavefront Zernike aberration coefficients are zero (the centre of the pupil is undetectable). We found problems with using some images captured during the downward and upward phases of a blink even though the pupil centres of these images were detectable. Firstly, the topography information was incomplete because of the low position of the eyelid, and in some cases the images were blurred or distorted due to the lid movement. As an
Figure 2.3: Example of ocular surface Zernike wavefront coefficient signals derived from the high speed videokeratoscopy for a 5 mm pupil size for subject DF. The ordinate is the value of the wavefront error in microns. Blinks can be seen at 6 sec, 11 sec, 21 sec, 28 sec and 37 sec.

example, we have plotted some raw images captured before, during and after a blink for subject DF at time intervals of 0.02 second (Figure 2.4). In nine images frames (6-14), the cornea was largely covered by the eyelid and the pupil centre was not detectable. Two image frames (4 and 5) captured during the downward phase and three images frames (15, 16 and 17) captured during the upward phase had the pupil centre detectable, but part of the ring information above
Figure 2.4: Raw ocular surface videokeratoscopy images captured during a blink for subject DF.
the pupil centre was unavailable in image frames 5, 15 and 16 and the ring pattern was blurred in image frames 4 and 17. These problems could lead to inaccurate estimations of the ocular surface wavefront Zernike aberration coefficients and unstable signals (sudden changes). Therefore we decided to ignore 3 images (0.04-0.06 secs) immediately before and after each blink and interpolate according to the remaining signal information.

**Eye position**

When the ocular surface topography data were acquired, the high speed videokeratoscope also recorded the eye position including x (left-right), y (up-down) and z directions (anterior-posterior). The distances between the ocular surface apex and the instrument’s position sensing system were used by the Medmont E300 instrument to calibrate the topography results. These anterior-posterior eye position measurements were later used to investigate the microfluctuations of the anterior-posterior eye position. Any unusual x, y lateral eye movements (eg. Due to loss of subject fixation) were evident in the high speed videokeratoscope record and these signals were not used in subsequent analysis.

**Power spectrum analysis**

Before temporal or frequency analyses of the Zernike coefficient signal is conducted, the signals are first detrended by removing a linear trend and then band-pass filtered to extract the frequency range of interest (0.1 Hz – 2 Hz). Detrending is a standard signal processing procedure that removes the DC component from a signal (see Figure 2.5 as an example). It is performed because the fluctuations in each of the Zernike aberration signals are of interest
rather than their actual values. As a band-pass filter, a digital filter was used to remove the low frequency (<0.02 Hz) and high frequency (>2 Hz) components contained within the signal.

For each of the 12 Zernike coefficient signals (prison and prisms excluded) \( a_i(t) \), \((i = 4, 5, \ldots, 15)\), a procedure of power spectrum estimation techniques based on the Fast Fourier Transform (FFT) was used to estimate the power spectra of the aberration signals. The same procedure of spectral analysis was applied to the pulse and the instantaneous heart rate signals. The spectral representations of aberration and pulse signals were then used to determine the similarities (common frequency peaks) between the signals.

Figure 2.5: An example of the same signal before (top) and after (bottom) the detrending process.
Coherence Analysis

Another measure of the interrelation between two signals is the coherence. When two sets of data have been acquired from simultaneous measurements on two systems, the coherence function can be calculated as (Eadie et al. 1995):

$$\gamma^2 = \frac{|P_{xy}(f_k)|}{P_{xx}(f_k)P_{yy}(f_k)}$$

where $P_{xy}(f_k)$ is the cross-power spectrum, while $P_{xx}(f_k)$ and $P_{yy}(f_k)$ are the auto power spectra of signals $x(t_n)$ and $y(t_n)$, $n = 0, \ldots, N-1$, respectively. The coherence function can take values between 0 and 1, which determine the independence or incoherence (zero) and dependence or coherence (one) of the two signals.

2.4 Results

Within the first 0.5 seconds after the blink, the tear film became significantly thicker at the top of the topography map and became thinner at the bottom region of the map. The ocular surface topography became relatively stable after 2-3 seconds post-blink. There were no clear trends in ocular surface dynamics between subjects in the subsequent inter-blink period. Pulse had no significant effect on fluctuations in ocular surface topography.
An example of the variations in ocular surface vertical coma within a blink interval (first blink interval for subject DF in Figure 2.3) is depicted in Figure 2.6. Generally, changes in ocular surface vertical coma occurred in two phases. Up to 1.2 seconds post blink, the ocular surface vertical coma changed significantly and this time is often termed the tear ‘build-up’ phase (Montes-Mico et al. 2004a). Between 1.2 seconds and 5.2 seconds of the ‘inter-blink’ phase, the ocular surface vertical coma did not have much change and was comparatively stable.

Figure 2.6: Example of changes in the ocular surface vertical coma coefficient during the tear film build-up phase and inter-blink phase in the first blink interval for subject DF. WFE (y axis) is wavefront error.
2.4.1 Changes in tear film surface height

To illustrate the ocular surface dynamics in the inter-blink interval, ocular height difference maps for subject ZD representing the difference between the 1st and 2nd, 1st and 12th, 1st and 22nd up to 3.82 seconds post blink are shown in Figure 2.7. If we assume that the underlying corneal topography is stable, then changes in surface height reflect changes in the tear film thickness. In this example, thickening at the superior edge of the map was observed after the blink as the tears presumably moved upward following the upward movement of the upper eyelid. Up until 0.62 sec following the blink, the superior region of the tear film became progressively thicker; with 4 to 8 µm increase. At the same time, the inferior region of the map became thinner by 2 to 3 µm compared with the baseline map taken immediately after the blink.

In the next phase of the post-blink interval (0.62 to 3.82 sec) the thickness of the tears decreases slightly in the superior region of the map and increases slightly in the inferior region. This presumably reflects a slow downward flow of tears. The temporal changes in the tear film at 3 mm above and below the centre are depicted in Figure 2.8. The tear film at 3 mm above centre became 7 µm thicker at 0.6-0.7 sec after the blink and then within the next 3 sec became gradually thinner by 2 µm (Figure 2.8 top). The changes at 3 mm below the centre were smaller, with a decrease in thickness by 3 µm over the first 0.5 sec after the blink and an increase by 3 µm in the next 3 sec (Figure 2.8 bottom).
Figure 2.7: Ocular surface height difference maps for subject DZ derived at time t=0.02 sec, 0.22 sec, 0.42 sec... The height difference was derived by subtracting the map at t=0 immediately after blink from subsequent maps. Positive values (red) therefore indicate a relative thickening and negative values (blue) a relative thinning of the tear film. The colour bar represents the height scale (in units of micron).
Figure 2.8: Ocular surface height changes for subject DZ at location of 3 mm above the centre (top) and 3 mm below the centre (bottom) derived by subtracting the height at t=0 immediately after blink from subsequent maps.

‘Build-up’ phase

To explore the tear film dynamics during the tear film build-up phase immediately after each blink with better time resolution (0.04 secs), ocular surface height difference maps for subject DZ representing the difference between the 1st and 2nd, 1st and 4th, 1st and 6th up to 0.78 seconds post blink are shown in Figure 2.9. There is a rapid increase in tear thickness from 0.02 to 0.26 sec post blink in the superior region of the map. From 0.26 to 0.62 sec post blink, the tear surface height is relatively stable with a slight increase in the thickness continuing to occur at the superior edge of the map.
Figure 2.9: Ocular surface height difference maps for subject DZ derived at time $t=0.02$ sec, $0.06$ sec, $0.1$ sec… The height difference was derived by subtracting the map at $t=0$ immediately after blink from subsequent maps. Positive values (red) therefore indicate a relative thickening and negative values (blue) a relative thinning of the tear film. The colour bar represents the height scale (in units of micron).
‘Inter-blink’ phase

The changes in the tear thickness during the ‘inter-blink’ phase (Figure 2.7, 0.62 to 3.82 post blink) were comparatively smaller than those during the ‘build-up’ phase (up to 0.62 post blink). To highlight the height changes during the ‘inter-blink’ phase, the baseline height map was chosen at the t=0.62 sec post blink and difference maps were derived every 0.2 sec afterwards until 3.82 sec post blink (Figure 2.10). The tears appeared to flow downwards in this period since the tear film got thicker in the inferior region and thinner in the superior region compared with the baseline at t=0.62 sec post blink. Within 3.2 sec, at the superior edge of the map the tear film became thinner by 1.4 to 2.8 \( \mu m \) and at the same time became thicker by 0.7 to 1.4 \( \mu m \) at the inferior edge of the map.

For 9 of 10 subjects, the tear film initially got thicker at the superior edge of the map presumably due to the upward movement of the tears after a blink following the path of the upper eye lid. The data showed greater variability in the ‘inter-blink’ phase with opposite trend (see Figure 2.11 for an example, 2.02 to 7.52 sec post blink) or no obvious change in the tear thickness being observed. Furthermore, the tears sometime appeared to flow toward the nasal direction in the inter-blink phase, with the nasal tears becoming thicker (see Figure 2.10 for an example).
Figure 2.10: Ocular surface height difference maps for subject DZ derived at time t=0.82 sec, 1.02 sec, 1.22 sec... The height difference was derived by subtracting the map at t=0.62 post blink from subsequent maps. Positive values (red) therefore indicate a relative thickening and negative values (blue) a relative thinning of the tear film. The colour bar represents the height scale (in units of micron).
Figure 2.11: Ocular surface height difference maps for subject SV derived at time $t=0.02$ sec, $0.52$ sec, $1.02$ sec... The height difference was derived by subtracting the map at $t=0$ immediately after blink from subsequent maps. Positive values (red) therefore indicate a relative thickening and negative values (blue) a relative thinning of the tear film. The colour bar represents the height scale (in units of micron).
Group ocular surface height changes were also examined and the mean changes at the vertical meridian 3mm above and below centre are presented in Figure 2.12 and Figure 2.13. The mean changes in the tear film found within the first 0.5 sec after a blink were a 2 µm (±2 µm) thickening 3 mm above the centre (Figure 2.12) and less than 0.5 µm (±1 µm) thinning 3 mm below the centre (Figure 2.13). The group mean surface height changes in the post blink interval were smaller than many individual results because of averaging of significant intra- and inter-subject variability. The one-way repeated measures analysis of variance (ANOVA) showed that the group ocular surface height 3 mm above the centre in the blink interval of 4.5 seconds significantly increased ($F = 1.691, \ df = 44, \ p=0.006$). However, no significant changes over time were found in the group ocular surface height 3 mm below the centre ($F = 1.025, \ df = 44, p=0.434$).

2.4.2 Changes in ocular surface wavefront aberrations in the blink interval

All of the ocular surface wavefront aberration signals measured exhibited temporal fluctuations. We examined the group mean changes in the ocular surface wavefront aberrations. Group data of ‘one-way’ repeated measures analysis of variance in ocular surface wavefront aberrations were calculated. Magnitudes of ocular surface horizontal coma (absolute values) and secondary astigmatism at 45 degrees significantly increased ($p<0.001$ and $p=0.007$) in the inter-blink interval and ocular surface secondary astigmatism at 0 degrees showed a significant decrease ($p=0.02$) in its magnitude. However the other ocular surface Zernike components measured showed no significant changes (see Table 2.1).
Figure 2.12: Group ocular surface height changes in the vertical meridian 3 mm above centre. Data are the mean of multiple signals for 9 subjects (only the blink intervals of at least 4.5 seconds were included in this analysis). Dotted lines indicate ±1 SD error bars. On the y axis, positive values represent increased height (i.e. tear thickening) and negative values represent decreased height (i.e. tear thinning) relative to the surface height immediately after the blink (t=0).
Figure 2.13: Group ocular surface height changes at the vertical meridian 3 mm below the centre. Data are the mean of multiple signals for 9 subjects (only the blink intervals of at least 4.5 seconds were included in this analysis). Dotted lines indicate ±1 SD error bars. On the y axis, positive values represent increased height (ie. tear thickening) and negative values represent decreased height (ie. tear thinning) relative to the surface height immediately after the blink (t=0).
Table 2.1: Group data of ‘one-way’ repeated measures analysis of variance in ocular surface wavefront aberration components in the first 4.5 seconds after a blink. Group data for 9 subjects.

In the surface height analysis, changes of tear film thickness assumed to be due to the tear flow were often apparent in the vertical direction. Therefore we investigated the temporal changes in the corresponding vertical prism and vertical coma Zernike terms in the same blink interval for subject DZ (Figure 2.14). Immediately after the blink, both the vertical prism and vertical coma dramatically decreased within 0.2 to 0.25 second due to the upward movement of the
tears (also see Figure 2.7 first two height difference maps). In the next 0.2 to 0.4 seconds, a slow decrease in these terms occurred. At 0.5 to 0.6 second post blink, both the vertical prism and vertical coma reached their minima and then started to increase in magnitude. After this tear film build-up phase, there was a slow increase in both vertical prism and vertical coma up to 3.82 seconds. This change can also be observed in the surface height difference maps between 0.62 and 3.82 seconds in Figure 2.7.

Figure 2.14: Temporal changes in vertical prism (top) and vertical coma (bottom) coefficients estimated from the same blink interval as in Figure 2.7 for subject DZ.
Trends in the ‘build-up’ phase

The effect of the blink on the ocular surface wavefront aberrations can be easily seen from the raw signals in Figure 2.15. Directly after the blinks, some of the measured ocular surface Zernike wavefront aberrations appeared to have a large change (decrease or increase) in the overall magnitude and then within a couple of seconds they stabilized until the next blink (for example, horizontal and vertical prisms).

To investigate the general trends in the ocular surface Zernike wavefront aberrations following a blink, we calculated the group mean changes in the each Zernike component. Among the 14 ocular surface Zernike wavefront aberrations measured, the vertical prism term showed greatest changes directly after a blink and vertical coma term also exhibited a similar trend. The group mean changes in vertical prism, vertical coma and secondary astigmatisms are shown in Figure 2.16. The changes in group mean vertical prism and vertical coma were not consistent between and within subjects over multiple blinks. The changes in horizontal prism and coma showed better repeatability, though they were smaller in magnitudes. After 1.5 to 2 seconds post blink, these changes in the magnitude tended to stabilize and then remain relatively constant. During the build-up phase, the dynamics in the surface height were generally a vertical and horizontal movement instead of localized changes or global symmetrical changes, hence ocular surface wavefront Zernike components such as trefoils, tetrafoils, defocus and spherical aberration were less affected.
Figure 2.15: Ocular surface Zernike wavefront aberration signals for subject DF after removing the blink artefacts for a 5 mm pupil size (arrows on the top indicate where a blink occurred. The ordinate is the value of the wavefront error in microns. Zernike terms are arbitrarily separated on the y axis for ease of viewing.
Figure 2.16: Group mean changes in vertical prism, vertical coma (top) and secondary astigmatism (bottom) coefficients. In the top plot, vertical coma has been shifted vertically by 0.032 μm for clarity of presentation.

‘Inter-blink’ phase

We examined the temporal changes of the ocular surface wavefront aberrations in the inter-blink phase and the most obvious changes were found in the prisms and comas. However, the
results showed great intra- and inter-subject variability. For example, the general magnitude of vertical coma increased in the inter-blink phase in two out of ten subjects (see Figure 2.17 top plot as example) while the opposite were observed in five other subjects (example in Figure 2.17 bottom plot) and in the other three subjects did not show an obvious trend. In these examples, within the three seconds from 0.5 to 3.5 sec post blink, subject DZ’s vertical coma increased by 0.01 $\mu m$, while subject SV showed greater than 0.01 $\mu m$ decrease in the five seconds from 2 to 7 sec post blink (Figure 2.17). In five out of ten subjects, their horizontal coma appeared to slightly decrease during the ‘inter-blink’ phase. One subject showed the opposite trend and in the remaining four subjects no obvious trends were observed.

Figure 2.17: Post blink changes in ocular surface vertical coma for subject DZ (top) and subject SV (bottom).
2.4.3 Microfluctuations in ocular surface wavefront aberrations

Time domain representation

To investigate the microfluctuations of ocular surface Zernike aberrations up to the 4th radial order, the signals with blinks removed for subject DF are shown in Figure 2.15. It appears that some of the paired ocular surface Zernike aberrations, such as prisms, astigmatisms and coma share certain similarity in terms of time domain characteristics. The changes in both prisms (vertical and horizontal) showed the same changes in coefficient sign direction after a blink (Figure 2.15). However, changes in the astigmatism signs (at 0 degrees and at 45 degrees) went in the opposite directions post blink.

All of the 14 ocular surface Zernike aberration signals measured exhibit temporal fluctuations. To examine the magnitude of fluctuations contained in the signals, the variance of the stable segments (ie, ignoring the build-up phase, see Figure 2.6) from all the blink intervals for each ocular surface Zernike aberration were calculated. Figure 2.18 shows the group average standard deviation in each ocular surface Zernike coefficient. The prisms exhibited the largest variations among all the ocular surface Zernike wavefront aberrations measured. The microfluctuations in the astigmatisms, trefoil, and tetrafoil were found to be greater than those in defocus, comas, secondary astigmatism, and spherical aberration. It appeared that the variations in ocular surface defocus wavefront aberration were the lowest among the 14 ocular surface wavefront aberrations that were measured.
Figure 2.18: Group mean standard deviation of signals for each ocular surface Zernike wavefront aberration. Data are the mean of multiple signals for 10 subjects. Error bars are ±1 SD.

**Frequency domain representation**

Figure 2.19 shows the simultaneously recorded pulse signal and the derived instantaneous heart rate for subject DF. To determine if there was a dominant frequency component contained within the measured signals, the power spectra of the ocular surface Zernike aberration signals, pulse and instantaneous heart rates were estimated by using the FFT technique. Figure 2.20 presents an example of the power spectra of signals corresponding to astigmatism at 0 degrees, defocus, vertical trefoil, vertical coma, tetrafoil at 22.5 degrees and secondary astigmatism at 45 degrees for subject DF. For clarity of presentation, the spectra of the pulse and instantaneous heart rate signals have been normalised to the peaks of the aberration spectra. The subject was
Figure 2.19: Original signal of pulse (top) and the derived signal of instantaneous heart rate (bottom). BPM is beats per minute. Instantaneous heart rate is the time difference between consecutive heart beats.

instructed to breathe on a metronome beat at 0.5 Hz and the power spectrum of the instantaneous heart rate shows a frequency component with a peak at 0.5 Hz, presumably due to sinus arrhythmia (Angelone and Coulter 1964). However in this example, the fluctuations of subject DF’s aberrations did not contain any major fluctuation frequency components which show agreement with the frequency components of pulse at around 1.3 Hz or instantaneous heart rate at about 0.5 Hz. The ocular surface data were acquired for a period of 40 seconds;
Figure 2.20: Power spectra of astigmatism at 0 degrees and defocus (top), vertical trefoil and vertical coma (middle), tetrafoil at 22.5 degrees and secondary astigmatism at 0 degrees (bottom) for subject DF plotted with the scaled normalised power spectra of the subject’s pulse (dashed line) and instantaneous heart rate (IHR) (dotted line).
therefore the frequency resolution was 0.025 Hz. With the other nine subjects’ power spectra of these Zernike aberrations, similar frequency spectra with no major peaks close to the pulse and instantaneous heart rate frequency locations were found. Due to the effect of the tear film break-up and blinking, there were often low frequency components (<0.2 Hz). For example, both vertical trefoil and vertical coma have a low frequency component at about 0.1—0.125 Hz in the power spectra (Figure 2.20). For a total measurement period of 40 seconds subject DF had 5 blinks, hence this low frequency component is likely to be caused by the changes in tear film thickness due to the upward tear flow with blinking (see the previous section on surface height and Zernike wavefront analysis).

Coherence Analysis

To further statistically examine the correlation between the ocular surface Zernike wavefront aberrations and pulse and instantaneous heart rate signals, we calculated the coherence function between them. An example of the estimated coherence functions of the astigmatism at 0 degrees signal, pulse, and instantaneous heart rate for subject DF are shown in Figure 2.21. The frequency peaks for the pulse and instantaneous heart rate are indicated by dotted lines. The group average coherence analysis results are presented in Figure 2.22 and averaged coherence between the 12 Zernike aberration signals (excluding piston and prisms), and pulse and instantaneous heart rates are as low as 0.12 and 0.11 respectively, which suggests that the signals examined are uncorrelated (Eadie et al. 1995).
Figure 2.21: Estimated coherence functions of astigmatism at 0 degrees, pulse, and instantaneous heart rate (IHR) for subject DF. Vertical dotted lines indicate the frequency locations of the pulse and instantaneous heart rate.

Eye position

Temporal changes in the axis of asymmetric aberrations (such as astigmatism) were investigated to see if they were correlated with pulse rate due to cyclo-torsions in the ocular surface associated with pulse. For all the subjects we examined, the power spectra of the astigmatism axis did not have a major frequency component that showed association with the pulse frequency. An example of temporal changes in the astigmatism axis and its derived power spectrum are shown in Figure 2.23. In this case, a frequency component at 0.05 Hz that
was also present in the power spectrum of some aberrations was probably due to the slight instability in the signals.

Figure 2.22: Group average data of coherence analyses of 10 subjects between aberration signals and pulse and instantaneous heart rate signals.

Changes in the anterior-posterior eye position (apex distance) were also examined and the power spectra were calculated. In Figure 2.24 we show the interpolated signal of the ocular surface apex distance (top) and the power spectra of the ocular surface apex distance plotted with the normalised spectra of the pulse and instantaneous heart rate signals (bottom) from subject DF. The average drift in the apex distance signal was approximately 0.2 mm with maximum range of 0.52 mm. In this example, the apex distance data was acquired at the same time as the ocular surface topography from which the ocular surface Zernike aberrations were derived in Figure 2.15. Fluctuations of the ocular surface apex distance have two frequency
components which show agreement with the pulse frequency at 1.3 Hz and the instantaneous heart rate frequency at 0.5 Hz while the fluctuations in ocular surface wavefront Zernike aberrations do not show this. With the other nine subjects’ power spectra of the apex distance, similar frequency spectra with two components at the pulse and instantaneous pulse frequencies were typically observed. There are a number of other peaks in the power spectra which were not related to pulse or IHR and their origin is unknown.

Figure 2.23: Temporal changes in astigmatism axis (top) and its power spectrum plotted with the scaled normalised power spectra of the subject’s pulse and instantaneous heart rate (IHR) (bottom) for subject DF.
Figure 2.24: Raw signal of apex distance (top) and power spectrum of apex distance plotted with the scaled normalised power spectra of the subject’s pulse and instantaneous heart rate (IHR) (bottom) for subject DF.

2.5 Discussion

The results of the ocular surface height analysis over time showed that the tear film became thicker at the superior cornea and thinner at the inferior cornea during the tear film ‘build-up’ phase. This was probably due to the rapid upward movement of the tears after a blink. It has been suggested that thinner lipid layer in the superior cornea immediately after a blink causes a high surface tension which results in upward drift of the tear film and then leads to a thicker tear film in the upper cornea (Benedetto et al. 1984; King-Smith et al. 2004). Owens and
Phillips (2001) found that tear spreading velocity decreased to minimum one second post blink. Our examples (Figure 2.8) also showed that the increase in tear thickness in the superior region of the map in the ‘build-up phase’ was first very rapid (< 1 sec) and then became slowly stable.

We studied the period of time between blinks to examine changes in ocular surface height and the ocular surface wavefront aberrations. Several ocular surface wavefront components such as the prisms, comas and astigmatisms showed the greatest change in magnitude after a blink. We found that on average these ocular surface wavefront components reached a stable level approximately 1.5 to 2 seconds (range between 0.4 to 3 seconds) after a blink. This suggests that it took the tear film this time to spread evenly on the corneal surface and to reach a relatively stable state. In previous studies, Owens and Phillips (2001) found the time of tear stabilization after a blink to be approximately 1 second. Buehren et al. (2001) found less ocular surface topography variability at 4 seconds post blink, compared with 8 and 12 second post blink. Nemeth et al. (2000) and Montes-Mico et al. (2004a) have suggested that vidokeratoscopy measurement should be made at a fixed time of approximately 5 second after blink. Recently, Iskander et al. (2005) estimated the tear film build-up time by using a RMS fit surface indicator based on Zernike polynomials. They estimated tear film build-up time to range between 1.5 and 7 seconds. Table 2.2 is the list of the studies that estimated the tear film stabilization time (build-up time) and their recommended post blink time delay to complete the vidoekeratoscopy measurements. Based on the results from both this study and previous studies, we suggest that clinical measurement of ocular surface topography using videokeratoscopy, 2 to 3 seconds after a blink would avoid the variability in results due to the tear film build up phase.
<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Year</th>
<th>Tear film stabilization time</th>
<th>Recommended time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nemeth <em>et al.</em></td>
<td>2000</td>
<td>—</td>
<td>5 seconds post blink</td>
</tr>
<tr>
<td>Owens and Phillips</td>
<td>2001</td>
<td>1.05± 0.30 seconds</td>
<td>—</td>
</tr>
<tr>
<td>Montes-Mico <em>et al.</em></td>
<td>2004a</td>
<td>3 to 10 seconds</td>
<td>4 to 5 seconds post blink</td>
</tr>
<tr>
<td>Iskander <em>et al.</em></td>
<td>2005</td>
<td>1.5 to 7 seconds</td>
<td>—</td>
</tr>
<tr>
<td>This study</td>
<td>2005</td>
<td>0.5 to 3 seconds</td>
<td>2 to 3 seconds post blink</td>
</tr>
</tbody>
</table>

Table 2.2: List of studies that estimated the tear film build-up time and/or recommended time for completing a videokeratoscopy measurement.

Our results on the inter-blink temporal changes in ocular surface vertical coma showed different trends with different subjects. In the first case the ocular surface vertical coma increased with time in the inter-blink phase after a quick decrease in the build-up phase. This result is consistent with previous study by Montes-Mico *et al.* (2004b) that coma-like aberrations tend to increase with time after a blink. It was suggested that this increase in coma-like aberrations may result from the tear layer gravitational effects as the tear film gets thicker at the bottom edge or as a sign of recovery from the effects of lid pressure. In the example of subject DZ’s vertical coma (Figure 14 bottom plot), it was found to increase by 0.01 μm (post blink 0.6 second to 3.8 second). At the same time, this subject’s tear film became thinner at the superior edge of the map (-1.4 to -2.8 μm) and thicker at the inferior edge of the map (0.7 to 1.4 μm). A number of the subjects in this study showed this trend which is consistent with the findings of Montes-Mico’s who suggested that this increase in vertical coma might arise from inferior thickening of the ocular tear film. However, half of subjects in this study showed the opposite
trend, with ocular surface vertical coma decreasing in the inter-blink phase and in these cases the tear film was found to become thicker at the superior ocular surface and thinner at the inferior ocular surface. We suspect that the potential factors causing this variation between subjects could be: (1) continuing tear supply from under the upper lid, (2) tears leaving inter-palpebral space into the tear menisci and canaliculi (drainage system), (3) gravity effects, (4) tear evaporation, (5) tear flow difference related to lid velocity or blink completeness. However, changes in vertical coma showed good agreement with the changes in the tear thickness despite the variations between subjects. This would indicate that the changes in the tear film were the essential contributor to the changes in the coma terms (see Figure 2.8 and Figure 2.14 for comparison).

The anterior corneal surface is not likely to substantially change during the inter-blink period. Studies have found that accommodation does not have a significant effect on the corneal shape changes (Fairmaid 1959; Mandell and St. Helen 1968; Buehren et al. 2003b). Changes in ocular surface topography induced by the force of the eyelids have been observed (Mandell and St. Helen 1968; Bowman et al. 1978; Ford et al. 1997; Lieberman and Grierson 2000; Buehren et al. 2001; Buehren et al. 2003a). However, eyelid force should not significantly influence the data in this study because the location of the eyelids is normally at least 3 to 4 mm from the centre of the pupil and in this study data were analysed for a pupil size of 5 mm.

Both the low and high frequency components of accommodation microfluctuations have been found to be associated with pulse and instantaneous heart rate via the ocular pulse (Winn et al. 1990a; Collins et al. 1995a). However, in our investigation of the correlation between the
microfluctuations in ocular surface wavefront aberrations and pulse and instantaneous heart rates, we found that they were not correlated. We believe that the microfluctuations in the ocular surface wavefront aberrations are primarily the results of the dynamics of the tear film and blinking (Tsubota and Nakamori 1995) rather than pulse and instantaneous heart rate.

The variations in the fixation due to the natural microfluctuations in eye position have been reported to have an effect on ocular surface topography measurement by videokeratoscopy (Buehren et al. 2002). The fluctuations in the ocular surface apex distances in our example (Figure 2.24) showed similar magnitudes as previously reported (Collins et al. 1992; Collins et al. 1995a) and contained two frequency components showing agreement with the pulse and instantaneous heart rate frequencies. However this anterior-posterior ocular movement should not affect the data collected from the Medmont videokeratoscope because the topography calculation algorithm is based on the measured apex distance. If anterior-posterior movements of the ocular were not corrected, then Zernike aberrations such as defocus and spherical aberration terms derived from the topography would have shown pulse related frequencies. Hence the changes in ocular surface Zernike wavefront aberrations we found are most likely due to the dynamics in the tear film and not ocular micro-movements (x, y or z direction). We also examined the changes in the pupil central displacement in both x and y directions and found the impact of pulse and respiration was much smaller in the x or y direction (left-right and up-down) than in the z direction (apex distance). Furthermore, we did not find any cyclic changes in the axis of asymmetric astigmatism aberrations that could correlate with pulse rate and hence it is not likely that there were significant cyclo-torsions in the ocular surface associated with pulse.
In conclusion, we found that the wavefront aberrations introduced by the ocular surface exhibited temporal microfluctuations. Temporal changes of some ocular surface wavefront aberrations vary between subjects and are related to the changes in the tear film. We suggest that in case of clinical measurement of the ocular surface topography using videokeratoscopy, that capturing the image 2 to 3 seconds after a blink will avoid some variability due to the tear film build up phase. There was no association between the periodic cycles of the cardiopulmonary system (pulse and instantaneous heart rate) and ocular surface wavefront aberrations of the Zernike polynomial expansion.
Chapter 3

Microfluctuations of Wavefront Aberrations of the Eye

3.1 Introduction

It has been found that fluctuations in steady-state accommodation have amplitudes of about a quarter dioptre and a frequency spectrum extending up to a few Hz. In their pioneering work, Campbell et al. (1959) measured the dynamic characteristics of accommodation and noted that periodic fluctuations were present. The spectrum of accommodation microfluctuations is typically classified into low (<0.5 Hz) and high (>0.5 Hz) frequency components (Charman and Heron 1988).

A significant relationship between the dominant higher frequency components (1—2 Hz) of accommodation microfluctuations and arterial pulse was first demonstrated by Winn et al. (1990a). This correlation was maintained during the recovery phase of an exercise-induced increase in pulse rate and was absent for an aphakic eye, suggesting that the crystalline lens is the origin of these fluctuations. A correlation between respiration (instantaneous heart rate) and a low frequency component (<0.6 Hz) of accommodation microfluctuations was reported by Collins et al. (1995a). This apparent coherence was maintained during rapid breathing and was evident at the expected frequency during regulated breathing patterns. In the previous chapter (Chapter 2), the variations in the ocular surface wavefront aberrations were examined and found not to be related to pulse.
There are three possible mechanisms that have been proposed through which the ocular pulse could be associated with high frequency accommodation fluctuations: pulsatile blood flow in the ciliary body affecting the ciliary ring diameter; intraocular pressure pulse displacing the crystalline lens, and reduced resistance to lens elasticity with each cyclic reduction in intraocular pressure (Winn et al. 1990a). It has been proposed that respiration could influence accommodation fluctuations through respiration’s modulation of instantaneous heart rate (Collins et al. 1995a). This modulation causes the heart rate to slightly increase during inspiration and reduce during expiration and is termed respiratory sinus arrhythmia (Angelone and Coulter 1964).

The low frequency components of accommodation microfluctuations have been found to vary in magnitude as a function of pupil size and as a function of target luminance (Gray et al. 1993a, 1993b). However the high frequency component does not show obvious systematic change with varying stimulus conditions such as pupil diameter or target luminance (Ward and Charman 1985; Gray et al. 1993b). There appears to be a general trend towards an increase in microfluctuation amplitude with increasing accommodation level (Arnulf and Dupuy 1960; Kotulak and Schor 1986b; Toshida et al 1998), while ageing appears to have the opposite effect by reducing the microfluctuation amplitudes (Heron and Schor 1995). Charman and Heron (1988) have suggested that the high frequency fluctuations are not likely to play a role in actively controlling the steady-state accommodation response, while the low frequency components seem to be more likely to be used in accommodation control feedback.
The presence of fluctuations in wavefront aberrations is not limited to defocus, but occur for low and high order aberrations (Hofer et al. 2001a; Larichev et al. 2001). Using a Hartmann Shack wavefront sensor to continuously measure the eye’s wavefront aberrations, Hofer et al. (2001a) reported that fluctuations in higher order aberrations share similar spectra and bandwidth both within and between subjects.

### 3.2 Aims

In this study we investigated the characteristics of the temporal variations of the wavefront aberrations of the total eye, the associations between wavefront aberrations’ fluctuations and cardiopulmonary rhythms (pulse & instantaneous heart rate). The findings of this study will provide useful information for the dynamic measurement and correction of the eye’s wavefront aberrations.

### 3.3 Methods

#### 3.3.1 Data acquisition

We used the Complete Ophthalmic Analysis System (COAS™, WaveFront Sciences, Inc., Albuquerque, NM, USA) which measures the wavefront aberrations of the human eye using a technique based on the Hartmann-Shack wavefront sensor to collect the wavefront aberrations data at a sampling frequency of approximately 11.5 Hz. A total of 256 Hartmann-Shack images were acquired during each recording resulting in a 22.2 seconds record of aberration data.
Simultaneously, the pulse signal was acquired with a MacLab/4s and Bio Amp (ADInstruments Pty Ltd, Castle Hill, NSW, Australia) which is designed to record the electrocardiogram (ECG) using electrodes connected to both wrists and the right ankle of the subject. The pulse signal was measured at a sampling frequency of 40 Hz for duration of 25.6 seconds. The acquired pulse signal was used to derive the instantaneous heart rate (Friesen et al. 1990). Instantaneous heart rate is the cyclic fluctuation in the time delay between each heart beat, whereas pulse rate is simply the number heart beats per minute. The configuration of the instruments used in the experiment is depicted in Figure 3.1.

Figure 3.1: Experimental set-up. A wavefront sensor is used for the dynamic wavefront aberrations measurement. Three electrodes from the MacLab system were attached to subjects’ wrists and right ankle to acquire the pulse signal.
The sampling rates of both the wavefront sensor (11.5 Hz) and pulse measurement system (40 Hz) were well above the Nyquist frequency for signals related to the cardiopulmonary system. There was minor instability in the sampling frequency of the wavefront sensor (jitter), but this was determined to have no significant effect on the frequency analysis of the acquired signals (Morelande and Iskander 2003).

Ten young subjects between 18 and 35 years of age (mean age: 27 years) were recruited for this study. Informed consent was obtained from all participants and the experiment conformed to a protocol approved by a Human Research Ethics Committee of the university. All subjects had refractive error of no more than 6 D and no significant ocular pathology. Measurements were taken from the left eyes of all subjects. No contact lenses or spectacles were worn by subjects during the experiment. The measurements were performed on undilated eyes and subjects were instructed to blink whenever necessary during the measurement period. Five recordings of pulse signals and wavefront aberration data were collected for each of the subjects for two breathing conditions, a normal breathing rate and 0.5 Hz breathing rate. For the 0.5 Hz breathing rate, an electronic metronome was used to guide the subject so that an inspiration/expiration cycle occurred every 2 seconds. The purpose of using both normal breathing rate and 0.5 Hz breathing rate was to increase the breathing rate range so as to allow more reliable linear regression analysis between the low frequency component of the Zernike aberrations and the instantaneous heart rate frequency.

A beam splitter was positioned between the eye and wavefront sensor so that the subject were able to focus on an external target (at the far point) instead of the internal wavefront sensor.
target. The purpose of using an external target was to allow accurate accommodation control of the measured eye since the internal COAS target relies on “fogging” to create far point focus which may lead to greater focus drifts and may be prone to cause instrument myopia (Hennessy 1975; Wesner and Miller 1986; Salmon et. al 2003). The internal wavefront sensor fixation target was only used for the alignment of the external target with the measurement axis of the wavefront sensor.

The use of a bite bar has been reported to have no significant influence on wavefront Root Mean Square for Hartmann-Shack wavefront sensing (Applegate et al. 2001; Cheng et al. 2004c). In pilot studies we also found that using a head strap to minimize head movements did not significantly alter the measurement of aberration fluctuations using the COAS wavefront sensor. Small eye movements and pupil fluctuation artefacts have also been shown to have minimal influence on wavefront fluctuations (Hofer et al. 2001a).

To estimate the underlying noise level of the wavefront sensor for dynamic wavefront measurements we conducted several pilot experiments. We found significant subject movement artefacts appearing in our wavefront measurements because of the table on which the wavefront sensor was mounted. To solve this problem, the wavefront sensor unit was fixed to a heavy and stable bench. Secondly, a model eye was fixed to the wavefront sensor headrest while a subject was simultaneously positioned in the headrest and instructed to breath at a normal rate. The power (variance) of the instrument noise for the model eye (with subject breathing in the headrest) was found to be at least an order of magnitude less than the power of the wavefront aberration signals from a real eye. This gave us confidence that the fluctuations
we observed in the wavefront aberration signals were related to ocular factors and not extraneous vibrations.

### 3.3.2 Data editing

The acquired data consisted of a set of 256 Hartmann-Shack images and a 1024 sample record of the pulse signal. The wavefront aberration data were then fitted by a series of Zernike polynomials up to the 4th radial order using a pupil analysis diameter of 5 mm, which resulted in 15 Zernike wavefront aberration coefficients for each of the 256 Hartmann-Shack images (Zernike wavefront signals). The first 3 Zernike signals corresponding to the piston and prism were not analysed. Estimating the Zernike coefficients from the Hartmann-Shack images was performed using the software of the COAS wavefront sensor.

Next, the blink artefacts from the wavefront signals were removed by using a third order polynomial interpolation technique. Specifically, a running window was applied to a wavefront signal to find the start and end points of the blinks. The maximum number of samples between the start and end points that could be interpolated should not exceed three image samples due to the frequency resolution constraint (frequency range of interest was 0.1 to 1.5 Hz). The wavefront signals for which the above blink artefact removal technique could not be applied were discarded, along with Hartmann-Shack images for which the pupil size was less than 5 mm diameter.

Originally, each wavefront signal consisted of 256 samples. However, it was noticed that many of the signals can not be uniquely characterised by their spectral representation, mainly because
of the natural drifts of accommodation (defocus) during the data acquisition period. A sub-
sample of 128 data points were extracted from each original Zernike coefficient signal resulting
in a 11.1 seconds record of aberration data for analysis (Figure 3.2). This was performed by
visually inspecting the time representation of the defocus signal and choosing either the first or
the second half of the record, based on the stability of the defocus signal.

Figure 3.2: Top left: original defocus signal of 256 data points (whole data set) from subject SR; Top
right: power spectrum of defocus (whole data set); Bottom left: second half of the defocus signal;
Bottom right: power spectrum of defocus for half data set from subject SR.
3.3.3 Data analysis

Power spectrum analysis

The signal analysis problem has to be mathematically formalised. Let the time-varying wavefront aberration, $w(\rho, \theta; t)$, be modeled by a sum of the Zernike polynomials up to the 4th radial order, i.e.

$$w(\rho, \theta; t) = \sum_{i=1}^{15} a_i(t) Z_i(\rho, \theta) + \varepsilon(\rho, \theta; t)$$

where $a_i(t)$, $i = 1, 2, \ldots, 15$, are the time-varying Zernike coefficient signals and $Z_i(\rho, \theta)$ are the orthogonal Zernike polynomials (Thibos et al. 2002a). Note that in the above equation the wavefront is a function of the radial distance $\rho$ and angle $\theta$ as well as the time $t$. The instrument and modelling noise is denoted by $\varepsilon(\rho, \theta; t)$. In order to examine the fluctuations in the Zernike aberrations, we explored the characteristics of the temporal variations of the Zernike coefficients $a_i(t)$, which are measured by the COAS wavefront sensor.

Before temporal or frequency analyses of the Zernike coefficient signal are conducted, the signals are first detrended by removing a linear trend and then band-pass filtered to extract the frequency range of interest (0.1 Hz – 1.5 Hz). Detrending is a standard signal processing procedure that removes the DC component from a signal. It is performed because the fluctuations in each of the Zernike aberration signals are of interest rather than their actual values. As a band-pass filter, a digital equivalent of a Butterworth filter was used (Iskander et al. 2004).
As mentioned earlier, the piston and prism signals are excluded from the analysis, although the latter may be useful in detecting eye blinks. For each of the remaining 12 Zernike coefficient signals \( a_i(t), \ (i = 4, 5, \ldots, 15) \), an Auto-Regressive (AR) process of order \( P \) is first fitted. The optimal order \( P \) is estimated via Minimum Description Length criterion (Rissanen 1978). The estimated coefficients of the AR process are then used to estimate the power spectra of the aberration signals. Iskander et al. (2004) have shown that this technique is more robust for the aberration signals than the conventional power spectrum estimation techniques based on the Fast Fourier Transform (FFT).

The same procedure of spectral analysis was applied to the pulse and the instantaneous heart rate signals. The spectral representations of aberration and pulse signals were then used to determine the similarities (common frequency peaks) between the signals.

**Cross-Spectrum Density Analysis**

A method to estimate the similarities between two signals is the cross-correlation function or its frequency equivalent, the cross-power spectrum defined as (Eadie et al. 1995)

\[
P_{xy}(f_k) = \frac{2}{N \cdot f_s} \left| \hat{X}(f_k) \cdot \hat{Y}(f_k) \right|
\]

where \( \hat{X}(f_k) \) and \( \hat{Y}(f_k) \) are the discrete Fourier Transform of signals \( x(t_n) \) and \( y(t_n) \), \( n = 0, \ldots, N-1 \), respectively, \( f_s \) is the sampling frequency, and the asterisk denotes the complex conjugation. We applied the cross-spectrum density analysis to estimate the similarity between each Zernike aberration signal and pulse signal as well as between each Zernike aberration signal and the instantaneous heart rate signal. Since the aberration signals and the
pulse and instantaneous heart rate signals were acquired at different sampling rates, the Zernike aberration signals need to be linearly interpolated to achieve sampling records of the same length or equivalently, the concept of zero-padding could be used. The AR based spectral estimation procedure mentioned earlier cannot be used when estimating the cross-spectra. The alternative is to use the traditional FFT based methodology or by taking Fourier transformation of the estimated cross-correlation function. Typical examples of spectra and cross-spectra of the aberration signal related to the defocus, and pulse and instantaneous heart rate signals for subject SP are shown in Figure 3.3. Several points can be noted. Firstly the major frequency peaks of the pulse and instantaneous heart rate signals are well defined. The frequency peak in

![Power Spectra and Cross Spectra](image)

Figure 3.3: Frequency analyses of defocus, pulse and instantaneous heart rate (IHR) signals for subject SP. Power spectra (top) and the normalised cross spectra (bottom).
the pulse signal is estimated with a greater precision than the instantaneous heart rate signal due to the slower frequency of respiration compared with pulse and the limited (11.1 sec) sampling time. The aberration signals exhibit several frequency peaks and there are no frequency resolution limitations due to the parametric (AR) modelling of the signals. The estimator of the cross-spectrum has poor precision due to the FFT based processing.

**Coherence Analysis**

The coherence analysis was used to examine the interrelation between each Zernike aberration signal and pulse signal as well as between each Zernike aberration signal and instantaneous heart rate signal. Details of how the interrelation between two signals estimated using coherence analysis have been described in Chapter 2.

**Correlation Analysis**

A standard correlation analysis was also used to assess the strength of the correlation among the Zernike aberration signals. For each pair of the Zernike aberration signals, the correlation coefficient was estimated using

\[
\rho^2 = \frac{\sigma_{xy}^2}{\sqrt{\sigma_x^2 \cdot \sigma_y^2}}
\]

where \(\sigma_{xy}^2\) is the covariance between \(x\) and \(y\), while \(\sigma_x^2\) and \(\sigma_y^2\) are the respective variances. Since the number of multiple measurements was not sufficiently large to calculate the statistics in ensembles, the assumption of ergodicity (same statistical characteristics in the time and ensemble domains) has been retained to ascertain the time correlation between each pair of the aberration signals.
3.4 Results

All of the measured 12 Zernike components of the wavefront aberration signals exhibit temporal fluctuations. Major fluctuation frequencies of most individual Zernike aberration components, including both lower and higher order aberrations were significantly associated with the frequencies of the pulse and instantaneous heart rate.

3.4.1 Time domain

To illustrate the nature of the wavefront aberration signals after data editing, 11.1 seconds of the Zernike aberration signals, captured for subject JB under the breathing condition of 0.5 Hz, are presented in Figure 3.4. It shows the variations in defocus and astigmatism signals (2nd order) as well as the 3rd and the 4th order aberration signals. Figure 3.5 shows the simultaneously recorded pulse signal and the derived instantaneous heart rate for subject JB.

To examine the magnitude of fluctuations contained in the signals, the variance of each measurement (128 HS images) for each Zernike aberration was calculated. Figure 3.6 shows the group average standard deviation of each measurement for both breathing conditions and their standard deviations. The group average ratios of the standard deviation and mean Zernike aberration signals are presented in Figure 3.7. Generally, the variations (in terms of magnitude change) in the Zernike aberrations decrease as the Zernike order increases (see Figure 3.6 and also see Figure 3.4 as an example for the raw signals). Note that although the lower order aberrations have greater magnitude fluctuations, they exhibit relatively small value of standard deviations/mean (ratio). However this ratio depends on the mean level of aberration, so the refractive error of the subjects determines the mean level of the 2nd order aberrations (defocus
and astigmatism) and is therefore highly dependent on the refractive error of the participating subjects.

![Diagram of Zernike aberration signals](image)

**Figure 3.4:** Original Zernike aberration signals for a 5 mm pupil size. The ordinate is the value of the wavefront error in microns (top). Contour plots of wavefront differences at every 2 seconds. The spacing in the contour plots is 0.025 microns (bottom).

\[ \Delta W(t), \quad t = 2, 4, 6, 8, 10 \text{ seconds} \]
Figure 3.5: Original signal of pulse (top) and the derived signal of instantaneous heart rate (bottom). BPM is beats per minute. Instantaneous heart rate is the time difference between consecutive heart beats.

3.4.2 Frequency domain

To determine if there was a dominant frequency component contained within the measured signals, the power spectra of the Zernike aberration signals, pulse and instantaneous heart rate were estimated by using the AR-based technique described in the previous section. Figure 3.8 presents an example of the power spectra of signals corresponding to defocus, vertical coma and spherical aberration for subject JB. For clarity of presentation, the spectra of the pulse and instantaneous heart rate signals have been normalised to the peaks of the aberration spectra. The subject was instructed to breathe on a metronome beat at 0.5 Hz and the power spectrum of
Figure 3.6: Group mean standard deviation of each measurement for each Zernike aberration. Data are the mean of multiple signals for 10 subjects. Error bars are ±1 SD.

Figure 3.7: Group mean ratios of the standard deviation versus the mean Zernike aberration value. Data are the mean of multiple signals for 10 subjects. Error bars are ±1 SD.
Figure 3.8: Power spectra of defocus (top), vertical coma (middle) and spherical aberration (bottom) for subject JB plotted with the scaled normalised power spectra of the subject’s pulse and instantaneous heart rate (IHR).

The instantaneous heart rate shows a frequency component with a peak at 0.43 Hz, presumably due to sinus arrhythmia. In this example, the fluctuations of subject JB’s defocus, vertical coma and spherical aberration signals have two major fluctuation frequency components which show agreement with the frequency components of pulse at around 0.98 Hz and instantaneous heart rate at about 0.43 Hz. Because the wavefront data acquisition time of 11.1 seconds, the frequency resolution is limited to 0.09 Hz, and this may cause frequency shifts of the Zernike
aberrations (in this example the coma). With the other nine subjects’ power spectra of these Zernike aberrations, similar frequency spectra with two major peaks were typically observed.

To investigate the interrelation between the defocus signal, pulse and instantaneous heart rate, a linear regression analysis was applied to the fluctuation frequency of defocus signals and pulse and instantaneous heart rate frequencies. Group data of the defocus fluctuation frequencies as a function of pulse and instantaneous heart rate frequencies are presented in Figure 3.9. It shows a significant direct linear relationship between higher frequency components of the defocus signals and pulse frequencies ($R^2=0.76$, $p<0.001$), as well as between lower frequency components of defocus signals and instantaneous heart rate frequencies ($R^2=0.49$, $p<0.05$).

The linear regression analysis was performed between the frequency components of all measured Zernike aberration signals and the pulse and instantaneous heart rate. The defocus signal was not the only one that showed correlation with the instantaneous heart rate frequency and pulse frequency, with other Zernike aberration signals (including 3rd order and 4th orders) also showing a direct linear relationship with the instantaneous heart rate and pulse frequencies. Table 3.1 shows linear regression results between the Zernike aberration fluctuation frequencies and pulse and instantaneous heart rate frequencies. A frequency component of all Zernike aberration signals up to 4th order were found to be significantly correlated with the pulse frequency ($R^2 \geq 0.51$, $p<0.02$), and a frequency component of 9 out of 12 Zernike coefficients were also significantly correlated with the instantaneous heart rate frequency ($R^2 \geq 0.46$, $p<0.05$).
Figure 3.9: Correlation between defocus fluctuation frequency components and pulse and instantaneous heart rate of the group data (50 measurements in total). Due to the limitation of the frequency bin of 0.089 Hz, many points in this plot are overlapped (the numbers beside the symbols indicate the number of data points at each location).

3.4.3 Coherence Analysis

An example of the cross power spectra and estimated coherence functions of the defocus signal, pulse, and instantaneous heart rate for subject JB are shown in Figure 3.10. The frequency position for which the cross power spectra achieve their maxima is indicated by dotted lines and there is a concurrent significant increase in the coherence around these frequencies.
<table>
<thead>
<tr>
<th>Zernike Aberrations</th>
<th>Zernike-Pulse</th>
<th>Zernike-Instantaneous heart rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope (m)</td>
<td>Intercept (b)</td>
</tr>
<tr>
<td>$Z_{2}^{-2}$</td>
<td>Astigmatism ($45^0$)</td>
<td>1.03</td>
</tr>
<tr>
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<td>Defocus</td>
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</tr>
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<td>0.81</td>
</tr>
<tr>
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<td>Trefoil ($90^0$)</td>
<td>1.08</td>
</tr>
<tr>
<td>$Z_{3}^{-1}$</td>
<td>Horizontal Coma</td>
<td>1.09</td>
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<td>Vertical Coma</td>
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<td>$Z_{3}^3$</td>
<td>Trefoil ($0^0$)</td>
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</tr>
<tr>
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<td>Tetrafoil ($22.5^0$)</td>
<td>0.83</td>
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<tr>
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<td>Sec Astigmatism ($45^0$)</td>
<td>1.06</td>
</tr>
<tr>
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<td>Spherical Aberration</td>
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<tr>
<td>$Z_{4}^4$</td>
<td>Tetrafoil ($0^0$)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Table 3.1: Linear regression results between the Zernike aberration fluctuation frequencies and pulse and instantaneous heart rates. Group data for 10 subjects. (* $p<0.05$; ** $p<0.001$)
Figure 3.10: Cross power spectra (top) of defocus, pulse, and instantaneous heart rate (IHR), and estimated coherence (bottom) for subject JB. Vertical dotted lines indicate the frequency locations of the maxima of the cross power spectra.

Group data of the coherence functions for both breathing conditions has been calculated to determine the relationship between Zernike aberration signals, the pulse signals and the instantaneous heart rate signals. The group average of coherence analysis results is presented in Figure 3.11 and the averaged coherence between the 12 Zernike aberration signals, and pulse and instantaneous heart rate are 0.51 and 0.55 respectively. However, note that the estimation of the coherence has some limitations. In particular, the coherence analysis based on FFT requires data from the two considered signals to be split into at least two (often overlapping) parts. One part of the data is used to estimate the cross power spectrum while the other part is
used for the auto spectrum. The coherence analysis has low reliability given the small sample data records (128 measurements) available in the study.

Figure 3.11: Group data of coherence analyses for both breathing conditions between aberration signals and pulse and instantaneous heart rate signals.

### 3.4.4 Correlation analysis

The interactions among the Zernike aberrations were determined by using the correlation coefficient. We estimated the group average data of correlation coefficients between each pair of the Zernike aberration signals for both breathing conditions. The major correlations among Zernike aberration signals occurred between astigmatism at 45 degrees and secondary astigmatism at 45 degrees ($Z_2^{-2}$ and $Z_4^{-2}$) with a negative correlation of 0.53, between defocus and spherical aberration ($Z_2^0$ and $Z_4^0$) with a negative correlation of 0.38, and between astigmatism at 0 degrees and secondary astigmatism at 0 degrees ($Z_2^2$ and $Z_4^2$) with a negative correlation of 0.34 (Table 3.2).
Table 3.2: Group data of correlation coefficient analysis among Zernike aberrations for both breathing conditions (n=10).

<table>
<thead>
<tr>
<th>$Z^{-2}_2$</th>
<th>$Z^0_2$</th>
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<th>$Z^1_3$</th>
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<td>0.05</td>
<td>0.01</td>
<td>0.08</td>
<td>-0.02</td>
<td>-0.01</td>
<td><strong>-0.53</strong></td>
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<td>0.09</td>
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<td>0.07</td>
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<td>-0.02</td>
<td>0.003</td>
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<td>-0.007</td>
<td></td>
</tr>
<tr>
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<td>-0.02</td>
<td>0.02</td>
<td>0.05</td>
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<td></td>
<td></td>
</tr>
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<td>-0.008</td>
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<td>$Z^3_3$</td>
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3.5 Discussion

Temporal variations in the optical characteristics of the crystalline lens are the most likely source of the fluctuations in both defocus and other Zernike aberrations of the total eye measured in this study. These temporal changes in the crystalline lens may reflect subtle changes in the lens shape and/or position due to blood flow through the ciliary muscle or the intraocular pressure pulse. Hofer et al. (2001a) noted that the fluctuations in defocus are not of sufficient magnitude to cause the observed fluctuations in higher order aberrations of the eye, given that higher order aberrations are known to change with accommodation.
Chapter 3

The fluctuations which occur in the crystalline lens must affect both the central and peripheral regions of the lens, since the higher order aberrations primarily reflect optical changes in the periphery of the lens. Winn et al. (1990b) have studied the fluctuations in both the central and peripheral crystalline lens and noted the presence of similar low and high frequency spectral peaks in both locations. Using the Foucault knife-edge test, Berny (1969) and Berny and Slansky (1970) were able to show that the peripheral lens shows substantial fluctuations in optical power.

The human eye suffers asymmetrical aberrations because of the lack of rotational symmetry of optics or pupil displacement. Any rotation, or lateral or vertical movement of the crystalline lens could affect the asymmetric aberrations fluctuations. Therefore the ocular pulse could cause fluctuations in both symmetrical and asymmetrical aberrations.

Higher order aberrations appear to be related to the cardiopulmonary system in a similar way to that reported for accommodation (Winn et al. 1990a; Collins et al. 1995a) and pupil fluctuations (Daum and Fry 1982; Ohtsuka et al. 1988). The mechanisms linking the accommodation fluctuations with pulse and instantaneous heart rate are presumably also the origin of fluctuations in the other Zernike aberrations. For the twelve Zernike aberration coefficients examined, the correlation between the high frequency components of the Zernike aberration microfluctuations and the pulse frequency are higher than the correlation between the lower frequency components of the Zernike aberrations and the instantaneous pulse rate. This is probably due to a direct association between the ocular pulse and the higher frequency
Zernike aberration fluctuations through the pulsatile ocular blood flow through the ciliary muscle or intraocular pressure pulse. The association between instantaneous heart rate and the Zernike aberration fluctuations are likely to be indirect, through respiration’s modulation of the ocular pulse (sinus arrhythmia). It is likely that this proposed mechanism would “dampen” or filter the strength of the correlation.

For the subjects in this study, the lowest pulse frequency was 0.9 Hz and the highest frequency was 1.26 Hz, and the corresponding higher frequency components of the defocus varied between 0.72 Hz and 1.35 Hz. For this small range, the linear regression between the higher frequency components of the defocus and the pulse frequencies still gave a strong direct linear relationship with slope close to one. This finding is consistent with the findings of Winn et al. (1990a) who measured accommodation microfluctuations and found a strong correlation with pulse frequency.

In some cases, we observed multiple frequency components (more than 2 peaks) within the frequency range of our interest (0.1 to 1.5 Hz) in the power spectrum of the Zernike aberrations measured. For example, in Figure 1.8 the power spectrum of spherical aberration showed a frequency component at around 0.6 Hz and another frequency component between 1.2 Hz and 1.4 Hz. We can not be certain what causes these fluctuations since there are many other potential sources that might also introduce fluctuations to the eye aberrations such as fluctuations in the retina (Fercher et al. 1982) and axial length of the eye (van der Heijde et al. 1996). It is also possible that other rhythms in the cardiopulmonary system are evident in the signals, such as the Mayer wave and Traube Hering waves (Raschke and Hildebrandt 1982).
We found some correlations among the Zernike aberration terms, unlike Hofer et al. (2001a). For our subjects the highest correlations occurred between 2nd and 4th order Zernikes with the same angular frequencies (between defocus and spherical aberration, between primary astigmatism at 45 degrees and secondary astigmatism at 45 degrees, as well as between primary astigmatism at 0 degrees and secondary astigmatism at 0 degrees). These correlations were all negative and we could have assumed that they reflect the underlying mathematical relationship between the 2nd and 4th order Zernike coefficients (Figure 3.12). For example, as the spherical aberration increases in magnitude, the balancing defocus coefficient decreases in magnitude (to maintain the orthogonal nature of the Zernike polynomials) because mathematically Zernike ‘spherical aberration’ contains a balancing component of defocus aberration. In this way, the negative correlation would simply reflect the Zernike fitting process rather than a true correlation in the optical changes occurring in the eye. Alternatively the correlation could reflect shape changes of the crystalline lens that simultaneously influence both the 2nd and 4th order components.

Clinical measurement of the wavefront aberrations of the eye requires multiple wavefront measurements. The optimal sampling frequency and duration is influenced by a variety of factors including the microfluctuations of the wavefront, the stability and dynamics of the tear film, the effects of blinking, and the quality of the patient’s attention and fixation. To adequately sample the low frequency components of the wavefront requires a sampling duration of at least 4 seconds to cover at least one period of the typical respiration frequency of approximately 0.25 Hz. However it should be noted that we found very low frequency drifts in
defocus (<0.25 Hz) as previously noted by Collins et al. (1995a), that we chose to “detrend” from the data because of their lack of periodicity. To capture these slow drifts in the wavefront would require at least a 10 second sampling period. The high frequency components of the wavefront have most of their power at a frequency which corresponds to the pulse frequency, so the sampling rate to adequately measure these changes is at least 4 Hz (assuming a maximum pulse rate of 2 Hz). There are also frequencies in the wavefront spectra extending to approximately 10 Hz (Hofer et al. 2001a), but the power at these higher frequencies is relatively low compared with frequencies below 2 Hz.

Figure 3.12: Wavefront maps for the 2nd (top three), 3rd (middle four) and 4th (bottom five) order Zernike aberrations, the arrows connect those Zernike aberrations that have higher correlation.
In conclusion, we found that the higher order components of the eye’s wavefront exhibit similar frequencies of fluctuations to those of defocus. In general, the magnitude of the fluctuations diminishes with the radial order of the aberrations. There was an association between the periodic cycles of the cardiopulmonary system (pulse and instantaneous heart rate) and a high and low frequency component of most of the wavefront aberrations up to 4th radial order. This suggests that it is the cardiopulmonary system via the ocular pulse which causes at least some of these temporal fluctuations in the wavefront aberrations of the eye.
Chapter 4

Factors Influencing the Microfluctuations of Wavefront Aberrations of the Eye

4.1 Introduction

Monochromatic aberrations of the human eye arising from both the cornea and internal optical components degrade the image quality on the retina. There have been several studies on the contribution of the wavefront aberrations induced by cornea and internal ocular optics to the wavefront aberrations of the total eye. Smaller levels of aberrations of the total eye compared with those of the cornea have been reported in young subjects and this has led to the suggestion that aberrations induced by the cornea are partially compensated by the internal optics of the eye (Artal and Guirao 1998; Artal et al. 2001; Artal et al. 2002a; Kelly et al. 2004). Corneal astigmatism and spherical aberration of the anterior corneal surface were found to be partially compensated by the internal optics while some other Zernike terms showed addition effects (He et al. 2003a). In another study, the compensation between corneal aberrations and internal aberrations were reported to be evident in astigmatism, vertical coma and spherical aberration (Kelly et al. 2004). However, the contributions of the microfluctuations of ocular surface wavefront aberrations compared to those of the total eye optics are still unknown.

The optical characteristics of the human eye are not static and constantly fluctuate over time. Accommodation microfluctuations during steady-state viewing have amplitudes of about a
quarter dioptre and a frequency spectrum extending up to 2-3 Hz. The spectrum of accommodation microfluctuations is typically classified into low (<0.5 Hz) and high (>0.5 Hz) frequency components (Charman and Heron 1988). The associations between the periodic cycles of the cardiopulmonary system (pulse and instantaneous heart rate) and a high and low frequency component of accommodation microfluctuations were demonstrated by Winn et al. (1990a) and Collins et al. (1995a).

The microfluctuations of steady-state accommodation can be influenced by various conditions and subject characteristics. The low frequency components of accommodation microfluctuations have been found to vary in magnitude as a function of pupil size and as a function of target luminance (Gray et al. 1993a; Gray et al. 1993b). However the high frequency component does not show obvious systematic change with varying stimulus conditions such as pupil diameter or target luminance (Ward and Charman 1985; Gray et al. 1993b). It has been suggested that the high frequency fluctuations are not likely to play a role in the control of steady-state accommodation while the low frequency components seem to be more likely to be used to maintain the accommodation response (Charman and Heron 1988).

The dependence of accommodation microfluctuations on target vergence was first systematically studied by Alpern (1958) who found an increase in accommodation microfluctuations magnitude when subjects viewed closer objects. Denieul (1982) reported that increasing target vergence resulted in an increase of the mean spectrum magnitude of accommodation microfluctuations.
Kotulak and Schor (1986b) demonstrated a statistically significant positive correlation between the standard deviation (or variance) of the accommodative response and the mean level of accommodation response (1 D to 4 D). They also showed that the amplitude of the ‘2 Hz’ component of accommodation increased linearly with the mean level of accommodation response. The microfluctuations of accommodation over a large dioptric range (+3 D to −9 D) were explored by Miege and Denieul (1988). They found that both of the magnitudes of accommodation microfluctuations and the 2 Hz relative activity increased with target vergence up to −3 D and then decreased.

Toshida et al. (1998) investigated the effects of the accommodative stimulus on accommodative microfluctuations in young subjects at various accommodative stimulus vergence levels (+5 D to −12 D). The integrated power of the high frequency component, chosen as (1.3 Hz – 2.2 Hz), of accommodation microfluctuations was found to be minimum with the accommodative stimulus at the far point, to increase with accommodative stimulus until reaching a peak at −5 D, and then to gradually decrease with closer stimuli. The integrated power of the low frequency component (<0.5 Hz), was found to be at a minimum at the far point, to increase for stimuli closer than the far point, and to stabilise for stimuli closer than the near point. Recently Strang et al. (2004) found that the magnitude of microfluctuations in accommodation significantly increase with target vergence in both myopes and emmetropes due to an increase in the power at the low frequency region.

Variation of the high frequency components of accommodative microfluctuations with accommodative stimulus was suggested to be associated with factors such as lens elasticity,
zonular tension, ciliary muscle pulse and intraocular pressure (Kotulak and Schor 1986b; Toshida et al. 1998). It has also been suggested that the increase of the total value of accommodative microfluctuations as stimulus vergence increases might be due to increased activity of the low frequency components which are thought to be used in the control of the blur-driven accommodative response (Miege and Denieul 1988; Toshida et al. 1998).

Recent studies indicate that all components of the wavefront aberrations of the eye fluctuate while viewing a fixed target (Hofer et al. 2001a; Zhu et al. 2004). It has been found that the higher order components of the eye’s wavefront aberrations exhibit similar frequencies of fluctuations to those of defocus (Zhu et al. 2004). It appears that there is an association between the periodic cycles of the cardiopulmonary system (pulse and instantaneous heart rate) and a high and low frequency component of most of the wavefront aberrations up to the 4th radial order of the Zernike polynomial expansion. Despite extensive studies on the relation between the fluctuations of accommodation and stimulus vergence, the relation between the fluctuations in individual Zernike aberrations including the higher order one and the stimulus vergence are unknown.

There have been studies on monochromatic aberrations in myopes and emmetropes. Potential differences in monochromatic aberrations in myopes and emmetropes were first suggested by Collins et al. (1995b) when they found significant differences in the magnitudes of the 4th order aberrations. Greater mean root mean square (RMS) value of wavefront aberrations were reported in myopic subjects than in emmetropic subjects by using a psychophysical ray-tracing technique (He et al. 2002). In the investigation of the relationship between monochromatic
aberrations of the eye and refractive error, no correlation were discovered between RMS of 3rd, 4th and total higher order (3rd to 10th) aberrations and refractive error (Cheng et al. 2003). However, there have been no published studies on the relationship between the microfluctuations in wavefront aberrations and refractive error magnitude.

Differences in the microfluctuations of accommodation in emmetropes and myopes were investigated by Strang et al. (2004) at accommodation stimulus levels ranging from 0 to 4 D in 1 D steps. The magnitudes of microfluctuations in accommodation were found to be significantly larger in myopic subjects than in emmetropic subjects at all stimulus levels examined. This study also showed that the differences in the accommodation microfluctuations in emmetropes and myopes were greater for closer stimuli and it was suggested that the low frequency component played an important role in the differences.

### 4.2 Aims

The aim of this study was to investigate various factors that might influence the microfluctuations of wavefront aberrations of the eye; (1) the relative contribution of the cornea, (2) accommodation, and (3) refractive error magnitude. The contributions of the microfluctuations in the ocular surface wavefront aberrations to those of the total eye are unknown. Also, there have been no published studies on the effect of accommodation on the microfluctuations of individual components of the wavefront aberrations. The association between the fluctuations of the eye aberrations and refractive error magnitude may help in understanding the relative visual performance of eyes with refractive error.
4.3 Methods

4.3.1 Data acquisition

For this study, 20 young subjects were recruited with mean ages of 23.8 years (range between 19 to 34 years) and mean refractive error -2.19 D (range 0 to -5.5 D). No significant ocular pathology that was likely to influence the eyes’ optical microfluctuations was present in any of the subjects. Informed consent was obtained from all participates and the experiment conformed to a protocol approved by a Human Research Ethics Committee of the university.

The ocular surface topography of the eye was measured continuously with a high speed videokeratoscopy system (E300 unit with Medmont Studio version 3.7, Medmont Pty Ltd, Melbourne, Australia) at a sampling frequency of 50 Hz and for each recording we collected 640 images resulting in a 12.8-second continuous record. The subjects did not wear contact lenses or spectacles and were instructed to focus on the Medmont E300 internal fixation target.

Soon after high speed vidiokeratoscopy measurements, the wavefront aberrations of the total eye were measured continuously with a Hartmann-Shack (HS) sensor, the Complete Ophthalmic Analysis System (COAS™, WaveFront Sciences, Inc., Albuquerque, NM, USA). Details of data collection from COAS and experimental setup have been described in Chapter 3. Based on the experience from previous studies, we collected 128 HS images resulting in a 11.1 seconds continuous record of wavefront aberration data. The subjects wore their own spectacles or a trial frame with full refractive correction of the eye under examination.
All the measurements were performed on undilated eyes and three recordings of ocular surface topography data were collected first. At each of three target vergences (0 D, 2 D & 4 D), six recordings of wavefront aberration data of the total eye were then collected for each of the subjects. During both the ocular surface and total eye data collection, subjects were instructed to have natural blinks whenever necessary and to breathe at 0.5 Hz guided by an electronic metronome. Both the total eye and ocular surface aberration data were initially analysed for a 5 mm pupil aperture for all subjects. However we found when our subjects accommodated at the near target, the data acquired from COAS had smaller pupil sizes leading to significant loss of data, hence we decided to analyse both the total eye and ocular surface aberration data at a pupil size of 4 mm.

4.3.2 Data editing and analysis

In the investigation of the ocular surface dynamics (Chapter 2), we found that the microfluctuations of wavefront aberrations introduced by ocular surface dynamics did not contain major frequency components which showed agreement with the pulse and instantaneous heart rates. Hence in this study, we only examined the magnitudes and not frequency response of microfluctuations in the ocular surface wavefront aberrations, along with their contributions to the wavefront aberrations of the total eye.

Microfluctuations in wavefront aberrations of the total eye were quantified by power spectrum analysis. The details of the procedure of power spectrum estimation using an auto-regressive (AR) process integrated power calculating have been described in Chapter 3. In this study, subjects’ pulse rates ranged between 0.9 Hz and 1.7 Hz and their respiration rate were
approximately equal to 0.5 Hz (i.e. one breath every 2 seconds). From the power spectra of all 12 measured aberrations (the piston and prism were omitted), the integrated power has been calculated for two frequency regions which can be defined as the low frequency region (0.1 Hz — 0.7 Hz) and the high frequency region (0.8 Hz —1.8 Hz) that resulting in two sub-bands of 0.6 Hz and 1.0 Hz width in the frequency domain. The frequency bands chosen in our study are similar to the high and low frequency bands of accommodation power spectra used in previous studies (Heron and Schor 1995; Toshida et al. 1998; Seidel et al. 2003).

4.4 Results

The fluctuations of the ocular surface wavefront aberrations were small compared with those of the total eye wavefront aberrations. Fluctuations in defocus of the total eye significantly increased when the stimulus vergence increased from 0 D to 2 D and 4 D in both the low and high frequency regions. Variations in primary astigmatism and most 3rd, 4th order aberrations significantly increased with refractive error magnitude, but surprisingly fluctuations in defocus did not increase with increasing refractive error magnitude.

4.4.1 Contribution of ocular surface to total eye microfluctuations

Absolute level of corneal and total wavefront

The group mean Zernike coefficients of the wavefront aberrations of the total eye optics and cornea are shown in Figure 4.1. The corneal wavefront aberrations were estimated by choosing the line of sight through the entrance pupil centre as the principal axis of the wavefront to match the axis of the COAS wavefront sensor used to measure the total eye wavefront aberrations.
The corneal aberrations showed smaller variations between subjects than those of the entire eye (Figure 4.1, see error bars). The magnitudes of both 3rd and 4th order corneal Zernike coefficients were typically smaller than those of the total eye. Corneal astigmatism at 0 degrees was compensated by the internal optics and the absolute magnitude of corneal astigmatism at 0 degree was greater than that of the total eye. Coma at 90 degrees term showed addition effect between cornea and internal optics with half of the total eye wavefront in this term being contributed by cornea. The magnitudes of astigmatism at 45 degrees, horizontal coma and trefoil induced by the cornea were substantially smaller than those of the internal optics.

Figure 4.1: Group mean Zernike coefficients from the total eye optics and cornea. The defocus term has been set to zero. Data are the mean of multiple signals for 20 subjects. Error bars are +/-1 SD.
Microfluctuation magnitude

In Chapters 2 and 3, we have shown that both of the ocular surface wavefront aberrations and the total eye wavefront aberrations exhibit temporal microfluctuations. To compare the magnitudes of the microfluctuations in the ocular surface aberrations and the total eye aberrations for unaccommodated eyes, the group variations in ocular surface aberrations and total eye aberrations for the 20 subjects are plotted in Figure 4.2. Microfluctuations in each ocular surface wavefront component were found to be significantly smaller than those in the wavefront aberration of the total eye. Microfluctuations in some ocular surface components such as trefoil and tetrafoil terms contributed more to the microfluctuations in these components of the total eye than other terms, ranging from 17-28%. Ocular surface primary and secondary astigmatism showed similar contributions and averaged 12%. The defocus term showed the largest difference, because the microfluctuations in the ocular surface defocus were the smallest among all the ocular surface wavefront components while those in the defocus of the total eye were the largest among all the aberrations.

4.4.2 Effect of accommodation

Time domain representation

The group mean Zernike coefficients of the total eye when the eye focused at the far target (0 D), intermediate target (2 D), and the near target (4 D) are shown in Figure 4.3. Most of the higher order aberrations did not change substantially when the eye accommodated compared with an unaccommodated eye. Spherical aberration showed the largest difference among the higher order aberrations with its dioptric value changing from positive to negative. The
magnitudes of both the defocus term and spherical aberration changed significantly with accommodation (both $p<0.0001$).

![Variations in Ocular Surface and Total Eye Wave Aberrations](image)

Figure 4.2: Group mean standard deviation of signals for each ocular surface component and wavefront aberration of the total eye. The wave aberrations of the total eye were taken for unaccommodated eyes. Data are the mean of multiple signals for 20 subjects. Error bars are ±1 SD.

All of the 12 measured ocular aberration signals exhibit temporal fluctuations at 0 D, 2 D and 4 D stimuli. To investigate how much the stimulus vergence effects the fluctuations of the ocular wavefront aberrations, the variance of each measurement (ie. 128 HS images) for each term was calculated for these three target distances. Figure 4.4 shows the group mean standard deviation (square root of the variance) of each Zernike term for far, intermediate, and near target conditions. The variation in defocus increased substantially with the stimulus vergence.
The variations in defocus when subjects viewed the near target were 1.4 times greater ($p<0.0001$) than those when viewing the intermediate target and were 2.6 times greater when viewing the intermediate target than the far target ($p<0.0001$). The differences of the variations in the other 11 aberration terms measured under far, intermediate and near target were found to be much smaller compared with those in the defocus term. The changes in variations of horizontal coma and spherical aberration with stimulus distance were the greatest (33% and 36% respectively) with the variations when viewing the near target increasing significantly ($p=0.01$ and $p=0.0005$ respectively) compared with the far target.

![Group mean Zernike coefficients](image)

Figure 4.3: Group mean Zernike coefficients of the total eye when focused at the far target (0 D), intermediate target (2 D), and near target (4 D). The defocus term has been set to zero. Data are the mean of multiple signals for 20 subjects. Error bars are ±1 SD.
Figure 4.4: Group mean standard deviation of signals at far target (0 D), intermediate target (2 D), and near target (4 D) for each Zernike term. Data are the mean of multiple signals for 20 subjects. Error bars are ±1 SD.
To provide a representative example of the acquired wavefront aberration signals, Figure 4.5 shows three recordings of the aberration signals for subject DZ, one when viewing the far target (0 D), one when viewing the intermediate target (2 D), and the other one when viewing the near target (4 D). It is apparent that the variation in defocus has increased substantially when the subject viewed the 2 D and 4 D stimuli compared with the 0 D stimulus. However, the variations in astigmatism, 3rd order and 4th order aberration signals did not change substantially between these three viewing conditions.

**Frequency domain representation**

Microfluctuations in wavefront aberrations can be also quantified by power spectrum analysis. Previous studies have found that accommodation microfluctuations under steady state viewing occur at both low frequency (<0.5 Hz) and high frequency (>0.5 Hz) regions (Charman and Heron 1988). The power magnitude of these two dominant frequency components can be used to describe the magnitude of the microfluctuations in the signals. Figure 4.6 presents an example of the power spectra of signals corresponding to defocus at the 0 D, 2 D, and 4 D stimuli for subject DZ. In this example, the microfluctuations of subject DZ’s defocus for 0 D, 2 D, and 4 D viewing stimuli all have two major fluctuation frequency components which show agreement with pulse frequency and respiration rate. The power spectrum peak value for both the high frequency and the low frequency components of defocus for the 4 D stimulus were approximately 3.5 times that of the 2 D stimulus and 20 times that of the 0 D stimulus.

The group mean data showed that the integrated power of the defocus in the low frequency region (0.1 — 0.7 Hz) increased by 6 times when the subjects viewed the 2 D stimulus
Figure 4.5: Zernike coefficient signals at stimulus vergence of 0 D (left), 2 D (middle) and 4 D (right) for a 4 mm pupil size for subject DZ. The ordinate is the value of the wavefront error in microns. Arrows indicate the Zernike coefficient signals associated with defocus. Signals have been shifted vertically to aid comparison of the same Zernike terms at 0 D, 2 D and 4 D stimulus levels.
compared with the 0 D stimulus and by 13 times when viewing the 4 D stimulus (Table 4.1). The integrated power in the high frequency region (1.0 – 1.8 Hz) of the defocus at the 4 D stimulus was 11 times higher when viewing the 2 D stimulus compared with the 0 D stimulus and was 22 higher at the 4 D stimulus (Table 4.2). The increases of the integrated power in both low and high frequency region when stimulus vergence increase from 0 D to 4 D by 2 D steps were found to be significant (t test all $p \leq 0.001$).

Figure 4.6: Power spectra of defocus at stimulus vergence 0 D (solid line), 2 D (dotted line), and 4 D (dashed line) for subject DZ. The pulse and respiration rates are likely to be reflected in the major peaks at around 0.5 Hz and 1.1 Hz.
<table>
<thead>
<tr>
<th></th>
<th>Low frequency region (0.1 Hz—0.7Hz)</th>
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<tbody>
<tr>
<td></td>
<td>Stimulus 0 Diopter ((\mu m^2 \times 10^{-3}))</td>
</tr>
<tr>
<td>(Z_{2}^2)</td>
<td>Astigmatism 45(^0)</td>
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<tr>
<td>(Z_{2}^0)</td>
<td>Defocus</td>
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<tr>
<td>(Z_{2}^3)</td>
<td>Astigmatism 0(^0)</td>
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<tr>
<td>(Z_{3}^{-3})</td>
<td>Trefoil 90(^0)</td>
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<tr>
<td>(Z_{3}^{-1})</td>
<td>Coma 90(^0)</td>
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<tr>
<td>(Z_{3}^{-1})</td>
<td>Coma 0(^0)</td>
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<tr>
<td>(Z_{3}^{3})</td>
<td>Trefoil 0(^0)</td>
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<tr>
<td>(Z_{4}^{-4})</td>
<td>Tetrafoil 22.5(^0)</td>
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<tr>
<td>(Z_{4}^{-2})</td>
<td>Sec Astigmatism 45(^0)</td>
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<tr>
<td>(Z_{4}^0)</td>
<td>Spherical Aberration</td>
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<tr>
<td>(Z_{4}^2)</td>
<td>Sec Astigmatism 0(^0)</td>
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<tr>
<td>(Z_{4}^4)</td>
<td>Tetrafoil 0(^0)</td>
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Table 4.1: Comparison of group mean integrated power in the low frequency region of the power spectra of wavefront aberrations at stimulus vergence levels of 0 D, 2 D, and 4 D (n=20).

For the remaining 11 aberrations (primary astigmatism, 3rd and 4th order) signals, the integrated power in both low and high frequency regions were also examined. In the low frequency region, the integrated powers in horizontal coma and spherical aberration were found to be significantly greater for the 4 D stimulus compared with the 0 D stimulus \((p=0.01 and...\)
The integrated powers in coma, horizontal trefoil and spherical aberration were also significantly greater for the 4 D stimulus compared with the 0 D stimulus in the high frequency region (0.005 ≤ p ≤ 0.03). However, these power changes in astigmatism, 3rd and 4th order aberrations were substantially smaller than those in defocus term.

<table>
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<tr>
<th></th>
<th>High frequency region (0.8 Hz–1.8Hz)</th>
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<tbody>
<tr>
<td></td>
<td>Stimulus 0 Diopter</td>
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<tr>
<td>( Z_{-2}^2 )</td>
<td>Astigmatism 45°</td>
</tr>
<tr>
<td>( Z_{0}^2 )</td>
<td>Defocus</td>
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<tr>
<td>( Z_{2}^2 )</td>
<td>Astigmatism 0°</td>
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<tr>
<td>( Z_{3}^3 )</td>
<td>Trefoil 90°</td>
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<tr>
<td>( Z_{-1}^3 )</td>
<td>Coma 90°</td>
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<tr>
<td>( Z_{-3}^3 )</td>
<td>Coma 0°</td>
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<tr>
<td>( Z_{3}^3 )</td>
<td>Trefoil 0°</td>
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<tr>
<td>( Z_{4}^4 )</td>
<td>Tetrafoil 22.5°</td>
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<tr>
<td>( Z_{-2}^4 )</td>
<td>Sec Astigmatism 45°</td>
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<tr>
<td>( Z_{-4}^4 )</td>
<td>Spherical Aberration</td>
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<tr>
<td>( Z_{4}^4 )</td>
<td>Sec Astigmatism 0°</td>
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<tr>
<td>( Z_{-4}^4 )</td>
<td>Tetrafoil 0°</td>
</tr>
</tbody>
</table>

Table 4.2: Comparison of group mean integrated power in the high frequency region of the power spectra of wavefront aberrations at stimulus vergence levels of 0 D, 2 D, and 4 D (n=20).
4.4.3 Effect of the Refractive Error

The variations in wavefront aberrations of the total eye and their association with the subjects’ refractive error magnitude were also investigated. As an example, the correlations between the microfluctuations in defocus and in astigmatism at 0 degrees and the refractive error magnitude when viewing the far target are depicted in Figure 4.7. It appeared that there was no significant correlation between the variations in defocus and the refractive error magnitude (Figure 4.7 top plot). The variations in astigmatism at 0 degrees were significantly associated with the refractive error magnitude ($R^2 = 0.53, p<0.05$) (Figure 4.7 bottom plot).

Group data of correlations between the fluctuations in all of 12 measured wavefront aberrations of the total eye and the refractive error magnitude are listed in Table 4.3. Defocus was the only Zernike term that did not show any significant associations between its fluctuation magnitude and the refractive error magnitude at all three stimulus vergences (all $R^2 \leq 0.06, p>0.05$). When viewing the far and near targets, the variations in astigmatism, 3rd and 4th Zernike terms were all significantly correlated with the refractive errors with the magnitudes of the fluctuations increasing with refractive error magnitudes (all $R^2 \geq 0.21, p<0.05$).

Association with mean magnitudes

To investigate if there was an association between the magnitude of the microfluctuations and the absolute level of the wavefront error, the variations in wavefront aberrations of the total eye and their associations with the mean magnitudes of the wavefront aberrations were also examined. The variations in astigmatism at 45 degrees were found to be significantly associated with their mean magnitudes when viewing the intermediate target ($R=0.23, p<0.05$)
and near target ($R=0.24, p<0.05$). In addition, the variations in Trefoil at 0 degrees were also associated with its mean magnitude at the near target ($R=0.35, p<0.05$). However, there were no significant correlations found between the variations in the other ten Zernike terms tested and their mean magnitudes for all three stimulus conditions tested (all $R^2 \leq 0.15, p>0.05$).

Figure 4.7: Fluctuations in defocus (top) and astigmatism at 0 degrees (bottom) as a function of the refractive error magnitude (n=20). Both data were acquired for unaccommodated eye.
Table 4.3: Association between variations in wavefront aberrations and refractive error (slope units are in $\mu m$/Diopter).

| Zernike Component | Far Target | | | Intermediate Target | | | Near Target | | |
|-------------------|------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                   | Slope (m)  | Intercept (b)   | $R^2$ (p value) | Slope (m)       | Intercept (b)   | $R^2$ (p value) | Slope (m)       | Intercept (b)   | $R^2$ (p value) |
| $Z_2^{-2}$        | -0.0029    | 0.028           | 0.35 *          | -0.0028         | 0.031           | 0.24 *          | -0.0034         | 0.031           | 0.21 *          |
| $Z_2^0$           | -0.006    | 0.037           | 0.02            | -0.0007         | 0.099           | 0.005           | -0.0035         | 0.135           | 0.06            |
| $Z_2^2$           | -0.0048   | 0.028           | 0.50 *          | -0.0044         | 0.034           | 0.41 *          | -0.0038         | 0.033           | 0.52 *          |
| $Z_3^{-3}$        | -0.0023   | 0.015           | 0.53 *          | -0.0007         | 0.019           | 0.10            | -0.0017         | 0.017           | 0.47 *          |
| $Z_3^{-1}$        | -0.0014   | 0.018           | 0.27 *          | -0.0010         | 0.021           | 0.10            | -0.0028         | 0.019           | 0.36            |
| $Z_3^1$           | -0.0023   | 0.017           | 0.33 *          | -0.0018         | 0.021           | 0.23 *          | -0.0036         | 0.022           | 0.42            |
| $Z_3^3$           | -0.0018   | 0.016           | 0.34 *          | -0.0015         | 0.018           | 0.32 *          | -0.0027         | 0.017           | 0.45            |
| $Z_4^{-4}$        | -0.0014   | 0.012           | 0.51 *          | -0.0012         | 0.014           | 0.35 *          | -0.0009         | 0.013           | 0.25            |
| $Z_4^{-2}$        | -0.0012   | 0.011           | 0.37 *          | -0.0014         | 0.012           | 0.29 *          | -0.0021         | 0.011           | 0.35            |
| $Z_4^0$           | -0.0011   | 0.010           | 0.38 *          | -0.0013         | 0.012           | 0.38 *          | -0.0023         | 0.011           | 0.50            |
| $Z_4^2$           | -0.0018   | 0.011           | 0.29 *          | -0.0015         | 0.014           | 0.31 *          | -0.0022         | 0.013           | 0.32            |
| $Z_4^4$           | -0.0017   | 0.013           | 0.39 *          | -0.0013         | 0.014           | 0.47 *          | -0.0013         | 0.014           | 0.38            |

Linear regression results between the Zernike aberration fluctuations and refractive errors. Group data for 20 subjects. (* $p<0.05$)
4.5 Discussion

This study showed that some corneal aberrations were partially compensated by the internal optics of the eye, similar to results that have been previously reported (Artal and Guirao 1998; Artal et al. 2001; Artal et al. 2002a; He et al. 2003a; Kelly et al. 2004). There was a compensation of corneal astigmatism by the internal astigmatism, which is well known and reported by many studies (Artal et al. 2001; Artal et al. 2002a; He et al. 2003a; Kelly et al. 2004). An additive effect between corneal and internal optics of the eye was found in some Zernike terms as reported by He et al. (2003a).

The microfluctuations of the wavefront aberrations induced by the ocular surface were not found to play a significant role in those of the total eye, with the contribution ranging from 4-28%. This suggests that the instability in the ocular surface is not the main source of microfluctuations of the total ocular wavefront. Similar to what has been reported in Chapter 2, ocular surface Zernike terms such as astigmatism, trefoil, and tetrafoil in this study showed greater microfluctuations than those in other terms such as defocus, comas, secondary astigmatism, and spherical aberration.

In this study, the ocular surface data was estimated by choosing the line of the sight through the entrance pupil centre to minimize to the misalignment effect on the data acquired from both the COAS and the videokeratoscope (Salmon and Thibos 2002). It should be noted that there is a potential source of error, since the assumption was made that the pupil centre was at the same
position during the data acquisition with both the COAS and high speed videokeratoscopy even though the overall pupil size could have been slightly different with each technique.

Buehren et al. (2002) measured the corneal topography of 10 subjects 20 times each and compared the results with those when the fixation error (induced by micro-movements of the eye) was minimised. In the Buehren et al. (2002) study, the corneal topography were taken after the subjects were instructed to have a blink and open the eyes wide, hence differences in the corneal topography due to the tear film dynamics would be the minimal. The standard deviation for the 3rd and 4th order Zernike coefficients estimated from the surface showed little difference between analysis before and after fixation error minimization. This indicates that the microfluctuations in the ocular surface wavefront aberrations we measured were more likely to be due to the dynamics in the tear film not the micro-movements of the eye.

We examined the magnitudes of the Zernike coefficients at stimulus vergence levels of 0 D, 2 D and 4 D and found that the magnitudes of most of high order aberrations did not change substantially as the stimulus vergence changed. However the amplitude of spherical aberration $Z_4^0$ was found to significantly change from positive to negative magnitude (in diopter) when the stimulus vergence increased from 0 D to 4 D. This is a similar trend to that previously reported (Atchison et al. 1995; He et al. 2000; Ninomiya et al. 2002). The magnitude of microfluctuations in spherical aberration also showed small but significant changes with stimulus vergence and increased when the stimulus changed from 0 D to 2 D (p=0.001) and from 0 D to 4 D (p=0.0005). This suggests that there might be an association between the magnitude of the aberration and the magnitude of the microfluctuations in the same aberration.
in certain aberration terms. This trend appeared in the rotationally symmetrical aberrations of defocus and spherical aberration. The group average standard deviations in defocus were $0.039 \mu m$, $0.1 \mu m$ and $0.14 \mu m$ for the 0 D, 2 D and 4 D stimuli compared with the magnitudes of $-0.35 \mu m$, $-1.68 \mu m$ and $-3.48 \mu m$ (Figure 4.8, left plots). At the same time, the group average standard deviations in spherical aberration were $0.012 \mu m$, $0.014 \mu m$ and $0.016 \mu m$ for the 0 D, 2 D and 4 D stimuli with the magnitudes of $-0.02 \mu m$, $0.03 \mu m$ and $0.09 \mu m$ (Figure 4.8, right plots). It is also possible that this trend may simply reflect the underlying mathematical relationship between defocus and spherical aberration. Mathematically Zernike ‘spherical aberration’ contains a balancing component of defocus aberration and when the magnitude of spherical aberration term changes the magnitude of defocus term will alter at the same time as a result of Zernike fitting process.

The results have shown that increasing the stimulus vergence from 0 D to 4 D significantly increases the magnitude of microfluctuations in defocus. However all the other aberrations up to the 4th radial order showed much smaller changes in fluctuation power. This increase in defocus microfluctuations resulted from an increase in both the low and high frequency regions of the microfluctuations. This finding is consistent with previous studies that have shown accommodation microfluctuations to increase with target vergence (Arnulf and Dupuy 1960; Denieul 1982; Kotulak and Schor 1986b; Strang et al. 2004). Toshida et al. (1998) reported an increase in both the low and high frequency components of defocus microfluctuations for a stimulus range of 0 D to 5 D while Strang et al. (2004) found the increase of accommodation microfluctuations was due to the increase in the power in the low frequency region.
Figure 4.8: Changes in the variations and magnitudes of two rotationally symmetrical aberrations with stimulus vergence: defocus term (left plots) and spherical aberration (right plots). Data are the mean of multiple signals for 20 subjects. Circles represent the microfluctuations or magnitude of defocus or spherical aberration. Error bars are ±1 SD.

Gray et al. (1993a, 1993b) have demonstrated that pupil size and target luminance can influence the low frequency components of accommodation microfluctuations. These factors presumably alter the eye’s depth of focus and thereby lead to increased accommodation microfluctuations to maintain a similar range of retinal image contrast. In our study, these factors should not have affected the microfluctuations in accommodation. Measurements were
performed under constant conditions of target luminance and target detail size at both the 0 D and 4 D stimuli. Only the data for pupil sizes at and above 4 mm were included in our study and it has been reported that pupil sizes greater than 3 mm have no significant effect on the microfluctuations of accommodation (Gray et al. 1993a)

Both the low and high frequency components of accommodation microfluctuations have been found to be associated with ocular pulse (Winn et al. 1990a; Collins et al. 1995a). Temporal changes associated with ocular pulse may reflect subtle changes in the crystalline lens shape and/or position due to ciliary muscle pulse (zonular tension), intraocular pressure pulse (lens movement) and variations in intraocular pressure (lens elasticity). We believe that deformation caused by the intraocular pulse pressure and/or ciliary muscle pulse on an accommodated crystalline lens may be larger than that on an unaccommodated lens. This would account for the observed increase in defocus microfluctuations with increased accommodation stimulus level. When viewing a far target, the zonules contract to maximum tension and the crystalline lens is tightly suspended. When viewing a near target, the zonular tension is low, the lens is less constrained and could become more sensitive to pressure fluctuations. With relaxed zonules, the crystalline lens structure is also more flexible and potentially more sensitive to the ciliary muscle pulse and variations in the intraocular pressure. The associated changes of the crystalline lens could resemble a small accommodation response where the thickness and shape of the crystalline lens changes.

The magnitude of defocus microfluctuations at the 4 D stimulus was found to range between 0.3 D and 0.75 D and this is similar to the results recorded by Miege and Denieul (1988). We
used a model of a schematic eye (Navarro et al. 1985) to calculate the distance that an accommodated crystalline lens (4 D) would need to move in the anterior-posterior direction to introduce a 0.5 D defocus change and it was found to be 0.44 mm. However, the crystalline lens is unlikely to move by 0.44 mm with each intraocular pulse beat. The standard deviation of anterior chamber depth measurements during accommodation is reported to be not more than 0.0116 mm (Drexler et al. 1997) which is far smaller than the required 0.44 mm. Furthermore, microfluctuations in accommodation have been found to reduce in older eyes (Toshida et al. 1998; Heron and Schor 1995). This suggests that the defocus microfluctuations of the crystalline lens involve decreased elasticity of the lens and not anterior-posterior lens movement.

The human eye suffers from asymmetric aberrations due to the lack of rotational symmetry of the optics of the eye or pupil displacement (Campbell et al. 1990; Cheng et al. 2003). Our finding that the microfluctuations in most asymmetric aberrations did not significantly change with accommodation suggests that the factors causing the rotational asymmetry of the eyes optics, such as planar displacement of the crystalline lens or pupil location, do not substantially change or become unstable as a function of accommodation. Measurements of ocular alignment such as eye rotation, crystalline lens tilt and decentration were not found to be significantly different for a relaxed eye and an accommodated eye focused at 4 D stimulus (Kirschkpamp et al. 2004).

The microfluctuations in most wavefront aberrations measured, except for the defocus term, were found to be significantly associated with refractive errors and to increase with refractive
error magnitude. Atchison et al. (2004) found that myopic eyes became larger not only in axial length but in all three dimensions with an increase in refractive correction. A decreased ocular rigidity has also been reported with increased axial length of the eye (Pallikaris et al. 2005). Hence myopic eye with less ocular rigidity and expanded ocular dimensions could be more susceptible to pressure variations in the eye such as caused by fluctuations in blood flow and intraocular pressure.

We found that microfluctuations in many wavefront components were significantly correlated with the refractive error magnitude (ie. all subjects were emmetropic or myopic). Rosenfield and Abraham-Cohen (1999) have shown that myopes are slightly less sensitive to defocus than emmetropes. If myopic eyes have reduced sensitivity to blur and greater depth of focus, then this could result in greater microfluctuations if the visual system makes functional use of microfluctuations. Strang et al. (2004) reported that the magnitude of microfluctuations in accommodation was significantly larger in myopic subjects than in emmetropic subjects. It should be noted that the accommodation measured using an auto-refractor by Strang et al. (2004) would include the effects of not only defocus but also astigmatism and all higher order aberrations. Hence it is possible that the significant differences between myopes and emmetropes reported by Strang et al. (2004) could reflect fluctuations in astigmatism and other higher order aberrations.

We conclude that the microfluctuations in the ocular surface wavefront aberrations do not significantly contribute to those in the total eye. Changing stimulus vergence primarily affects the microfluctuations in defocus for both the low and high frequency components of the power
spectrum. Microfluctuations in astigmatism and other high order aberrations show little change with accommodation stimulus level. We also found that the microfluctuations in astigmatism and most of the 3rd order and 4th order wavefront aberrations of the total eye significantly increase with refractive error magnitude.
Chapter 5

Conclusions

In the experiments described in this thesis the microfluctuations of wavefront aberrations of the eye were investigated. The frequency characteristics of the microfluctuations were studied along with the potential underlying causes of the eye’s optical microfluctuations.

5.1 Dynamics in the ocular surface

To investigate the sources of the microfluctuations in the optics of the eye, the dynamics in the ocular surface were first examined. The dynamics of the ocular surface topography were measured using a high speed videokeratoscope at a sampling frequency of 50 Hz. High speed videokeratoscopy is a new technology that has not previously been applied to study the optical microfluctuations of the ocular surface. Changes in the tear film during the inter-blink interval were visualised by computing the ocular surface height difference maps over time. The ocular surface wavefront aberrations up to the 4th radial order of the Zernike polynomials were derived and a Fast Fourier Transform based power spectrum analysis technique was applied to the wavefront aberration coefficients’ signals.

It has been suggested that a thinner lipid layer in the superior cornea immediately after a blink causes high surface tension which results in upward drift of the tear film, eventually leading to a thicker tear film covering the upper cornea (Benedetto et al. 1984; King-Smith et al. 2004). We also found that the tear film became thicker in the superior cornea
and thinner in the inferior cornea during the tear film ‘build-up’ phase, probably due to
the rapid upward movement of the tears after a blink. The group mean ocular surface
height at a position 3 mm above the centre of the cornea at 0.5 sec post blink, 1 sec post
and 2 sec post blink were all significantly greater than that immediately after a blink (all
$p<0.03$).

Several ocular surface wavefront components such as the prism, coma and astigmatism
showed the greatest change in magnitude after a blink. On average, these ocular surface
wavefront components reached a stable level approximately 1.5 to 2 seconds (range
between 0.4 to 3 seconds) after a blink. This suggests that a degree of optical instability
exists in the eye in the tear build-up phase following each blink.

### 5.2 Microfluctuations of wavefront aberrations of the eye

In previous research, the microfluctuations of accommodation have been found to be
associated with pulse and instantaneous heart rate (Winn et al. 1990a; Collins et al.
1995a). The presence of fluctuations in all wavefront aberrations including both low and
high order aberrations has been also been reported (Hofer et al. 2001a). However, there
have not previously been studies on the characteristics of the temporal variations of the
Zernike coefficients, or the associations between wavefront fluctuations and the
cardiopulmonary system.

Simultaneous measurement of microfluctuations in wavefront aberrations of the eye using
a COAS wavefront sensor, and pulse using a MacLab/4s and Bio Amp system were
carried to investigate the associations between the microfluctuations of the wavefront
aberrations of the eye and the pulse and instantaneous heart rate. Extensive analysis was
conducted on the measured signals using both time domain and frequency domain analysis. An Auto-Regressive (AR) process was used to derive the power spectra of the Zernike aberration signals, as well as pulse and instantaneous heart rate signals. This technique was more robust for aberration signal analysis than the conventional power spectrum estimation techniques based on the Fast Fourier Transform (Iskander et al. 2004). The microfluctuations of each Zernike component up to the 4th radial order were examined to investigate their relation to the pulse and instantaneous heart rate frequencies. Cross spectrum density and coherence analyses were applied to investigate the association between fluctuations of wavefront aberrations and pulse and instantaneous heart rate.

Both lower order and higher order aberrations were found to be related to the cardiopulmonary system (Zhu et al. 2004) in a similar way to that reported for accommodation (Winn et al. 1990a; Collins et al. 1995a) and pupil fluctuations (Daum and Fry 1982; Ohtsuka et al. 1988). The mechanisms linking the accommodation fluctuations with pulse and instantaneous heart rate are presumably also the origin of fluctuations in the other Zernike aberrations. Temporal variations in the optical characteristics of the crystalline lens are the most likely source of the fluctuations in both defocus and other low and high order aberrations. These temporal changes in the crystalline lens may reflect subtle changes in the lens shape and/or position due to blood flow through the ciliary muscle or the intraocular pressure pulse.

It was found that the higher order components of the eye’s wavefront exhibit similar frequencies of fluctuations to those of defocus. There was an association between the periodic cycles of the cardiopulmonary system (pulse and instantaneous heart rate) and a
high and low frequency component of most of the wavefront aberrations up to 4th radial order. There was no evidence of associations between the microfluctuations of the ocular surface wavefront aberrations and the pulse and instantaneous heart rate (Chapter 1). This suggests that it is the cardiopulmonary system via the ocular pulse which causes temporal fluctuations in the crystalline lens of the eye (Figure 5.1). On the other hand, tear flow following blinking causes relatively slow tear film thickness changes (and therefore wavefront changes) on the ocular surface (Figure 5.1).

5.3 Ocular factors influencing the microfluctuations of wavefront aberrations of the eye

A wavefront sensor and high speed videokeratoscopy were used to investigate the various ocular factors that might influence the microfluctuations of wavefront aberrations of the eye. These factors included the contribution of the cornea, accommodation, and refractive error magnitude. In this study, the microfluctuations in the wavefront aberrations of the total eye were measured at three stimulus vergences (0 D, 2D and 4 D) in subjects with various magnitudes of refractive error. Integrated power was determined in two spectral regions: 0.1 Hz — 0.7 Hz (low frequencies) and 0.8 Hz — 1.8 Hz (high frequencies).

Some corneal aberrations were found to be compensated by the internal optics of the eye, similar to results that have been previously reported (Artal and Guirao 1998; Artal et al. 2001; Artal et al. 2002a; He et al. 2003a). The microfluctuations of the ocular surface wavefront aberrations were found to make a relatively small contribution to those of the total eye measured with a wavefront sensor, with a range of 4-28% of the total microfluctuations.
Figure 5.1: Model showing possible factors influencing microfluctuations of the wavefront aberrations of the total eye. Possible mechanisms are indicated in the dashed boxes.
Changing stimulus vergence primarily affected the microfluctuations in defocus for both the low and high frequency components of the power spectrum, while microfluctuations in astigmatism and other high order aberrations showed little change with stimulus vergence. Deformation caused by the intraocular pulse pressure and/or ciliary muscle pulse on an accommodated crystalline lens with lower zonular tension may be larger than that on an unaccommodated lens with the higher zonular tension. The associated changes of the crystalline lens during steady-state accommodation may resemble a small accommodation response where the thickness and shape of the crystalline lens changes.

The microfluctuations in astigmatism and most of the 3rd order and 4th order Zernike wavefront aberrations of the total eye significantly increased with increasing refractive error magnitude (myopia). Atchison et al. (2004) found that myopic eyes could become larger not only in axial length but in all three dimensions with an increase in refractive correction. Pallikaris et al. (2005) reported decreased ocular rigidity with increased axial length of the eye. Hence a myopic eye with less ocular rigidity and expanded ocular dimensions could be more susceptible to pressure variations in the eye such as caused by fluctuations in blood flow and intraocular pressure.
5.4 Future Directions

In the results reported in Chapter 3, multiple frequency components (more than 2 peaks) were observed within the frequency range of our interest (0.1 to 1.5 Hz) in the power spectrum of the Zernike aberrations measured. Among these frequency components, a low and high frequency component were found to be associated with the pulse and instantaneous heart rate. However, it is not clear what caused or contributed to the other frequency components. There are some other potential sources that might also introduce fluctuations to the eye aberrations such as fluctuations in the retina (Fercher et al. 1982) and axial length of the eye (van der Heijde et al. 1996). It is also possible that other rhythms in the cardiopulmonary system are evident in the signals, such as the Mayer wave and Traube Hering waves (Raschke and Hildebrandt 1982). Future studies could be carried to investigate if there are any associations between these other factors and microfluctuations of wavefront aberrations of the eye.

Analysis of data in both time domain and frequency domain are adequate to extract general time-based information and the static frequency content of the signals. However, the variations in the frequency components can be only revealed by a combined time-frequency analysis as described by Iskander et al. (2004). Further analysis of the measured signals using time-frequency analysis could provide a better insight into the nature of the microfluctuations of wavefront aberrations and their associations to other rhythms in the cardiopulmonary system.

The microfluctuations of wavefront aberrations of the eye would cause temporal variability in retinal image quality. Studies have shown that visual acuity can be correlated with different metrics of image quality, in particular, the best correlation occurs
with the visual Strehl ratio that is calculated from the optical transfer function (VSOTF) (Cheng et al. 2004b; Marsack et al. 2004). As an example, retinal image quality was evaluated by calculating visual Strehl ratio using one of subjects’ data collected (in the main studies for Chapter 2 and 3). The mean defocus coefficient was made to equal zero to remove the overall defocus errors associated with refractive error and the natural lead or lag of accommodation. Due to the fluctuations in the wavefront Zernike aberrations of the eye, visual Strehl ratio also exhibited fluctuations when the subject viewed a near target at 4 D stimulus vergence (Figure 5.2, top plot). The impact of the microfluctuations in the visual Strehl ratio on the retinal image is shown in Figure 5.2, bottom plots (Iskander et al. 2000). Two Snellen E letters were estimated when the visual Strehl ratio reached a maximum (bottom left) and minimum (bottom right) and show perceptible differences in image quality. With smaller natural pupil sizes, the magnitude of these changes in image quality would be smaller and the increased depth of focus of the eye may result in the changes being imperceptible. In future studies, it would be of interest to investigate the impact of the microfluctuations of wavefront aberrations of the eye on characteristics of the retinal image quality and the contribution of high order aberrations to the stability of the retinal image quality.

Adaptive optics techniques have been recently developed for dynamic wavefront measurement and correction. Applications of the adaptive optics include an ophthalmoscope used for imaging the living retina (Roorda et al. 2002; Roorda and Williams 2002; Pallikaris et al. 2003; Carroll et al. 2005) and a confocal microscope used for sectioning specimens optically (Neil et al. 2000; Booth et al. 2002). Understanding the magnitude and frequency ranges of the microfluctuations of the wavefront aberrations is important in these adaptive optics systems.
Figure 5.2: Top: estimated visual Strehl ratio from Zernike aberration coefficients recorded from subject FK for a 5 mm pupil size. The mean defocus coefficient was made to equal zero to remove the overall defocus errors associated with refractive error and the natural lead or lag of accommodation. Two Snellen E letters are the reconstructed retinal images when the visual Strehl ratio reached a maximum (left) and minimum (right) value.
5.5 Summary

The experiments described in this thesis have demonstrated the characteristics of the microfluctuations of the wavefront aberrations in the human eye and have identified some of the factors that influence the microfluctuation magnitudes and frequencies. There was an association between the periodic cycles of the cardiopulmonary system (pulse and instantaneous heart rate) and a high- and low-frequency component of most wavefront aberrations of the eye up to 4th radial order. The microfluctuations in the ocular surface wavefront aberrations were found to make a relatively small contribution to those in the total eye, with a range of 4-28% of the total microfluctuations. Changing stimulus vergence caused large changes in the microfluctuations of defocus for both the low and high frequency components of the power spectrum, but little change was found in microfluctuations in astigmatism and other high order aberrations. The microfluctuations in astigmatism and most of the 3rd order and 4th order Zernike wavefront aberrations of the total eye appeared to increase with refractive error magnitude.

These findings are important for understanding the optical characteristics of the eye, which will aid in the development of more accurate measurement systems of the eye’s aberrations and may aid in correcting the aberrations (including both static and dynamic correction) to potentially allow better vision.
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sensor to measure the ocular wave aberration." *Optometry & Vision Science* 78(3): 152-156.


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Appendices


4. Pilot study results

5. Example of within-subject variance

6. Human Ethics forms
Analyzing the Dynamic Wavefront Aberrations in the Human Eye

D. Robert Iskander*, Senior Member, IEEE, Michael J. Collins, Mark R. Morelande, and Mingxia Zhu

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Microfluctuations of wavefront aberrations of the eye

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Abstract

To investigate fluctuations in the wavefront aberrations of the eye and their relation to pulse and respiration frequencies we used a wavefront sensor to measure the dynamics of the Zernike aberrations up to the polynomial fourth radial order. Simultaneously, the subject's pulse rate was measured, from which the instantaneous heart rate was derived. We used an auto-regressive process to derive the power spectra of the Zernike aberration signals, as well as pulse and instantaneous heart rate signals. Linear regression analysis was performed between the frequency components of Zernike aberrations and the pulse and instantaneous heart rate frequencies. Cross-spectrum density and coherence analyses were also applied to investigate the relation between fluctuations of wavefront aberrations, and pulse and instantaneous heart rate. The correlations between fluctuations of individual Zernike aberrations were also determined. A frequency component of all Zernike aberrations up to the fourth radial order was found to be significantly correlated with the pulse frequency (all \( R^2 \geq 0.51, p < 0.02 \)), and a frequency component of nine out of 12 Zernike aberrations was also significantly correlated with instantaneous heart rate frequency (all \( R^2 \geq 0.46, p < 0.05 \)). The major correlations among Zernike aberrations occurred between second-order and fourth-order aberrations with the same angular frequencies. Higher order aberrations appear to be related to the cardiopulmonary system in a similar way to that reported for the accommodation signal and pupil fluctuations.

Keywords: microfluctuation of ocular aberration, pulse and instantaneous heart rate, wavefront dynamics, Zernike aberrations

Introduction

It has been found that fluctuations in steady-state accommodation have amplitudes of about a quarter dioptre and a frequency spectrum extending up to a few Hertz. In their pioneering work, Campbell et al. (1959) measured the dynamic characteristics of accommodation and noted that periodic fluctuations were present. The spectrum of accommodation microfluctuations is typically classified into low- (<0.5 Hz) and high- (>0.5 Hz) frequency components (Charman and Heron, 1988).

A significant relationship between the dominant higher frequency components (1–2 Hz) of accommodation microfluctuations and arterial pulse, was first demonstrated by Winn et al. (1990a). This correlation was maintained during the recovery phase of an exercise-induced increase in pulse rate and was absent for an aphakic eye, suggesting that the crystalline lens is the origin of these fluctuations. A correlation between respiration (instantaneous heart rate) and a low-frequency component (<0.6 Hz) of accommodation microfluctuations was reported by Collins et al. (1995). This apparent coherence was maintained during rapid breathing and was evident at the expected frequency during regulated breathing patterns.

There are three possible mechanisms that have been proposed through which the ocular pulse could be associated with high-frequency accommodation fluctuations: pulsatile blood flow in the ciliary body affecting the ciliary ring diameter, intraocular pressure
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Pilot Study Results

USE OF A HEADSTRAP AND FELLOW EYE OCCLUSION

1. We hypothesised that a head strap would not reduce the fluctuations of the eye aberrations measured from the COAS wavefront Sensor. The use of a bite bar has been reported to have no significant influence on wavefront root mean square for Hartmann-Shack wavefront sensing (Applegate et al. 2001; Cheng et al. 2004c).

2. We hypothesised that occlusion of the untested eye would not influence the fluctuations of the eye aberrations measured from the COAS wavefront Sensor

Methods:

1. Subjects
   - Four subjects --an average age of 30.3 years, range of 23-39
   - Refractive error -- no more than 6 D and no significant ocular pathology

2. Test condition
   - Normal viewing
   - Normal viewing condition with a head strap
   - Normal viewing condition with an eye patch on the untested eye

3. 30×8 second recordings per condition

4. Calculation
   - Total power (in Watts) of temporal changes in defocus, lower order aberrations and radial order), higher order aberrations (3rd and 4th radial orders), and total eye aberrations (2nd, 3rd and 4th radial orders).

5. Statistical analysis
   - two-samples with unequal variance t-test analysis applied between conditions
Appendix

Results:

<table>
<thead>
<tr>
<th>Condition</th>
<th>P-Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Defocus</td>
</tr>
<tr>
<td>Normal Viewing/ Head Strap</td>
<td>0.998</td>
</tr>
<tr>
<td>Normal Viewing / Eye Patch</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Figure 1: Total power (in Watts) of changes in defocus, lower order, higher order and total eye aberrations in three different conditions for four subjects. (nv—Normal Viewing; hs—Head Strap; ep—Eye Patch).

Table 1: Results of T-test p values when comparing the condition of normal viewing with viewing with a head strap (top row) and comparing the condition of normal viewing with viewing with an eye patch on the unexamined eye (bottom row) for four subjects (average).

Conclusions:
Using a head strap or an eye patch did not significantly alter the measurement of aberration fluctuations using the COAS wavefront sensor.
Within-subject variations

This is an example of the within-subject variations of Zernike coefficients of the total eye for different stimulus vergences (for comparison of the inter-subject variations, refer to Figure 4.3 on page 128).

Figure: Mean Zernike coefficients of the total eye when focused at the far target (0 D), intermediate target (2 D), and near target (4 D) for subject DZ. The defocus term has been set to zero. Data are the mean of multiple measurements. Error bars are ±1 SD.
The experiments that I plan to undertake will allow a better understanding the fluctuations of the optical aberrations (imperfections) of the human eye.

In this study, the microfluctuations of wavefront aberrations of your eye will be measured using a Wavefront Sensor. In this technique you will be viewing a point source light spot through the wavefront sensor which will produce multiple measurements of the optics of your eye. The wavefront sensor is a normal clinical instrument and poses no risk to the health of your eyes.

The tests may take up to 30 minutes to complete.

Your participation is voluntary and you are free to withdraw from the study at any time without comment or penalty. Refusal or withdrawal from participation will involve no penalty or loss of care to which you are otherwise entitled from the QUT Optometry Clinic.

To ensure the confidentiality of your records, all information will be coded so that you will remain anonymous.

If you wish to discuss any aspect of this study feel free to contact Mingxia Zhu by telephone on (W) 3864 5715. You may also contact the Secretary of the University Research Ethics Committee on 3864 2902 if you wish to raise any concerns about the conduct of this research.
CENTRE FOR EYE RESEARCH
MICROFLUCTUATIONS OF WAVEFRONT ABERRATIONS OF EYES
RESEARCH CONSENT FORM

Participant's name: ......................................................................................................

Name of investigator: Mingxia Zhu Phne (W) 3864 5715

1. The tests and procedures involved in this study have been explained to me and I have been given the opportunity to ask questions regarding this project and the tests involved.

2. I acknowledge that:
   (a) The possible effects of tests and procedures have been explained to me;
   (b) I have been informed that I am free to withdraw from the study at any time, without comment or penalty;
   (c) The project is for the purpose of research and not for treatment;
   (d) I have been informed that the confidentiality of the information I will provide will be safeguarded.

3. At the completion of the study I can ask for feedback on my individual results.

4. I consent to participate in this project.

Signature: ................................................................. .....................................

Participant Date