Visual Interaction of Zernike Aberration Terms from 2nd to 5th Radial Orders with Vertical Coma

by
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DEDICATION

Dedicated to my family, old and new.

"Believe you can and you're halfway there."

—Theodore Roosevelt

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ABSTRACT

Purpose: Eyes with keratoconus suffer from an increased level of higher-order aberrations and decreased visual performance, even when corrected by conventional rigid contact lenses. This study aimed to characterize the visual interactions between the dominant residual aberration seen in this population (positive vertical coma: C7) and 2nd to 5th radial order Zernike aberration terms.

Methods: The experiment proceeded in two parts. In part 1, individual Zernike aberration terms from the 2nd to 5th radial orders were combined in 0.05 µm steps from -2.00 to +2.00 µm with +1.00 µm of C7. The resulting combinations were used to calculate the visual Strehl ratio (VSX), which was used as a surrogate for the relative beneficial/deleterious impact of the combined condition, compared to C7 alone. For conditions where an interaction was predicted to provide the largest improvement (C6 and C17), high-contrast logMAR acuity charts were constructed to simulate the manner in which the combined condition defines the retinal image of the blurred chart. These charts were then read by three well-corrected, typically-sighted individuals through a 3.0-mm artificial pupil. In part 2, the interactions that were predicted to have a deleterious (rather than beneficial) visual interaction with C7 were characterized in greater detail.

Results: In part 1, all aberration-containing conditions led to a reduction in visual image quality compared to the aberration-free condition. Levels of C6, C10, C15, C16, and C17 were identified that resulted in higher visual image quality than was observed with +1.00 µm of C7 alone. The acuities of subjects reading convolved charts had a strong correlation with the predicted performance from simulation (C6: $r^2 = 0.80$, and C17: $r^2 = 0.76$). In part 2, all combinations with C4, C5, C11, C12, C13, C18, and C19 were predicted to have worse logVSX than C7 alone.

Conclusion: While most interactions reduced visual image quality, limited combinations provided a clinically relevant beneficial effect in the presence of C7. Future work will examine whether these effects persist as the aberration structure of the eye is made increasingly complex, up to the point it mimics an individual with keratoconus.

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I. BACKGROUND

This study focuses on the visual interactions that occur between uncorrected higher-order aberrations in eyes of individuals with keratoconus when corrected with conventional rigid contact lenses. In this background chapter, we 1) introduce the language used to report ocular aberrations (the Zernike polynomial); 2) discuss the visual interactions that occur between individual Zernike aberration terms; and 3) discuss how these aberrations manifest in the eyes of individuals with keratoconus.

1. Zernike polynomial

The human eye is a remarkable yet imperfect optical system. The ANSI standard for quantifying and reporting these optical imperfections of the eye (known as ocular aberrations) is the Zernike polynomial (ANSI Z80. 28-2004).[1] The Zernike polynomial is an orthogonal basis function that allows the decomposition of the total optical error of the eye (referred to commonly as the eye's wavefront error) into individual aberration terms. This decomposition facilitates discussion (as will be seen below) as to the impact of these imperfections on retinal image quality and visual performance.

Mathematically, the Zernike polynomial is defined over a unit circle, and the definition of an eye's wavefront error most commonly occurs over the pupil of the eye. The mathematical definition of the Zernike polynomial is driven by two dimensionless parameters: a radial parameter "ρ" (extending from the center to the edge of the pupil) and a meridional parameter "θ" (angular orientation in ophthalmic notation), and two integer indices: radial order n (which for most practical purposes takes the values from zero to 10) and angular frequency m (which takes the values from –n to n, in steps of 2). As shown in Equations (1) to (4), each Zernike polynomial function is the product of three terms: a normalization term (N), a radial term (R), and a meridional term (M):

$$Z_n^m = N_n^m R_n^m(\rho) M(m\theta) \tag{1}$$

$$N_n^m = \sqrt{\frac{2(n+1)}{1+\delta_{m0}}} \tag{2}$$

$\delta_{m0} = 1$ for $m = 0$, $\delta_{m0} = 0$ for $m \neq 0$.

$$R_n^m(\rho) = \sum_{s=0}^{(n-|m|)/2} \frac{(-1)^s (n-s)!}{s!\,[0.5(n+|m|)-s]!\,[0.5(n-|m|)-s]!} \rho^{n-2s} \tag{3}$$

S is an integer summation index incremented by one unit.

$$M(m\theta) = \cos(m\theta)\, if\ m \geq 0, M(m\theta) = \sin(m\theta)\, if\ m < 0 \tag{4}$$

The above equations describe the function in polar form: vector ρ ranges from 0 to 1.0; angle θ ranges from 0 to 2π. Besides the polar form presented here, the function can also be described in Cartesian form (x,y), and it is up to the user's preference to choose from. Appendix 1 shows the list of functions including the symbols, functions in polar form, and common names between 2nd to 5th radial orders, which are defined in ANSI Z80.28-2004. In this thesis, we choose to use "C"

instead of "*Z*" when referring to the aberration term, as most of the time, we are describing the coefficient (magnitude) of this specific term.

The mathematical formulae in (1) to (4) above describe a three-dimensional surface, which is commonly referred to as a wavefront map. The wavefront map is a graphical representation of the optical error of the eye and is commonly used to visualize the shape of the cumulative error of the eye. The colors represent deviation (error) from the ideal condition, which in the case of the eye would be a condition where no error (or aberration) existed. Red/warm indicates portions of the wavefront that are "in front' of this ideal location, and blue/cool colors indicate portions of the wavefront that are "behind' this ideal location. Figure 1 shows an example wavefront map for +1.00 µm of vertical coma.

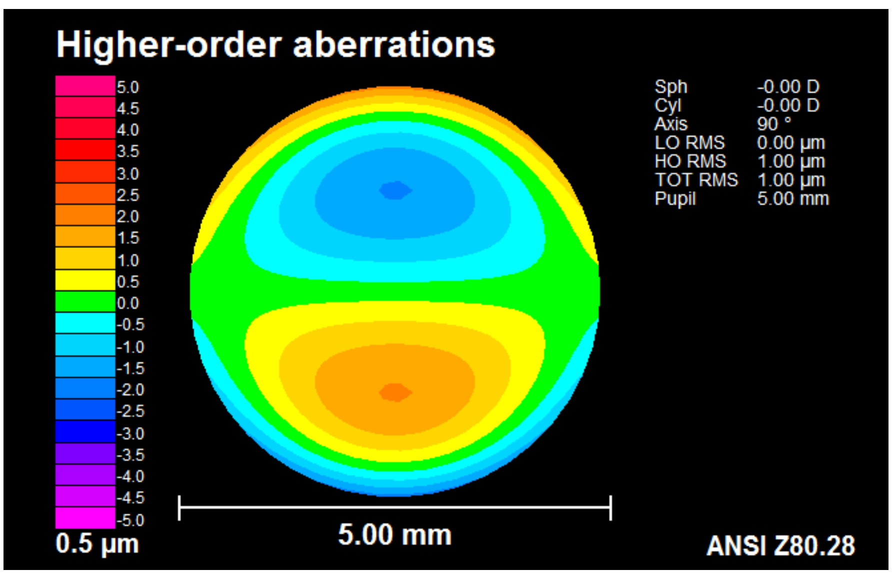

Figure 1. The demonstration of a wavefront map for +1.00 µm of vertical coma (C7) defined over a 5-mm diameter pupil.

When referring to individual terms in the Zernike polynomial, it is common to use one of two forms: single-index or double-index notation. In this work, we chose to use single-index notation. The Zernike pyramid labeling the individual terms C3 to C20 in single index notation can be found in Figure 2. Single index notation is referenced to the top of the pyramid and proceeds down, in a left to right fashion. For readers who are more familiar with the double index notation, the conversion between single index (Cj) and double index (C_n^m) is described in Equations (5) and (6):

$$j = (n(n+2)+m)/2 \tag{5}$$

$$n = \text{roundup}\left[\frac{(-3+(9+8\,j)^{\frac{1}{2}}}{2}\right], \qquad m = 2j - n(n+2) \tag{6}$$

For example, defocus can be described in single index notation as C4 and in double index notation as C_2^0. Similarly, C7 and C_3^{-1} are the single- and double-index representations of vertical coma, respectively.

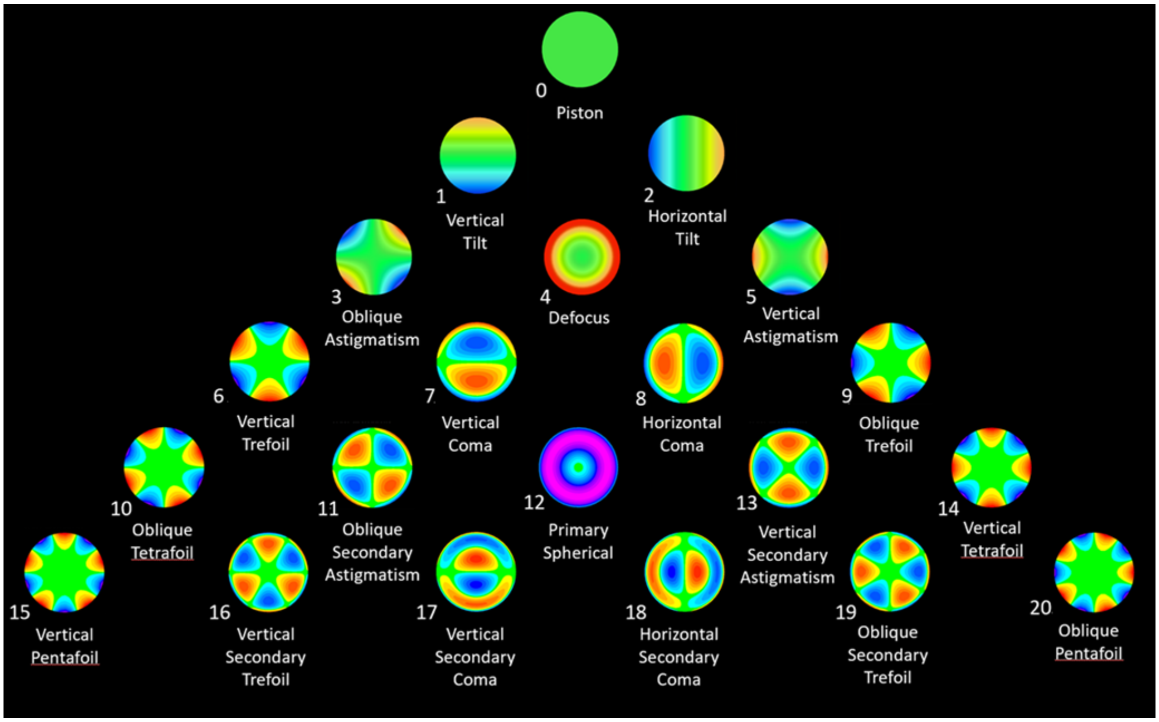

Figure 2. Zernike pyramid (including terms in the 0th through the 5th radial order). Here, individual terms are reported in single index notations (j). The terms on a common row share the same radial order (n, starting from 0 at the top, and working their way down). The terms lined up vertically share the same angular frequency (m = 0 for the terms at the midline of the pyramid, negative for the terms to the left and positive for the terms to the right of midline).

The Zernike polynomials are mathematically orthogonal to each other, meaning that each coefficient in the normalized Zernike expansion (reported most commonly in µm) reflects a unique contribution to the overall wavefront error. While the magnitude (amount) of each coefficient is orthogonal, the impact of these aberrations on visual performance is not, and the individual terms interact in complex ways that have an impact on retinal image quality and resulting visual performance.

2. Aberration interaction

While the Zernike polynomial does provide an exhaustive method to report the eye's monochromatic aberrations, the use of the Zernike polynomial in a clinical setting would be tedious. For instance, reporting the wavefront error through the 10th radial order for an individual patient would require 66 individual Zernike aberration terms. For those familiar with electronic medical or paper records, it need not be said that charting such data would be a logistical difficulty, to say the least. Further, when considered in isolation, the importance of an individual term is difficult to put in perspective. To alleviate these two concerns, significant effort has been placed on reducing these large datasets to single values that have a known visual or physical context.[2-4] This has two distinct advantages. First, the single value is much simpler to report. Second, the reduction of the individual Zernike terms to single values is mathematically made in a manner that addresses a specific question about the error of the eye. For instance, the single-value metric known as root mean square of the wavefront error (or RMS) is among the most commonly used single-value metrics. Mathematically, the RMS is computed as the square root of the variance of the wavefront error function.[1] If phrased as a question, RMS asks "How flat is the wavefront?" or "how much wavefront error is present?" The answer to this question ranges from perfectly flat or no wavefront error (an RMS value of 0) to increasingly positive numbers (representing an increasingly aberrated eye). While RMS is indeed popular and easy to calculate, RMS does not correlate well with resulting visual performance.[2, 5-8] This is because while individual aberration terms are weighted equally in the calculation of RMS, they do not affect vision equally, and they interact with each to increase or decrease vision.

Applegate et al. reported early work in the literature examining the visual consequence of a series of individual Zernike terms from the 2nd to 4th radial orders.[6] In that work, the amount of aberration was held constant at 0.25 μm RMS over a 6-mm pupil. The study found that individual Zernike aberration terms of the same magnitude reduced acuity at different levels, with the terms near the midline of the pyramid reducing vision more than those at the edge of the pyramid (defocus (C4) > astigmatism (C5, C3), coma (C7, C8) > trefoil (C6, C9), spherical aberration (C12) and secondary astigmatism (C11, C13) > quadrafoil (C10, C14), see Figure 2 for their locations in the Zernike pyramid). The authors hypothesized from their results that interactions between the terms could impact vision.

Applegate et al. performed a follow-up study that examined the interactions between individual terms, studying four different pairs of aberration terms to reveal the visual interaction: C4 and C12, (defocus and spherical aberration), C3 and C11 (astigmatism and oblique secondary astigmatism), C12 and C10 (spherical aberration and oblique quadrafoil), and C12 and C11 (spherical aberration and oblique secondary astigmatism).[9] The result showed that the visual outcome varied significantly for different proportions of the components in the studied aberration pairs. More specifically, terms that are two radial orders apart and have the same angular frequency (the same column in the Zernike pyramid) can be combined to improve visual acuity. When C12 was combined with other terms in the 4th radial order, acuity tended to decrease. That study only targeted at a limited number of combinations based on previous findings, held total RMS constant at 0.25μm, and emphasized interactions with spherical aberration (C12). But the results showed prominent evidence that there could be a pattern in the way those Zernike aberration terms interact visually.

To our knowledge, there is only limited literature that focuses on the aberration interaction between vertical coma and other aberration terms. Work by de Gracia et al. looked at the effect of combining coma (C7 and C8) and astigmatism (C3 and C5) on vision, and compared those outcomes to conditions that contained astigmatism alone.[10] Computer through-focus simulation using the Strehl ratio (the ratio of the peak of the actual point spread function to the point spread function under a diffraction-limited condition).[7] Chart reading tests similar to those performed by Applegate et al. were also performed. They found that for a fixed amount of astigmatism, there were specific levels of coma that could improve retinal image quality over astigmatism alone (by a factor of 1.7 or 70% improvement in the Strehl ratio, for 0.5 D of astigmatism and 0.23 μm of coma). When two subjects read acuity charts through adaptive optics-controlled conditions, the effect was at the factor of 1.28 and 1.47, for each subject, over the condition of astigmatism alone. This study used the retinal image and visual acuity to demonstrate the visual interaction between the terms that are one radial order apart (radial order of 3 for coma and 2 for astigmatism).

The previously mentioned studies are laboratory-based observations. Villegas et al. attempted to move one step closer to real-world conditions by evaluating the interaction between coma, trefoil, and spherical aberration, for a group of typically sighted subjects. First, they found that when vertical trefoil (C6) and vertical coma (C7) were present in real eyes at a specific ratio (coupling), the eye exhibited improved retinal image quality. C6 and C7 were found to have a negative correlation in this group of subjects, and most of the eyes with good vision (better than 1.2 decimal acuity) had this coupling. Importantly, this coupling existed regardless of the high level of higher-order aberrations (RMS>0.4 μm) present in these eyes, further demonstrating the inadequacy of RMS, which simply reports the amount of aberration, as a metric for predicting performance.

Those prior works have demonstrated the existence of the visual interaction that exists between aberrations through computer simulation and chart reading. The fact that these interactions lead to variation in visual performance led us to consider how the residual, uncorrected aberrations impact vision in the eyes of individuals that habitually experience elevated aberrations. We chose to model our experiments on observations recorded on individuals with keratoconus.

3. Keratoconus

Keratoconus is a condition characterized by paraxial corneal thinning and steepening.[11] The irregular corneal shape, including both anterior and posterior surfaces, results in increased levels of ocular aberration and decreased visual performance.[12-15] Alio et al. found that corneal higher-order aberrations, especially coma-like aberrations (3rd, 5th, and 7th radial order Zernike terms), are significantly higher in eyes with keratoconus than normal eyes.[15] The ocular 3rd and 5th radial order RMS in eyes with keratoconus was 1.88 ± 1.16 μm vs. 0.26 ± 0.10 μm in normal vision controls, for a 6-mm pupil.[16] The level of higher-order aberration is closely related to the severity of keratoconus, with more aberration being present with advanced disease.[15] For example, increased negative vertical coma is directly related to the inferior shifted cone location in eyes with keratoconus.[16, 17] This increased higher-order aberration is not corrected by traditional sphero-cylindrical spectacle corrections, indicating the need of other correction modalities that do target higher-order aberration.[17] Rigid forms of contact lens correction are the gold standard for individuals with keratoconus.[18] According to the Collaborative Longitudinal Evaluation of Keratoconus Study (CLEK study), 65% of the 1209 patients included wore rigid contact lenses in both eyes, and 8% wore rigid contact lenses in one eye.[18]

This preference for rigid contact lenses is due to the pseudo-refractive index matching provided by the tears (n = 1.334) that fill in the space between the anterior cornea (n = 1.376) and posterior contact lens surfaces (n of roughly 1.44 to 1.49 depending on the material used). That said, even when well corrected with a rigid contact lens, eyes of individuals with keratoconus remain highly aberrated, compared to typical eyes.[19-21] In particular, positive vertical coma is observed in well-corrected eyes of individuals with keratoconus. Kosaki et al. measured the Zernike aberration terms in eyes with keratoconus, with and without corneal rigid contact lenses.[22] They found prominent coma (a combination of C7 and C8) with an inferior slow pattern (meaning vertical coma is dominant and negative) in uncorrected eyes with keratoconus (RMS of 0.62 ± 0.35 µm for eyes with keratoconus vs. 0.06 ± 0.04 µm for the control group, for a 4-mm pupil). After correction with a rigid contact lens, the pattern of coma was reversed (positive C7, 0.27 ± 0.14 µm).

The origin of these residual aberrations is thought to be the irregular posterior corneal surface and the reverse refractive index paring at the posterior surface compared with its anterior counterpart (anterior: air-cornea (low-high), posterior: cornea-aqueous humor (high-low)).[19, 22]

Despite the fact that rigid contact lenses offer eyes with keratoconus better (but not typical) levels of optical quality, this elevated residual aberration results in poorer visual outcomes than a typically-sighted cohort.[19-21] Negishi et al. found that the mean ± SD area under the log contrast sensitivity function (AULCSF) in the rigid contact lens wearing keratoconus group was significantly lower than in groups of typical eyes with or without rigid contact lenses (1.158 ± 0.145, 1.411 ± 0.122, and 1.462 ± 0.102, respectively), while total higher order RMS, 3rd order RMS, and 4th order RMS were all significantly higher (in the order of: eyes with keratoconus wearing a rigid contact lens, typical eyes wearing a rigid contact lens, and typical eyes without a rigid contact lens; total higher-order aberrations: 0.538 ± 0.327, 0.188 ± 0.081, and 0.152 ± 0.037; 3rd order: 0.496 ± 0.297, 0.160 ± 0.079, and 0.123 ± 0.044; 4th order: 0.166 ± 0.134, 0.069 ± 0.034, and 0.067 ± 0.027, all units are in μm).[21] The authors attributed the lower than normal image quality to the increased residual higher-order aberrations, even with rigid contact lens correction.

Marsack et al. studied the uncorrected residual wavefront error and visual performance in eyes with keratoconus wearing rigid contact lenses.[19] They found that the magnitude of coma RMS (C7 and C8, 5-mm pupil) was 0.42 ± 0.32 μm vs. 0.10 ± 0.06 μm for normal eyes, and the majority of the eyes included in the study had high-contrast visual acuity outside of the normal range (five out of seven individuals).

Given the level of C7 observed in the eyes with keratoconus with or without conventional rigid contact lens correction and the interaction between C7 and other Zernike aberration terms, the goals of this thesis are to examine the visual interaction of Zernike aberration terms from the 2nd to 5th radial orders with vertical coma, and to determine the associated visual consequences of these interactions. We break the work up into two chapters: the first chapter focuses on beneficial interactions; the second chapter focuses on both deleterious interactions and additional factors that might affect the observed interactions.

II. BENEFICIAL VISUAL INTERACTION OF INDIVIDUAL ZERNIKE ABERRATION TERMS FROM 2ND TO 5TH RADIAL ORDERS WITH VERTICAL COMA

This chapter has completed the peer review process and was in press at the time of this thesis as:

Chuan Hu, Ayeswarya Ravikumar, Gareth D. Hastings, Jason D. Marsack, Visual Interaction of 2^{nd} to 5^{th} Order Zernike Aberration Terms with Vertical Coma. Ophthalmic Physiol Opt. 2020 in press.

The chapter is presented here as it appeared in Ophthalmic and Physiological Optics prior to the copy-editing phase of the publication process.

1. Introduction

Keratoconus is among the most common corneal ectatic conditions that present in clinic, and is characterized by progressive paraxial steepening and thinning of the cornea.[11] Prevalence estimates for keratoconus range from 1/2000 (a classical, conservative estimate)[23] to 1/375 (a more recent estimate).[24] Eyes of individuals with keratoconus continue to suffer from elevated levels of higher-order ocular aberration when compared to typical eyes,[15, 17, 25] even when these eyes are corrected with gold standard corneal or scleral rigid gas permeable lenses.[19-22, 26] In particular, positive vertical coma persists in the eyes of individuals with keratoconus wearing rigid contact lenses.[22]

The fact that coma continues to exist at elevated levels means that it can continue to impact visual performance. One commonly used metric to quantify the level of aberration present in the eye is root mean square (RMS) wavefront error (WFE). This metric is ubiquitous, even though it has been demonstrated to be a poor predictor of visual performance.[2, 5-8] Eyes with the same level of RMS can exhibit very different levels of visual performance, the reasons being 1) individual aberration terms do not affect vision equally,[6] and 2) aberration terms interact with each other visually, causing vision to be better or worse than if the aberration terms were acting alone.[9] Experiments have been conducted examining the visual consequence associated with different combinations of aberration terms.[9, 10, 27, 28] Applegate et al. found that individual Zernike modes with like-signed coefficients two radial orders apart and having the same angular frequency can be combined such that the effect on acuity is less deleterious than the effect of a single aberration term of the same magnitude.[9] One practical application of these beneficial interactions is seen in the design of multi-focal lenses, where the combination of higher order spherical aberrations can increase the depth of field.[29-31] The addition of coma to astigmatism has been shown to improve the image quality over astigmatism alone.[10, 32] Also, Villegas et al. showed that the positive coupling between the vertical component of trefoil and coma could improve retinal image quality in a group of subjects with natural aberration profiles.[28] In an effort to better understand the optical consequence of residual aberrations that exist during rigid contact lens wear in keratoconus, this study was designed to characterize the visual interaction that occur between individual 2nd to 5th radial order Zernike aberration terms (C3 to C20) and positive vertical coma (C7).

One method commonly employed to characterize visual interaction between aberration terms is to simulate letter charts via convolution with the point spread function (PSF) derived from the aberration terms.[9, 10] Once generated, typically sighted individuals read these letter charts while their natural aberrations are minimized with trial lenses and using a small artificial pupil,[9, 10] allowing the relationship between visual performance and the metric value derived from the aberration data used in the convolution to be examined. Ideally, the objective change in metric value would be predictive of a change in visual performance. One metric that has been shown to be predictive is the visual Strehl ratio calculated in the spatial domain (VSX). VSX is an inner product of the PSF with a neural weighting function normalized to the diffraction-limited condition.[7] VSX has a value between 0 to 1 with 0 being the worst and 1 being the best theoretical value. It has been shown to be able to predict a sphero-cylindrical prescription that performed equivalent to subjective refraction for typical eyes and those with keratoconus.[33, 34] Change in VSX has been demonstrated to predict the change in logMAR visual acuity linearly for both typical eyes and eyes of individuals with keratoconus, through normal eyes reading simulated charts.[35]

Based on this prior work with a knowledge of the levels of aberration present in rigid contact lens wearing eyes of individuals with keratoconus, the interactions that exist between aberrations and the predictive power of the metric VSX, this study sought to characterize interactions between individual 2^{nd} to 5^{th} radial order aberration terms (C3 to C20) and positive vertical coma (C7). In particular, an emphasis was placed on identifying interactions that would be beneficial (reduce the deleterious impact of C7).

2. Methods

The study adhered to the tenets of the Declaration of Helsinki and received approval of the Institutional Review Board of the University of Houston. Signed informed consent was obtained from subjects prior to participation in the study. The study was conducted in two parts. The first part used computer simulation to characterize a large number of interactions, and the second part recruited typically sighted subjects to read letter charts blurred to resemble retinal images for the aberration terms that were anticipated to have the largest beneficial effect when combined with C7.

2.1. Aberration combination and through-focus simulations

Simulation was employed as a first-pass evaluation of interactions between individual aberration terms in the 2nd to 5th radial orders of the normalized Zernike polynomial (term C3 to term C20 (excluding C7), referred to as *test* terms) and positive vertical coma (C7, the *target* term). All other aberration terms, other than the *test* term and the *target* term were set to 0.00 µm. All computations were performed over a 5.0 mm diameter pupil, and at a wavelength of 555 nm. The amount of C7 chosen for this simulation was +1.00 µm for simplicity of analysis (the effect of varying the magnitude of C7 is described in the discussion). A series of discrete steps of each *test* term (-2.00 µm to +2.00 µm, in 0.05 µm steps) were mathematically added to the static level of C7, for a total of 81 steps for each of the 17 *test* terms in the 2nd to 5th orders that were studied. The resulting combinations of *test* term and *target* term were reduced to a single value, the visual image quality metric VSX using custom written software (BatchMetrics1.6, UHCO Core Programming Module) based on the formulation described by Thibos et al.[7] and was further converted to logVSX. LogVSX was chosen as the summary metric due to prior reports demonstrating that a change in logVSX is predictive of a change in logMAR visual acuity.[33, 35] In general, more positive/less negative values of the VSX/logVSX represent better visual image quality.

The process above was repeated for +0.50 µm of C7 to test whether the ratio of the *test* term to the *target* term remained constant in conditions where a beneficial interaction existed. As the amount of positive C7 was reduced by half, the range of *test* terms was likewise reduced to ±1.00 µm, with a 0.05 µm step size.

For both the +0.50 µm and +1.00 µm levels of C7, the resulting change in logVSX, calculated as the change between the logVSX value for C7 only and C7 combined with the *test* term condition was used in the model of Ravikumar et al.[35] to predict a change in logMAR visual acuity (VA). Ratios calculated for each *test* term to the *target* term for conditions that resulted in a predicted gain in visual acuity were identified.

2.2. Chart reading tests in subjects

Having identified combinations of *test* and *target* terms that were anticipated to have a beneficial effect of more than 0.10 in logMAR acuity (one line on an Early Treatment Diabetic Retinopathy Study (ETDRS) acuity chart, corresponding to +0.25 in logVSX change),[35] logMAR acuity charts were convolved with the relevant PSFs to simulate the blurred retinal image resulting from the combination of positive vertical coma and the *test* terms that yielded the maximal beneficial effect against C7 (notably, C6 and C17), and these charts were then read by typically sighted individuals. The 11-line logarithmic progression visual acuity chart (0.7 to -0.3 logMAR in 0.1 steps, five Sloan letters in each line) of 100% contrast were generated using Visual Optics Laboratory (VOL) Professional software (version 7.4, Sarver & Associates, Inc.).[36] VOL uses equally identifiable letters to randomly generate logMAR charts such that no letter is repeated in any given line.[37] A custom Matlab program (The MathWorks, Inc., Natick, MA) was used to generate the convolved charts.[38]

Three subjects were recruited to be in this part of the study and chart reading tests were performed on right eyes. Details describing the subjects that read the convolved charts are listed in Table 1. Eligibility criteria for inclusion were: subjects consenting prior to data collection; best corrected distance visual acuity of 20/20 (Snellen) or better in either eye; no active ocular diseases (not including mild dry eye disease) or binocular abnormalities; no history of ocular surgery; no contraindication to pupil dilation.

Table 1. Subject information

Subject	Age/Gender	Correction (right eye)	HO-RMS* (μm)	Acuity with clear chart
01	33 M	-5.75 - 0.50×180	0.14±0.06	-0.28±0.02
02	34 F	pl	0.10±0.01	-0.23±0.02
03	33 F	-6.00 sph	0.11±0.02	-0.17±0.03

* HO-RMS: higher order RMS, average of three measurements, measured with a COAS-HD Shack-Hartmann aberrometer (Johnson and Johnson, Santa Ana, CA) under cyclopleged condition, output up to the 10th Zernike radial order, referenced to 555nm wavelength and rescaled to a 3.0 mm pupil.

A detailed description of the method employed here has been previously published. [35, 39] In brief, monocular visual acuity was recorded for the simulated logMAR acuity charts through a custom Matlab program using a letter-by-letter scoring system (subjects start with the line which they easily read with all five letters correctly, credit was given for each letter read correctly up to the fifth miss).[40] The charts were digitally displayed on a high contrast, gamma corrected, 11-bit depth monitor, which the subject viewed while dilated through a unit magnification telescope with a 3.0 mm pupil aperture conjugate to the pupil plane of the eye. The subject's correction from subjective refraction was placed in front of the 3.0 mm pupil and all subjects achieved high-contrast logMAR visual acuity better than -0.10 (-0.28, -0.23, and -0.17). In total, 83 conditions were tested, which comprised 40 conditions that combined varying levels (-2.00 μm to +2.00 µm in 0.10 µm steps) of C6 with +1.00 µm of C7, 41 conditions that combined various levels (-2.00 µm to +2.00 µm in 0.1 µm steps with one additional chart of +0.35 µm in an attempt representing the peak of the simulated benefit) of C17 with +1.00 µm of C7, one condition with +1.00 µm of C7 only, and one aberration-free condition to determine the baseline acuity. Each condition was repeated 3 times using a unique letter chart, for a total of 249 unique charts read by each typical observer. Charts were grouped into ten sets (one set of 24 charts, nine sets of 25 charts). Charts were randomized in each set prior to testing and each subject read each set in a randomized order during testing. Each chart took about one minute to read. The data collection for each subject was completed in a single visit, the alignment was monitored throughout the test, and breaks were taken between sets and within sets at the subject's discretion to avoid fatigue.

Visual acuity data were averaged across the three repeated trials. Comparison of the visual acuity for each condition was made to the subject's mean logMAR acuity achieved in the presence of +1.00 µm of C7. This allows both beneficial (gain of acuity) and deleterious (loss of acuity) effects with regard to C7 alone to be quantified.

The correlation between the logMAR acuity change from chart reading test and the predicted logMAR acuity change was analyzed using Pearson correlation test. A p-value less than 0.05 was considered significant. Statistical analyses were conducted using Stata (version SE 15.1), and the results are reported as the mean ± standard deviation.

3. Results

3.1. Combining aberrations using through-focus experiments

LogVSX values resulting from the addition of each Zernike aberration term to +1.00 µm of *target* term relative to *target* term alone are shown in Figure 3. As expected, the majority of combinations led to a reduction in logVSX (negative values, compared to C7 alone). Terms C4, C5, C11, C12, C13, C18, and C19 had significantly worse logVSX (below y equals zero) in the majority of the tested range while terms C3, C8, C9, C14, and C20 showed less variation (close to where y equals zero) for all combinations. However, terms C6, C10, C15, C16, and C17, in limited combinations, resulted in higher logVSX values (above y equals zero) than C7 alone. Here, a threshold of more than 0.05 in logMAR of predicted improvement (half a line on an ETDRS acuity chart, corresponds to +0.06 in logVSX change) was chosen as a meaningful increase in acuity. [33]

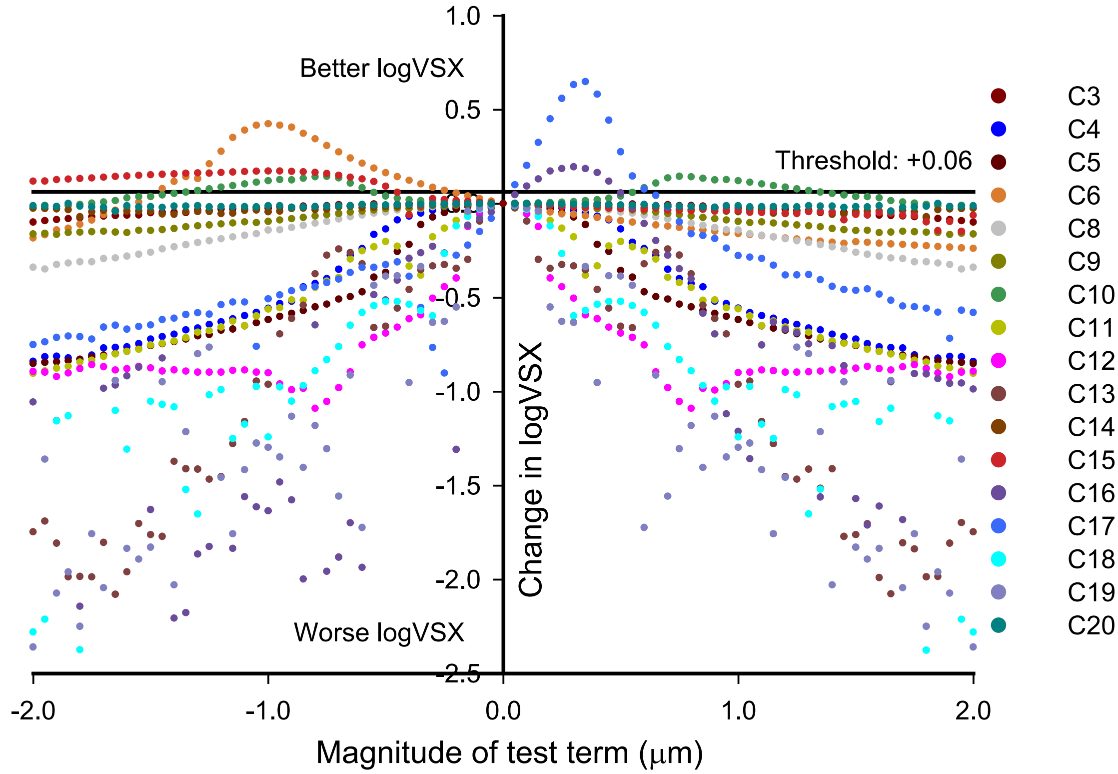

Figure 3. Change in logVSX (value difference between logVSX(C7+CX) and logVSX(C7), CX being the *test* term) for all *test* terms from 2nd to 5th radial orders when combined with +1.00 μm of C7, in comparison to C7 alone (where y equals zero). Positive values indicate better logVSX, negative values indicate worse logVSX, when the *test* term (legend) is added to C7.

Figure 4 displays the subset of combinations that led to higher logVSX values (beneficial interactions). The *test* terms C17 and C6 provided the highest level of beneficial effect against C7. The maximal benefit for C17 occurred when +0.35 μm of C17 was combined with +1.00 μm of C7 (or a C17 to C7 ratio of +0.35), resulting in a +0.65 increase in logVSX (corresponding to -0.22 predicted change in logMAR acuity). The range of C17 predicted to improve acuity by an amount over 0.05 logMAR acuity (+0.06 change in logVSX) was between +0.05 and +0.60. The maximal benefit for C6 occurred when -1.00 μm of C6 was combined with +1.00 μm of C7 (or a C6 to C7 ratio of -1.00), resulting in a predicted benefit of +0.42 increase in logVSX (corresponding to -0.15 predicted change in logMAR acuity). The range of C6 predicted to improve acuity by an amount over 0.05 logMAR (+0.06 change in logVSX) was between -1.45 and -0.25.

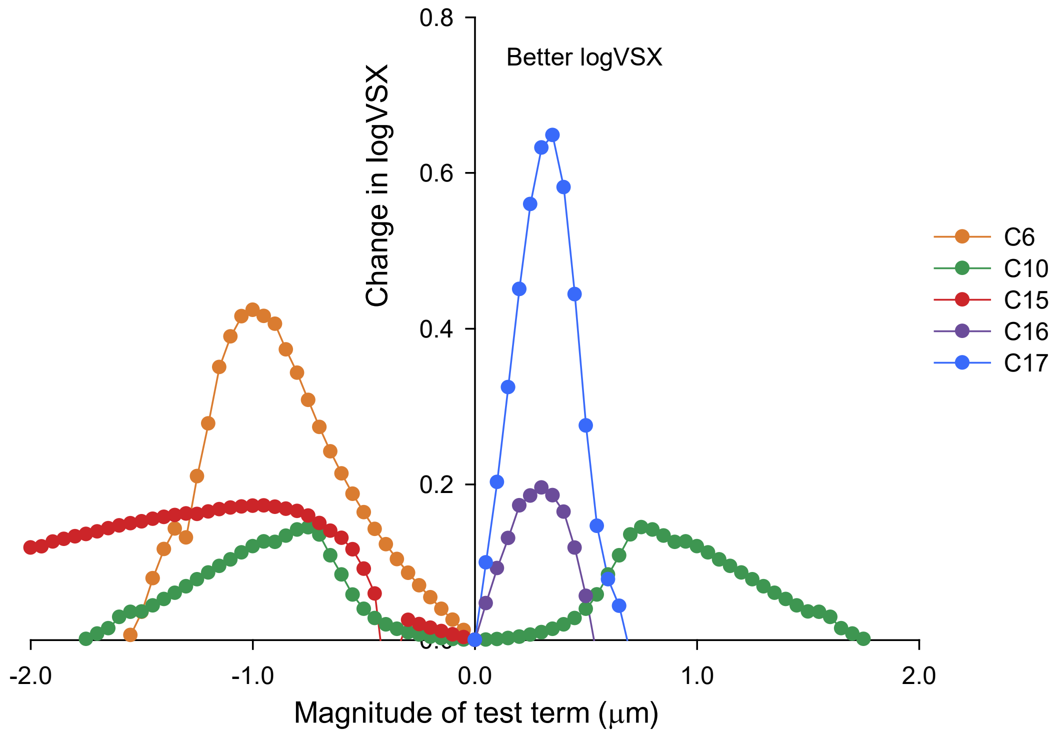

Figure 4. Change in logVSX as function of the magnitude of the *test* term. The individual aberration terms C6, C10, C15, C16, and C17 had a maximum logVSX increase that predicted to be at least a -0.05 change in logMAR VA (+0.06 change in logVSX), for +1.00 μm of C7.

Repeating the above process with +0.50 μm of the *target* term yielded similar results as those seen for +1.00 μm of C7 (Figure 5). The maximal benefit for C17 occurred when +0.20 μm of C17 was combined with +0.50 μm of C7 (or a ratio of +0.40), resulting in a predicted benefit of +0.47 in logVSX which corresponds to -0.16 predicted change in logMAR acuity. The range of the C17 to C7 ratio predicted to provide a beneficial effect over 0.05 in logMAR acuity (+0.06

change in logVSX) was between +0.10 and +0.60. The maximal benefit for C6 occurred when -0.50 µm of C6 was combined with +0.50 µm of C7 (or a C6 to C7 ratio of -1.00), resulting in a predicted benefit of +0.29 in logVSX which corresponds to -0.11 predicted change in logMAR acuity. The range of the ratio of C6 to C7 predicted to provide beneficial effect over 0.05 in logMAR acuity (+0.06 change in logVSX) was between -1.40 and -0.30. The ratio of the *test* term to *target* term remained similar for both +0.50 µm and +1.00 µm of *target* term. The comparison of the results between the two levels of C7 is shown in Table 2.

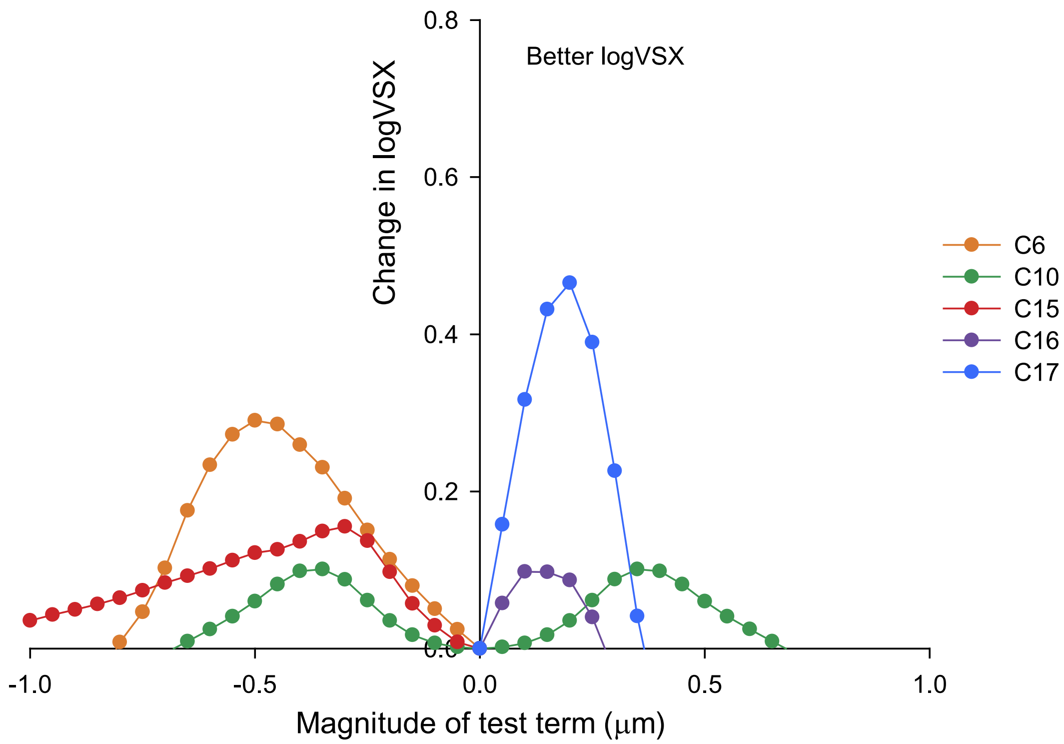

Figure 5. Change in logVSX for +0.50 µm of C7. The individual aberration terms C6, C10, C15, C16, and C17 had a maximum logVSX increase predicted to be at least a -0.05 predicted change in logMAR acuity (+0.06 change in logVSX).

Table 2. Summary of the results for *test* terms C6 and C17, for both +1.00 and +0.50 µm of *target* term.

Target term magnitude (µm, C7)	*Test* term	*Test* term magnitude for maximum effect (µm)	Change in logVSX	Predicted improvement acuity in logMAR*	Range of *test* term to *target* term ratio for improving VA by 0.05 in logMAR*
+1.00	C6	-1.00	+0.42	-0.15	-1.45 to -0.25
	C17	+0.35	+0.65	-0.22	+0.05 to +0.60
+0.50	C6	-0.50	+0.29	-0.11	-1.40 to -0.30
	C17	+0.20	+0.47	-0.16	+0.10 to +0.60

* $\Delta \log MAR = -0.285(\Delta \log VSX) - 0.0317$, see ref. 24

For a direct visual illustration of the interaction, Figure 6 shows the wavefront map, 2D PSFs, and simulated retinal images for conditions with the maximum beneficial effect for *test* terms C6 and C17, compared with +1.00 µm of *target* term only.

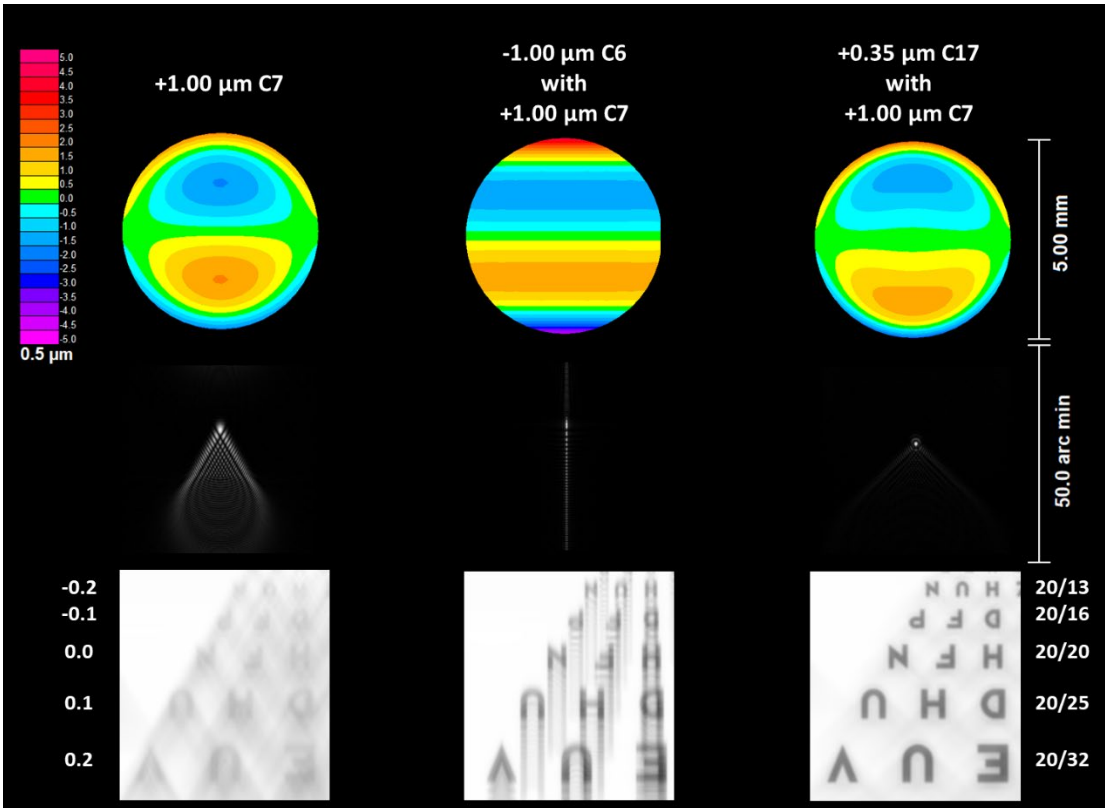

Figure 6. Wavefront maps (top row), 2D PSFs (middle row), and simulated sample charts (bottom row) for the three conditions (left: +1.00 µm of C7 alone, middle: -1.00 µm C6 with +1.00 µm C7, right: +0.35 µm C17 with +1.00 µm C7). Both PSFs and simulated charts are inverted with respect to the visual percept (as they appear at the retinal plane).

3.2. Visual acuity estimation of the beneficial effect using simulated charts in typically sighted subjects

Having established (through simulation) which terms were anticipated to have a beneficial effect, visual acuity was recorded as subjects read simulated acuity charts (*test*+*target* combination). The results displayed a similar pattern (Figure 5) as was predicted by the model including the peaks for the most beneficial and deleterious conditions. The maximum beneficial effect was -

0.27 in logMAR acuity change (logMAR acuity of test conditions - logMAR acuity of charts with C7 only) for C6 and -0.36 in logMAR acuity change for C17. The measured and predicted change in logMAR acuities showed a significant positive correlation for both C6 ($p<0.001$, $R^2=0.7991$) and C17 ($p<0.001$, $R^2=0.7647$) (Figure 8).

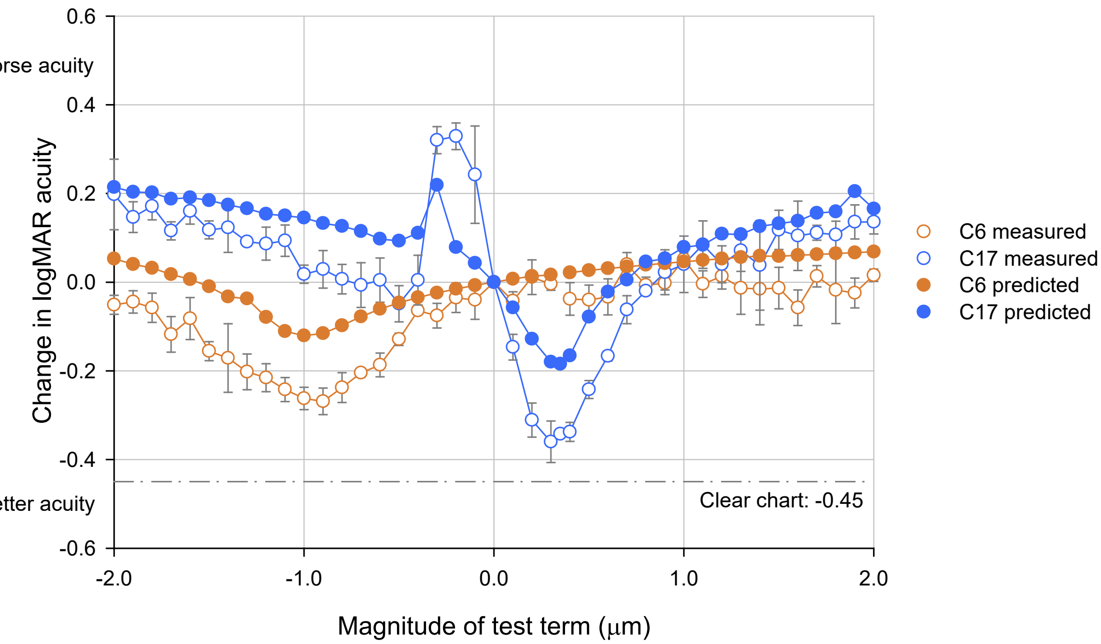

Figure 7. The change in logMAR acuity with simulated chart reading for conditions combining C6 (open blue) and C17 (open orange) with +1.00 μm of C7. The value shown in the figure represents the average of the three subjects. Data were in the form of change in logMAR acuity as the difference between logMAR acuity with the test condition and acuity with +1.00 μm of C7 alone. The expected change in logMAR acuity from simulation were included for C6 (filled blue) and C17 (filled orange). Error bars represent standard deviation. Dashed straight line represents the change in logMAR acuity with clear charts.

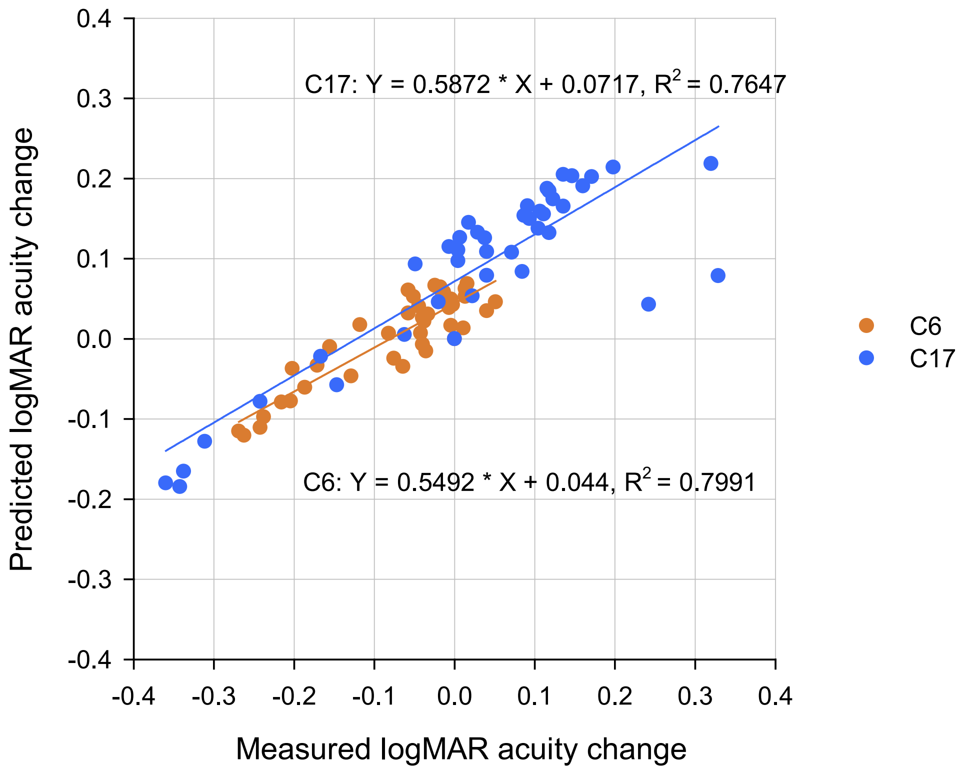

Figure 8. Correlation between measured and predicted change in logMAR acuities, for C6 and C17 with +1.00 µm of C7.

There were two data points with larger discrepancy between the observed and predicted acuity, they resulted when the magnitude of C17 was -0.1 and -0.2 µm, respectively. In Figure 7, it can be seen that with those two combinations, the predicted logMAR acuities were approaching the peak of the maximum deleterious effect and the variance of the measured acuity among the subjects was larger especially for the condition with -0.1 µm (0.16, 0.37, and 0.2 in logMAR acuity for the three subjects).

4. Discussion

4.1. What terms are predicted to have beneficial visual interaction between *test* terms and *target* term?

In this study, positive vertical coma was combined with individual aberration terms in the 2nd to 5th radial orders, and certain terms were demonstrated to have a beneficial effect compared to vertical coma alone. But it must be said forcefully that none of these beneficial effects allowed an individual to perform better than the aberration free case. In this way, the interactions are beneficial, but do not allow the individual to do better than they would if all aberrations were corrected.

That said, C17 was found to have the maximum beneficial effect when combined with C7, those two terms have the same angular frequency of -1 with radial orders of 5 and 3, respectively. This is in agreement with a previous study finding that the combination of Zernike terms that are two radial orders apart with the same angular frequency can improve visual acuity.[9] In addition to C17, C6 also had a sizeable beneficial effect. This is in agreement with Villegas et al.[28] who also found that C6 and coma had a positive coupling that, in certain (but not all) combinations, can improve retinal image quality in a group of eyes with typical vision. Terms that had minimal effect regardless of the ratios (C3, C8, C9, C14, and C20) are those that mainly fall near the edge of the Zernike pyramid (Figure 2).[5, 6]

4.2. Additional factors to consider in the simulation

A note to the reader of this thesis: These summaries of other interactions were kept here to preserve the integrity of the OPO manuscript, and in the next chapter, we explore them in a manner that we simply could not (due to length) in that manuscript.

The analysis of +1.00 µm of C7 with a single *test* term, while consistent with prior studies for aberration interactions,[9, 10] is not representative of the real-world rigid contact lens corrected keratoconus condition. An eye in the real world suffers from a much more complicated aberration profile, with residual aberration in many terms, not just two.[20, 22] To broaden the application and our interpretation of the interaction of two terms studied here, the factors below were considered, but did not exhibit significant influence on the results reported above.

4.2.1. The expected effect as function of the level of *target* term

The magnitude of C7 for eyes with keratoconus and wearing rigid contact lenses varies with the severity of the condition and scales with pupil size. For the eyes without correction, Alio et al.[15] found that coma-like RMS (3rd, 5th, and 7th orders) was about 2.90±1.40 µm for a 6-mm diameter pupil; Pantanelli et al.[17] found that C7 accounted for about 53±32% of the higher order variance for a group of keratonic eyes with 2.24±1.22 µm total HO-RMS over a 6-mm diameter pupil. With the conventional rigid contact lens, the median value for C7 in 20 eyes was +0.153 µm over a 6-mm diameter pupil (Hastings et al.[41]); the magnitude of C7+C8 RMS was 0.42±0.32 µm for a 5-mm diameter pupil (Marsack et al.[19]); 3rd order RMS was 0.496 ±0.297 µm for a 4-mm diameter pupil (Negish et al.[21]). Given the variability in reported values, we presented the results of visual interaction for two levels of C7: +0.50 and +1.00 µm, which can reasonably represent the observed magnitude (if not the sign) of keratoconic eyes with and without right contact lens corrections. There was a slight difference in values for the maximum effect condition and ratios, as well as the ranges that resulted in an improvement of 0.5 line or more between two levels of *target* term (Table 2), this is due to the discrete 0.05 µm steps of the *test* term used in the simulation. The difference in maximum effect is due to the fact that the magnitude of the effect is dependent on the level of the *target* term. In addition to the two levels of *target* term analyzed, different levels of the *target* term were studied to reveal the maximum effect on the predicted change in logMAR visual acuity for C6 and C17. As expected, the ratios of the *test* terms to *target* term remained unchanged for the maximum effect conditions.

4.2.2. Opposite signs of *target* term

This study focused on positive levels of C7, as it is the dominant Zernike aberration term in eyes with keratoconus corrected with conventional rigid contact lenses.[21, 22, 26] For an uncorrected eye with keratoconus, the sign of C7 is almost always negative as the cone is generally located inferior to the pupil center.[42] We studied the visual interaction between negative C7 with other terms. As would be expected, the beneficial effect is observed when the opposite sign of the *target* term was simulated with the same steps described above, with the change of the sign for the *test* terms (e.g., -0.35 μm of C17 was combined with -1.00 μm of C7 to reach the same maximum beneficial effect compared with the combination of +0.35 μm of C17 and +1.00 μm of C7). This finding suggests that the visual interaction results can also be applied to uncorrected eyes with keratoconus or those corrected with soft lenses or spectacles, where C7 values are most often negative.

4.2.3. Combination of both vertical trefoil and vertical secondary coma

As C6 and C17 separately were both found to provide a multi-line benefit in acuity, their combined effect was also studied. The expected change in logVSX values was calculated for conditions combining both C6 and C17 each from -2.00 µm to +2.00 µm in 0.05 µm steps with +1.00 µm C7. Negligible additional benefit was observed when combining C6 and C17 together with C7.

4.2.4. Effect of changing the orientation of the *test* terms

The non-rotational symmetrical terms (terms that are not on the midline of the Zernike pyramid) exist in pairs (e.g., C6 and C9 are trefoils, C7 and C8 are comas) with meridians at different orientations. The corresponding paired terms with different magnitudes can be combined mathematically as vectors and represented as one single aberration with different orientations. In detail, the effect of changing the orientation of the non-rotationally symmetric terms (Zernike aberration terms with a non-zero angular frequency) was achieved by combining the two Zernike aberration terms having the same radial order but opposite signs of angular frequency, with different proportions, while keeping the RMS value constant, e.g., combining vertical trefoil (C6) and oblique trefoil (C9) with different proportions to yield trefoil at different orientations. The number of cycles in 360 degrees is determined by $N = |m|$, m is the angular frequency, e.g., $m = 3$ for trefoil. For one full cycle, the magnitude of C6 varies from 0 to minimum (-1.00 µm) to 0 to maximum (+1.00 µm) to 0 µm, corresponding to the orientation of 0 to 120 degrees (The example of trefoil is shown in Figure 9).

The beneficial effect in logVSX change varies with the orientation of trefoil (Figure 9). The maximum beneficial effect occurred when the orientation of trefoil was at 30/150/270 degrees which correspond to the combination of -1.00 µm of C6 and 0 µm of C9, with the total RMS for trefoil being +1.00 µm. The maximum effect of +0.42 in logVSX change remained at the same level as when single term C6 was tested, which demonstrates that the effect observed for single C6 term is the maximal effect that one would expect for trefoil at any orientation.

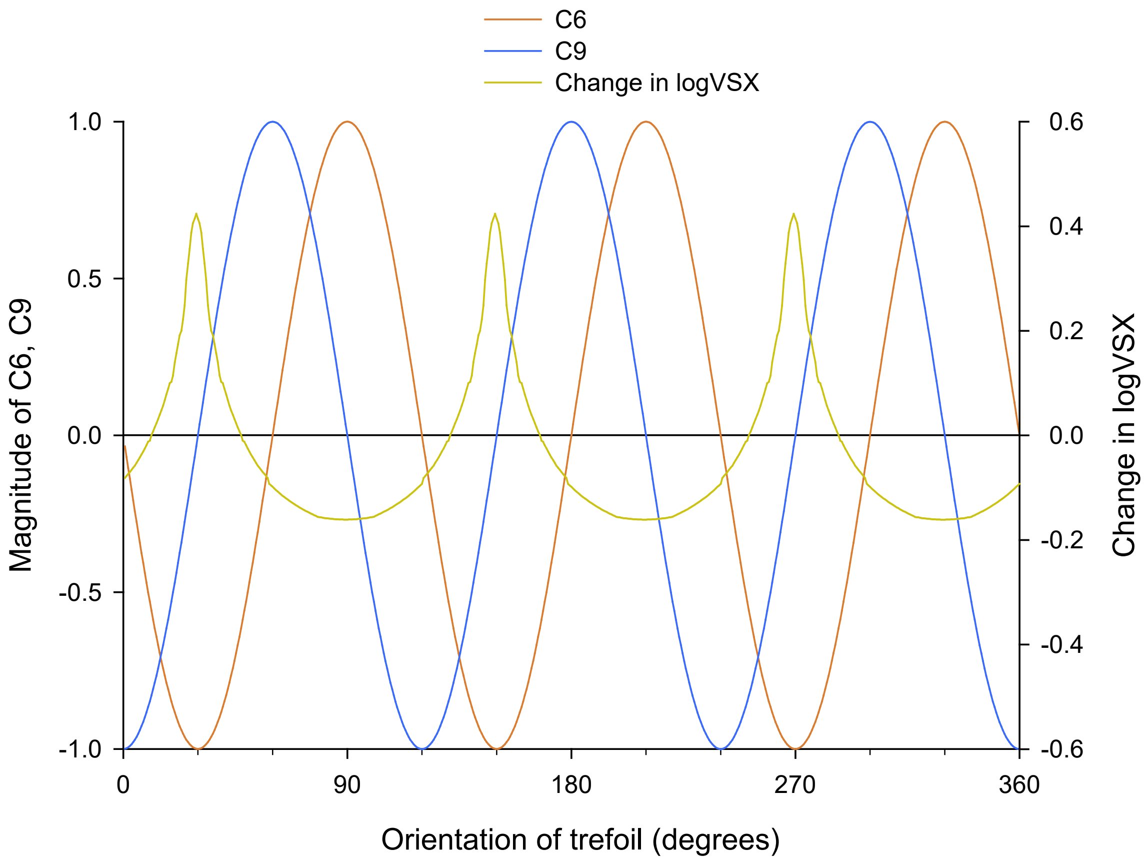

Figure 9. Trefoil: change in logVSX compared to the condition of *target* term alone when changing the orientation of trefoil for +1.00 μm of C7, the orientation change is achieved by combining C6 and C9 with different proportions while maintaining the total RMS of +1.00 μm (as the maximum effect happens when -1.00 μm of C6 combined with +1.00 μm of C7).

The maximum beneficial effect for other non-rotationally symmetric terms (e. g. astigmatism, quadrafoil) showed similar results as trefoil: no additional benefit was seen by changing the orientation of those *test* terms.

4.3. Observing aberration interaction in real eyes with simulated charts

There are different approaches that can be used to test vision under controlled aberration conditions, common ones being the source method and observer method.[43] The source method works by imposing a specific aberration structure on the eye with lenses, phase plates, or adaptive optics.[4] The observer method requires a typically sighted individual to read blurred letter charts under a controlled pupil size (typically 3 mm under cyclopleged conditions) as was done in this study. The blurred letter chart is generated by convolving a clear chart with the PSF derived from the desired WFE. Both methods have shown similarity in the ability to perform this type of study.[44] The source method using a deformable mirror allows the WFE to vary in a dynamic fashion. The observer method holds the advantages of requiring a less complicated apparatus, setting, and ability to test a large range of WFEs.

Visual acuity from typical subjects reading simulated acuity charts confirmed the existence of the interactions for the two terms that were expected to have the most beneficial effect. The results followed a similar pattern as the prediction when the magnitude of the *test* term varied from -2.00 µm to +2.00 µm with the maximum beneficial condition being around -1.00 µm for C6 and +0.30 µm for C17, and the peak of deleterious condition being around -0.25 µm for C17. The magnitude of the beneficial effect was larger than predicted, and the majority of the conditions tested resulted in better acuity (more beneficial effect or less deleterious effect). This is likely due to the fact that the model used to predict the visual acuity from visual image quality metrics was generated based on more complete aberration profile (testing conditions were generated by scaling up or down measured WFEs of eyes with keratoconus to represent a continuous range of logVSXs) and our analysis only included two terms (*target* term and *test* term). It suggests that the simulation using VSX as the metric may underestimate visual performance for these incomplete representations.

4.4. Limitations in predicting visual performance from objective wavefront measurement

Numerous studies have examined the use of metrics calculated from objective wavefront measurements in an attempt to predict visual performance.[2, 3, 7] Vision is affected by multiple factors, like light scatter, that are not characterized by wavefront aberration. In addition, most of the metrics only consider monochromatic light, which would not be representative of the polychromatic world. Further, the neural factor included in the metrics reporting visual image quality currently being used have been shown to vary with different illumination and pupil sizes,[45] along with age and other physiological and pathological conditions,[46-49] but they do not currently vary in the metric calculation used here. There is also a lack of information on neural factors for individuals with keratoconus and other conditions with increased aberration. Further work is being done to evolve this objective representation of visual image quality to more accurately reflect the performance of individuals.

4.5. Application of the visual interaction

In this study, we focused on the visual interaction between individual 2nd to 5th Zernike aberration terms and C7. We found that a limited set of ratios of selective *test* terms to *target* term could improve the visual image quality metric VSX, compared to C7 alone, while the combinations with other ratios or other terms could decrease acuity dramatically. The study screened the terms up to the 5th radial order and found that two terms C6 and C17 had the largest beneficial effect. The results from the simulation study have shown a variety of interactions among different terms which could help understand the diverse visual performance observed in eyes with keratoconus and other ectatic conditions of the cornea. The fact that aberrations interact may help explain the varied visual performances observed in clinics despite having similar levels of RMS. RMS is currently the most common method used to quantify aberration. These findings call for additional metrics for describing visual image quality that consider interactions between aberration terms. Coma (the dominant aberration term in keratoconus) is a logical aberration to employ when examining the interactions that occur between individual terms. This chart reading study also provided evidence supporting the ability of using VSX as a reliable tool to predict visual performance for eyes viewing through a set of limited (rather than the whole eye) aberration terms.

III. NON-BENEFICIAL VISUAL INTERACTIONS AND FACTORS AFFECTING THE MAGNITUDE OF VISUAL INTERACTION

1. Introduction

As stated above, the results of the first experimental chapter had been accepted for publication in Ophthalmic and Physiological Optics at the time of this thesis.

Chuan Hu, Ayeswarya Ravikumar, Gareth D. Hastings, Jason D. Marsack, Visual Interaction of 2nd to 5th Order Zernike Aberration Terms with Vertical Coma. Ophthalmic Physiol Opt 2020, in press.

Those results focused on interactions with positive vertical coma that provided a beneficial visual result. This method of presentation was chosen, in part, due to the length limitations associated with publishing a manuscript in that particular journal. Simply put, we explored an exhaustive set of interactions with C7, and length limitations would not allow them all to be reported in detail in the manuscript. With this chapter, we return to many of the results that were only briefly mentioned in the discussion of the published work (and therefore, also in the previous chapter), and report a more complete examination of those observations. Specifically, in this chapter, we focus on 1) non-beneficial visual interactions and 2) factors affecting the magnitude of the visual interactions that are observed.

2. Methods

Through-focus simulation, which was described in detail in the previous chapter, was used exclusively in this part of the study. Chart reading was not employed in the following analyses.

While all sub-studies employed here utilized the same basic method, each is described in greater detail in sections 2.1 to 2.5 under this chapter below.

For all analyses in this chapter, the change in logVSX and the corresponding predicted change in logMAR acuities were used to analyze the visual effect of the interactions. Table 3 shows the nomenclatures describing the types of visual interactions and some examples of the representative values (0.5-line of gain and 1,0-line of loss in logMAR acuity). We chose a 1.0-line loss in logMAR acuity as a threshold for deleterious effects as opposed to a beneficial threshold of 0.5-line gain for the following reasons: 1) The asymmetrical characteristic of the model (see Table 2 caption) used for predicted change in visual acuity on the positive and negative sides indicates different values for a beneficial and deleterious effect. This is because the change in logMAR acuity predicted from the formula does not equal zero even when the change in logVSX is zero. 2) A threshold for loss of acuity does not serve the purpose of differentiating results in the same way that the beneficial threshold does. Patient's tolerance to benefit and loss are different, making it unnececssary to set the same threshold for both gain and loss. 3) This value was chosen based on the observation that its use separated the 12 non-beneficial terms into two distinct clusters, as shown in Figure 3. The equation to convert between the change in logMAR acuity and change in logVSX can be found in the Table 2 caption. As was done above, the wavefront aberration was referenced to a wavelength of 555 nm over a 5mm diameter pupil.

Table 3. Demonstration of nomenclatures and examples of representative values for the visual interaction.

	Beneficial effect		Deleterious effect	
	Symbol	**0.5-line**	**Symbol**	**1.0-line**
Change in logVSX	positive	+0.06	negative	-0.46
Change in logMAR acuity	negative	-0.05	positive	+0.10
Number of letters read	gain	2.5	loss	5

2.1. Interactions of *test* terms predicted to have no beneficial effect on vision when combined with C7.

As described in the previous chapter, individual terms ranging from -2.00 to +2.00 µm in 0.05 µm steps were mathematically combined with +1.00 µm of C7. The range for the test terms (±2.00 µm) used here was kept the same as the range used in Chapter 2 for the following reasons: 1) With the fact that C7 is the dominant term in the eyes with keratoconus, one might consider that the maximum values of the test terms should be equal to that of C7 (+1.00 µm or -1.00 µm). Extending the range from ±1.00 µm to ±2.00 µm allows adequate coverage of extreme cases. 2) This selection was proved acceptable when examining the through-focus curve in Figure 3, which showed that all the conditions with maximal beneficial effect were included in this test range. In this section, we concentrated on describing interactions that were not predicted to have a beneficial effect on vision, regardless of the magnitude of the *test* term.

2.2. Interactions when combining two individually beneficial *test* terms together with C7.

The two *test* terms in the earlier experiment that were predicted to have the largest beneficial effect (C6 and C17, independently ranging from -2.00 to +2.00 μm in 0.05 μm steps) were themselves combined and then added to +1.00 μm of C7 to assess whether this resulted in an additional beneficial effect.

2.3. Interactions associated with a change in the orientation of non-rotationally symmetric aberrations with C7.

The non-rotationally symmetric Zernike aberrations (that are not on the midline of the Zernike pyramid) exist in pairs (e.g., C6 and C9 are trefoils, C7 and C8 are comas) with meridians at different orientations. Those pairs share the same radial order and the same magnitude of angular frequency but opposite signs (sine vs. cosine in polar notation, see Appendix). The corresponding paired terms describing an aberration (C6 and C9 for trefoil) with different magnitudes can be combined mathematically as vectors and represented as one single aberration, the result of which will be to alter the angular orientation. In detail, the effect of changing the orientation of the non-rotationally symmetric terms (Zernike aberration terms with a non-zero angular frequency) was achieved by combining the two Zernike aberration terms having the same radial order but opposite signs of angular frequency, with different proportions, while keeping the RMS value constant. For example, one can combine vertical trefoil (C6) and oblique trefoil (C9) with different proportions to yield trefoil at different orientations. The number of cycles in 360 degrees is determined by $N = |m|$, m is the angular frequency, e.g., $m = 3$ for trefoil (Figure 10). For one full cycle, the magnitude of C6 varies from 0 to minimum to 0 to maximum to 0 μm, corresponding to the orientation of 0 through 120 degrees.

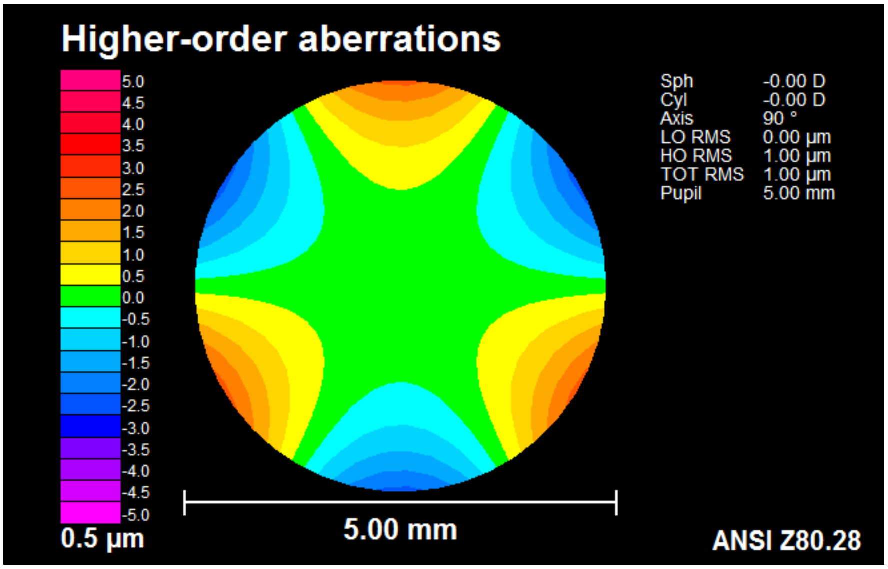

Figure 10. Wavefront map for trefoil. This is the wavefront for a -1.00 µm of vertical trefoil with a 5-mm diameter pupil.

From the *test* terms in experimental chapter 1 that were predicted to have beneficial visual interaction, we further studied the effect of changing the orientation. As described above, this was achieved by combing two corresponding individual terms (varying the magnitude of the each of the two terms while keeping the total RMS magnitude the same). The RMS magnitude we chose to hold constant for the combined terms was the magnitude of the term when the maximum effect was exhibited. For example, C6 and C9 were combined for trefoil (RMS of 1.00 µm, as the maximum effect was observed when -1.00 µm of C6 was combined with +1.00 of C7). The details of the five aberrations included in this part of the analysis are shown in Table 4.

Table 4. The aberrations included in the orientation analysis.

Aberration	Combination	Magnitude at maximum beneficial effect (µm)
Trefoil	C6 and C9	-1.00 (C6)
Quadrafoil	C10 and C14	±0.75 (C10)
Pentafoil	C15 and C20	-0.95 (C15)
Secondary trefoil	C16 and C19	+0.30 (C16)
Secondary coma	C17 and C18	+0.35 (C17)

2.4. Interactions of *test* terms with a changing magnitude of C7.

The two *test* terms predicted to have the largest beneficial effect from the previous chapter (C6 and C17) were then applied to varying levels of C7. C6 or C17 ranging from -2.00 to +2.00 µm in 0.05 µm steps were mathematically combined with a series of C7 from -2.00 to +2.00 µm in 0.05 µm steps. After identifying the magnitude of the *test* term that was predicted to have the maximum beneficial effect for each level of C7, the corresponding ratios of *test* term over C7 (C6:C7 or C17:C7) were calculated.

2.5. Interactions of *test* terms with negative, as opposed to positive, C7.

With a similar approach from the previous chapter, *test* terms ranging from -2.00 to +2.00 µm in 0.05 µm steps were combined with -1.00 µm of C7 instead of +1.00 µm.

This examination was considered relevant due to the fact that uncorrected eyes of individuals with keratoconus exhibit negative vertical coma. This is in contrast to eyes of individuals with keratoconus wearing rigid forms of corrections, which tend to exhibit positive vertical coma

3. Results

3.1. Interactions of *test* terms predicted to have no beneficial effect on vision when combined with C7.

Terms C3, C8, C9, C14, and C20 showed no beneficial effect for any of the conditions studied and no significant deleterious (a predicted loss of more than one line of acuity in logMAR, corresponds to -0.46 change in logVSX) visual effect for the majority of combinations studied (Figure 11). The maximum deleterious effects were -0.10, -0.35, -0.17, -0.07, and -0.04 in logVSX change, corresponding to a change in logMAR of -0.00, +0.07, +0.02, -0.01, and -0.02 for C3, C8, C9, C14, and C20, respectfully. In general, for terms C3, C8, and C9, the deleterious effect gets worse when the *test* terms are larger even though the maximum effect was still less than -0.46 in logVSX change; C14 and C20 showed almost no effect on expected change in vision regardless of the level the *test* term.

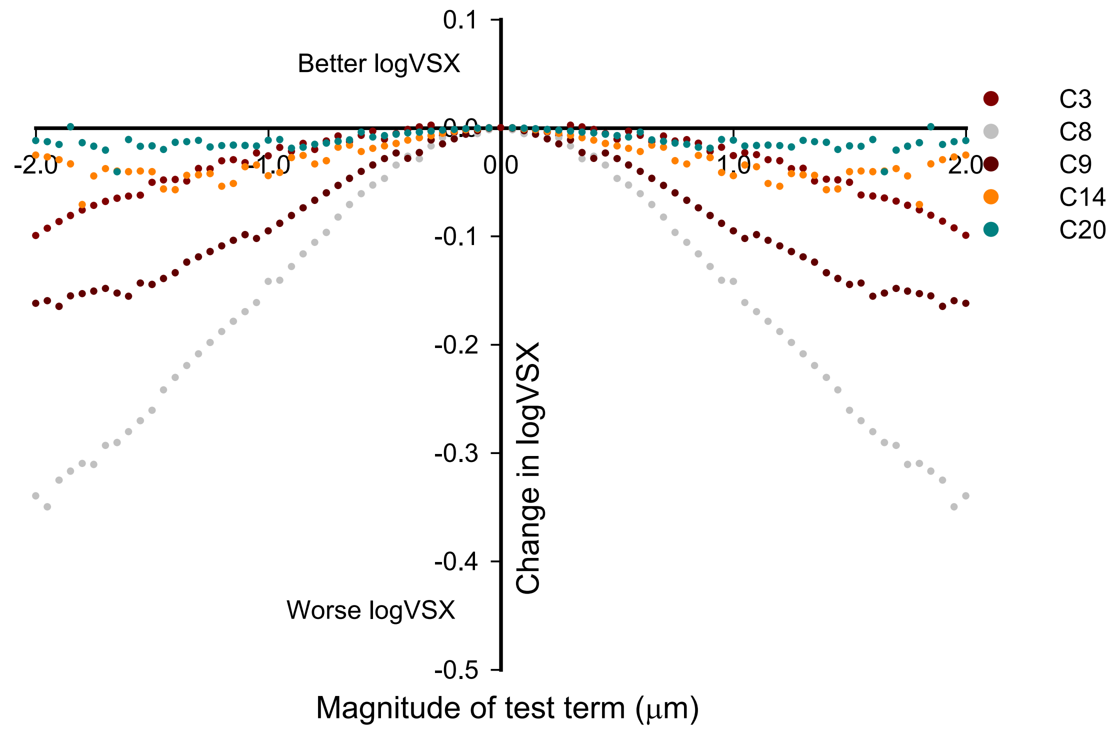

Figure 11. The individual terms (C3, C8, C9, C14, and C20) that were predicted to have no significant visual effect when combined with +1.00 μm of C7.

Terms C4, C5, C11, C12, C13, C18, and C19 all reached levels of significantly worse logVSX (more than -0.46 change in logVSX) in the majority of the tested range. The magnitude of the effect tended to become larger as the value magnitude of the *test* term increased (except for C12, the deleterious effect increased with the magnitude of C12 first then returned slightly to a steady level over the range tested here). The maximum deleterious effects were higher than -0.83 in logVSX change (corresponds to a +0.20 change in logMAR), for all these terms.

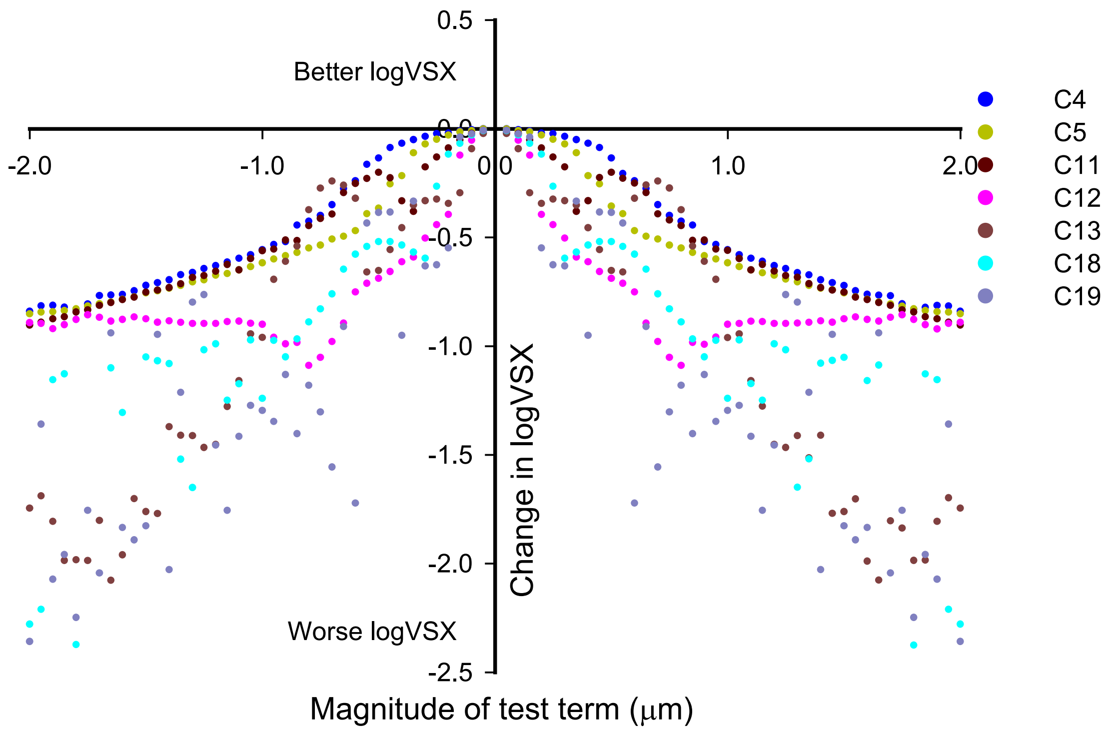

Figure 12. The individual terms (C4, C5, C11, C12, C13, C18 and C19) had significantly worse logVSX (more than -0.46 change in logVSX) in the majority of the tested range when combined with +1.00 μm of C7.

All the terms shown in Figure 11 and Figure 12 showed a symmetrical pattern along the y-axis, meaning that whether the term is positive or negative had no effect on the visual interaction with C7.

3.2. Effect of combining C6 and C17 together with +1.00 μm of C7.

The maximum effect of +0.655 change in logVSX was observed when -0.05 μm of C6 and +0.35 μm of C17 were combined together with +1.00 μm of C7, compared with the +0.42 change in logVSX when individual C6 was studied and +0.648 change in logVSX when individual C17 was studied. The difference in magnitude was negligible (change in logVSX: +0.6554 vs. +0.6484).

There were a range of combinations that resulted in positive logVSX change when C6 and C17 were combined together with C7 (shown with warmer colors in Figure 13). With the appropriate combination (coupling), the ranges of the *test* term (the range = the highest value with the threshold beneficial effect – the lowest value of the *test* term with the threshold beneficial effect) that was predicted to have a change in logVSX > +0.06 were 0.95 µm (-0.35 to +0.60 µm) and 3.45 µm (-2.00 to +1.45 µm) for C17 and C6, respectively, compared with 0.65 µm (+0.05 to +0.60 µm) and 1.25 µm (-1.45 to -0.25 µm) when the *test* term was analyzed alone. There were some invalid data points in the conditions studied due to the values of VSX being negative from the metric calculation. These are associated with conditions where VSX approaches 0 (poor levels of visual image quality), and the negative value of VSX originates in the metrics computational engine. This did not affect the main outcome of this analysis, as the preponderance of those invalid data points were in areas consistent with non-beneficial combinations.

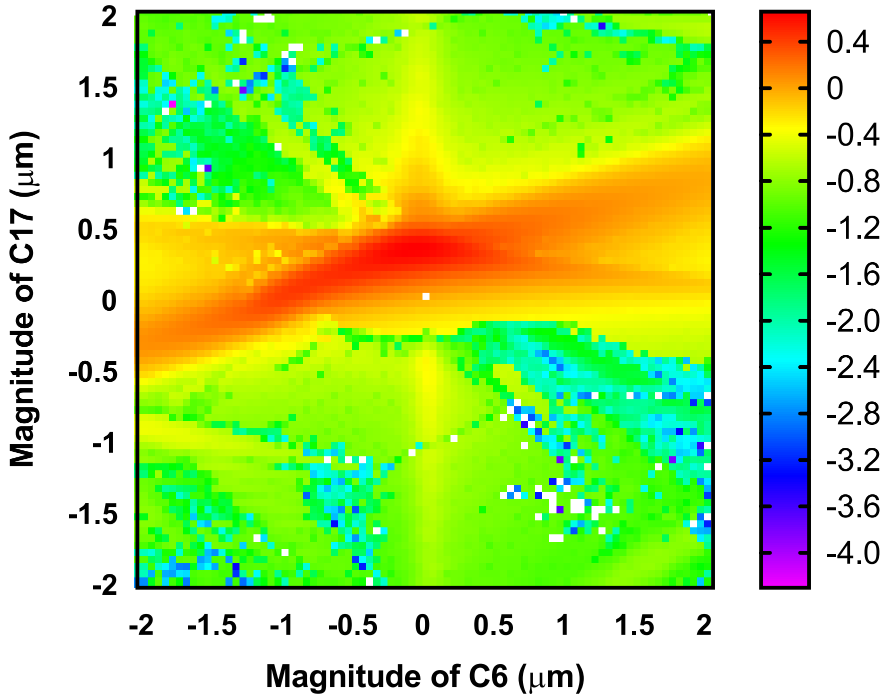

Figure 13. The visual interaction in logVSX change when combining both C6 and C17 each from -2.00 μm to +2.00 μm in 0.05 μm steps together with +1.00 μm of C7. The data points with white in color are invalid data.

3.3. Interactions associated with a change in the orientation of non-rotationally symmetric aberrations with C7.

The results of changing the orientation of the non-rotationally symmetric terms are shown in Figure 9 (in the previous chapter), and Figure 14 to Figure 17 below. The change of orientation resulted in no extra beneficial effect compared with the condition of individual terms alone as they are defined by the Zernike polynomial. The maximum effect was observed when one of the two components (the one with the same sign of angular frequency as the *target* term, negative in this case) was at the maximum magnitude, and the paired term was at zero.

The beneficial effect in logVSX change varies with the orientation of trefoil (Figure 9). The maximum beneficial effect happened when the orientation of trefoil was at 30/150/270 degrees which correspond to the combination of -1.00 µm of C6 and 0 µm of C9, with the total RMS for trefoil being +1.00 µm. The maximum effect of +0.42 in logVSX change remained at the same level as when single term C6 was tested, which demonstrates that the effect observed for single C6 term is the maximal effect that one would expect for trefoil at any orientation.

The maximum beneficial effect for other non-rotationally symmetric terms (quadrafoil, pentafoil, secondary astigmatism, and secondary coma) showed similar results as trefoil: no additional benefit was observed by changing the orientation of those *test* terms.

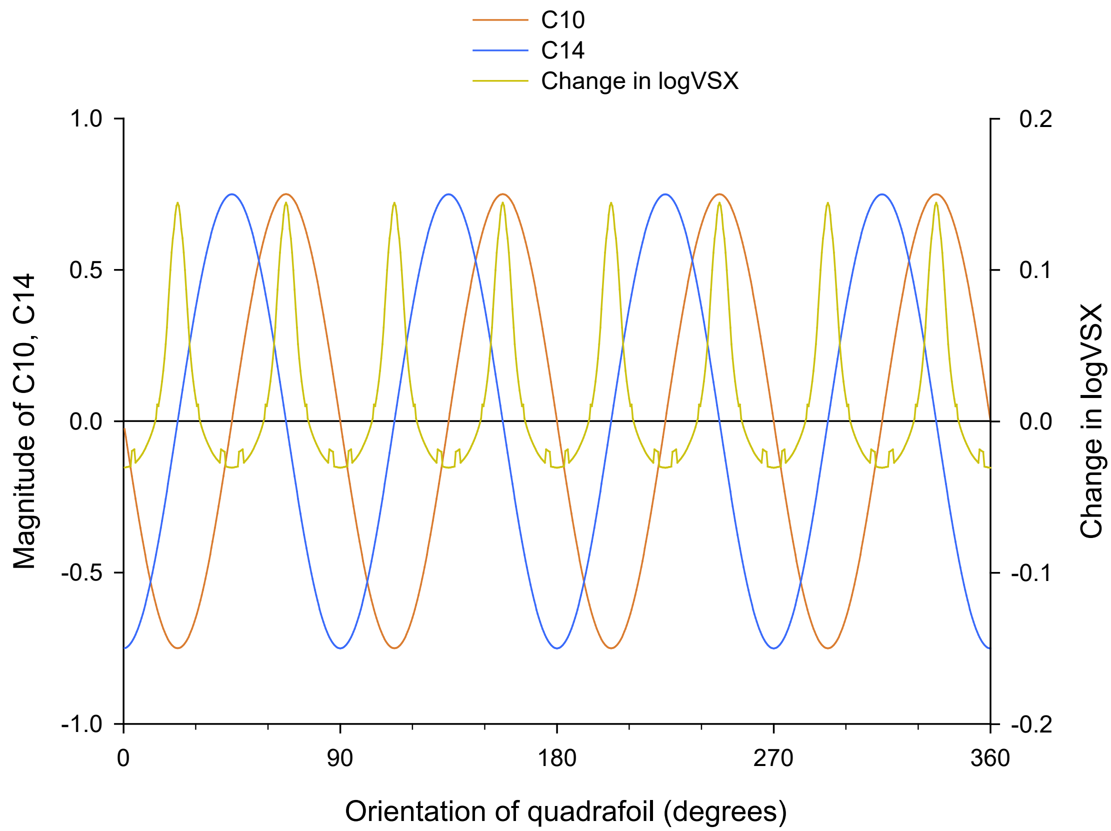

Figure 14. Quadrafoil: change in logVSX compared to the condition of *target* term alone when changing the orientation of quadrafoil for +1.00 µm of C7, the orientation change is achieved by combining C10 and C14 with different proportions while maintaining the total RMS of +0.75 µm (as the maximum effect happens when -0.75 or +0.75 µm of C10 combined with +1.00 µm of C7). There are four full cycles for quadrafoil through 360 degrees.

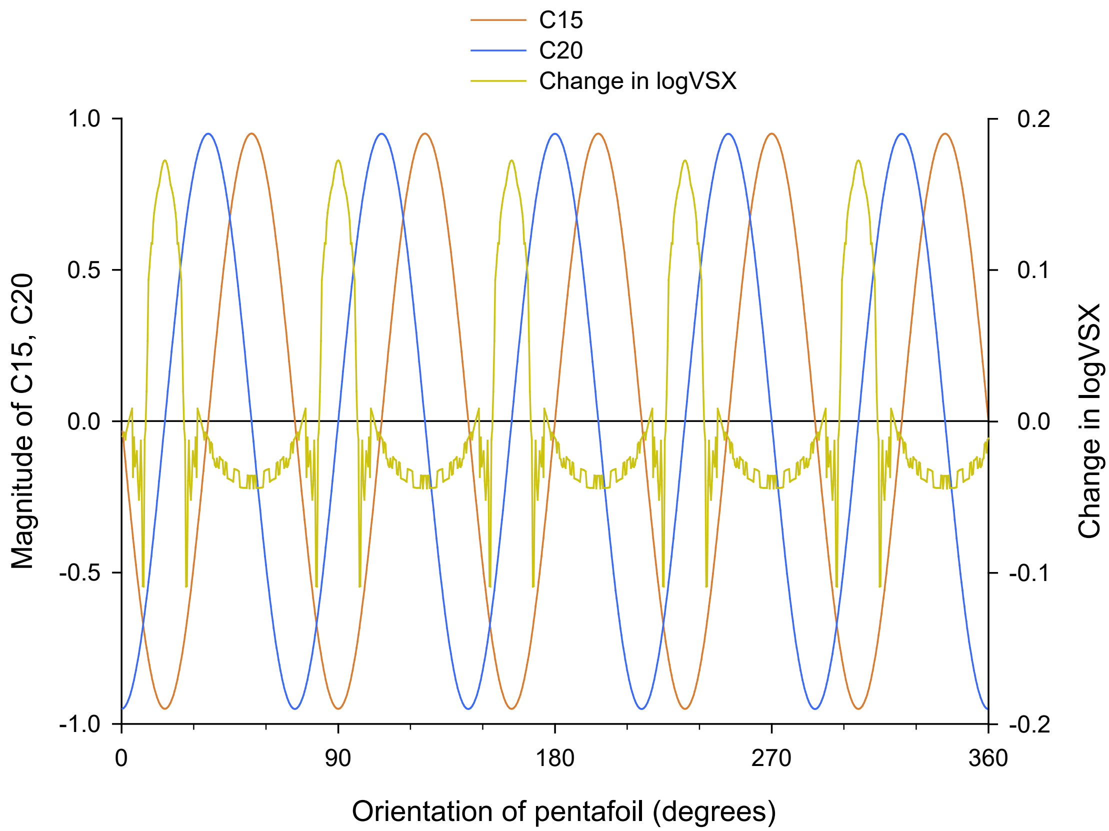

Figure 15. Pentafoil: change in logVSX compared to the condition of *target* term alone when changing the orientation of pentafoil for +1.00 µm of C7, the orientation change is achieved by combining C15 and C20 with different proportions while maintaining the total RMS of +0.95 µm (as the maximum effect happens when -0.95 µm of C15 combined with +1.00 µm of C7). There are five full cycles of pentafoil through 360 degrees.

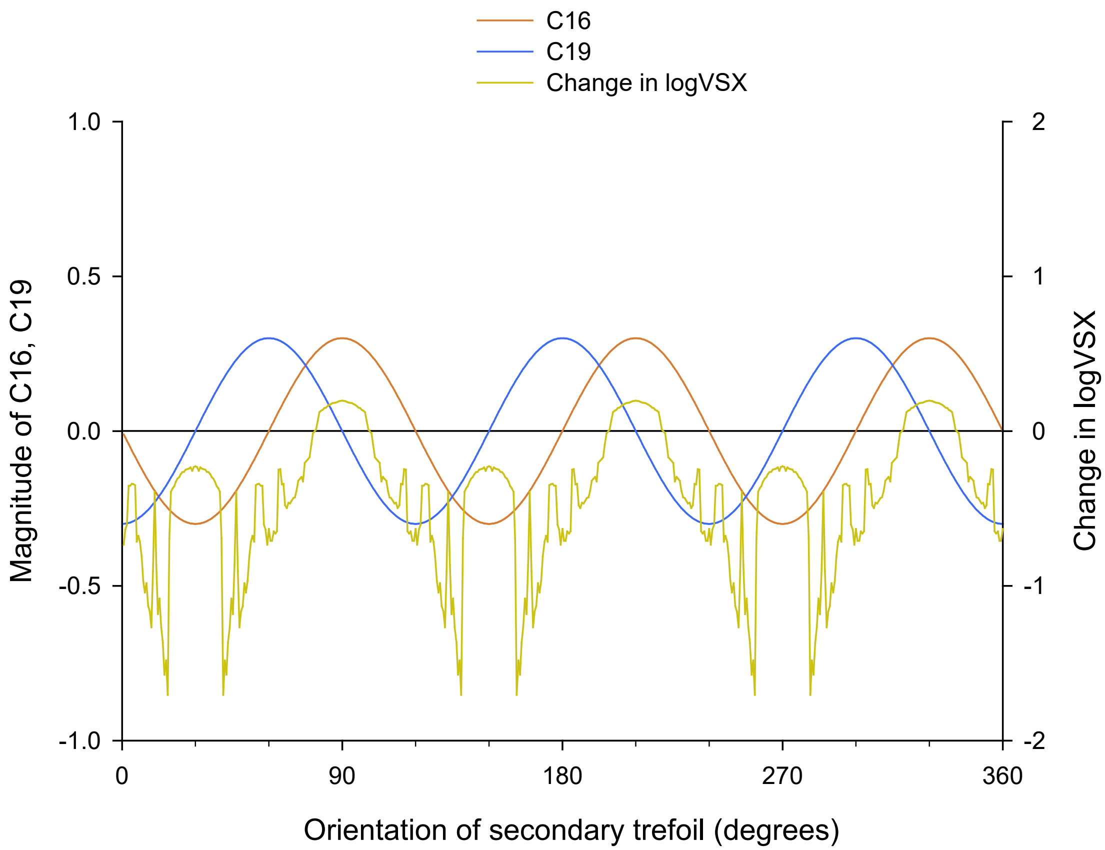

Figure 16. Secondary trefoil: change in logVSX compared to the condition of *target* term alone when changing the orientation of secondary trefoil for +1.00 µm of C7, the orientation change is achieved by combining C16 and C19 with different proportions while maintaining the total RMS of +0.30 µm (as the maximum effect happens when +0.30 µm of C16 combined with +1.00 µm of C7). There are three full cycles of secondary trefoil through 360 degrees.

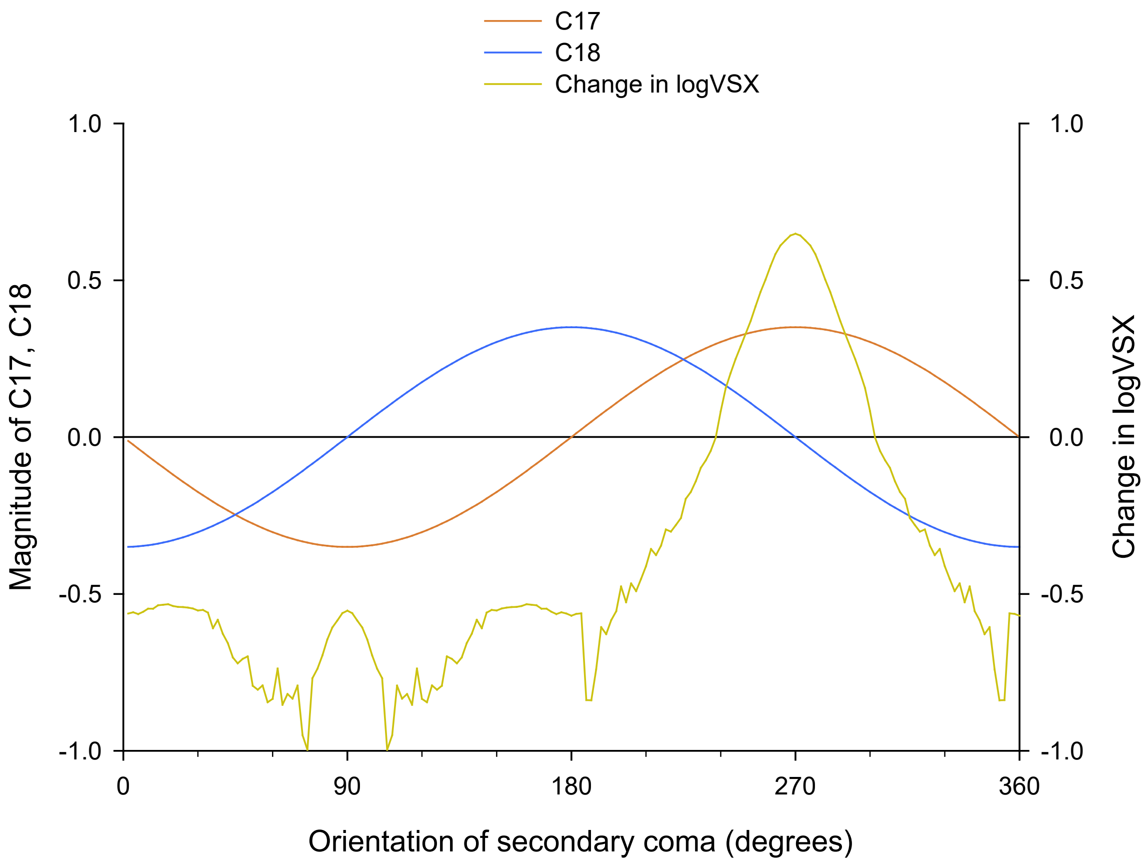

Figure 17. Secondary coma: change in logVSX compared to the condition of *target* term alone when changing the orientation of secondary coma for +1.00 μm of C7, the orientation change is achieved by combining C17 and C18 with different proportions while maintaining the total RMS of +0.35 μm (as the maximum effect happens when +0.35 μm of C17 combined with +1.00 μm of C7). There is one full cycle of secondary coma through 360 degrees.

3.4. Interactions of *test* terms with a changing magnitude of C7.

The analyses reported to date in this chapter and the previous chapter leveraged +1.00 μm of C7. Further, in the last chapter, the beneficial effects of C6 and C17 are described. In this section, the beneficial effects of combining C6 and C17 are examined for levels of C7 ranging from -2.00 to +2.00 μm. The results are plotted in Figure 18 and Figure 19. Both figures showed a symmetrical pattern to the origin of coordinates (negative and positive C7 had the same results as long as the sign of the *test* term was also negated). For the conditions with maximum effect (red color in the figure), both C6 with C7, and C17 with C7 showed a linear correlation (negative correlation for C6 and positive correlation for C17). When C7 is at zero, the level of maximum effect was close to zero. The ratio of the *test* term (C6 or C17) over *target* term (C7) observed in the previous chapter for the maximum effect remained constant for the range of C7 tested here: around -1:1 for C6 and +0.35:1 for C17.

The magnitude of the maximum beneficial effect for C6 and C17 with different levels of C7 is shown in Figure 20 (only showing the positive C7 as the sign of C7 does not affect the magnitude of the beneficial effect, see Figure 18 and Figure 19). The maximum effect (color) increases as the magnitude of C7 gets larger. When fitted with a one-phase association equation (Equations (7) and (8)), the r^2 values were 0.994 and 0.995 for C6 and C17 respectively (x is the level of C7, y is the change in logVSX):

$$C6\text{: } Max\ change\ in\ logVSX = -0.0210 + 0.6464 * (1 - e^{-1.226*C7}) \tag{7}$$

$$C17\text{: } Max\ change\ in\ logVSX = -0.0216 + 0.8676 * (1 - e^{-1.545*C7}) \tag{8}$$

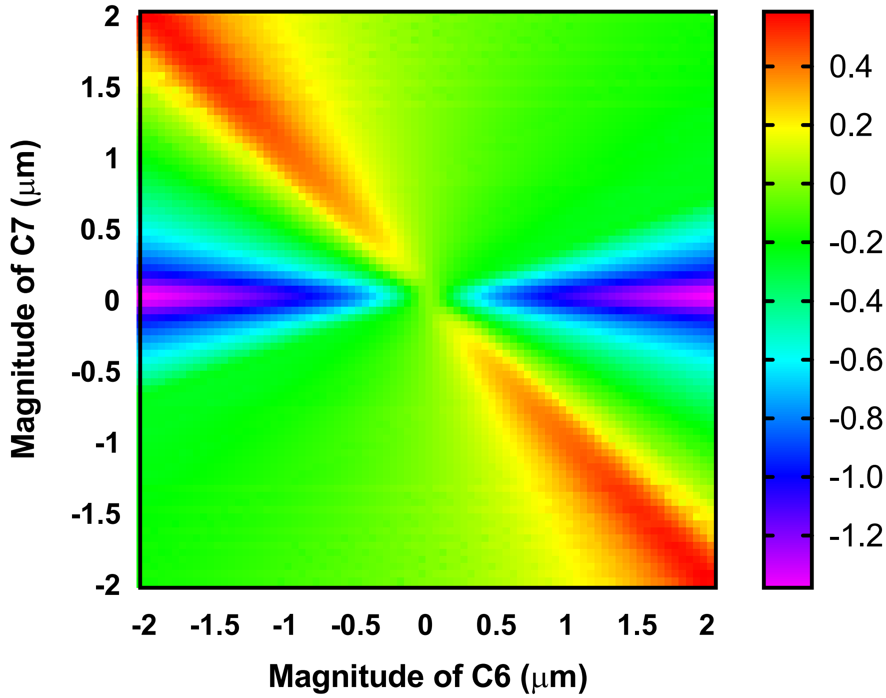

Figure 18. The visual interaction in logVSX change for C6 and C7 both ranging from -2.00 to +2.00 μm from through-focus simulation. The conditions with the maximum beneficial effect are in dark red color.

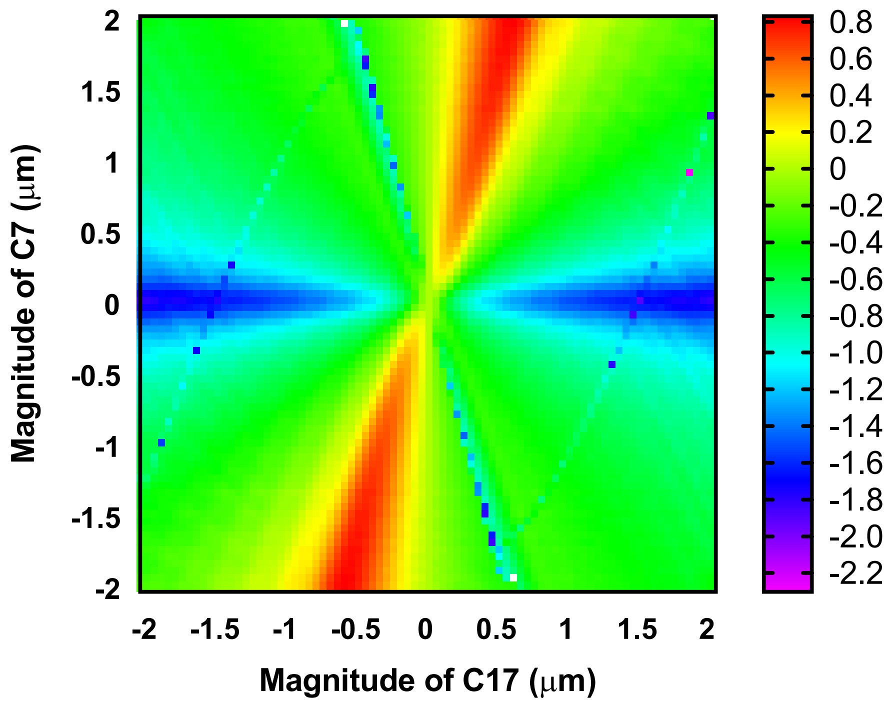

Figure 19. The visual interaction in logVSX change for C17 and C7 both ranging from -2.00 to +2.00 μm from through-focus simulation.

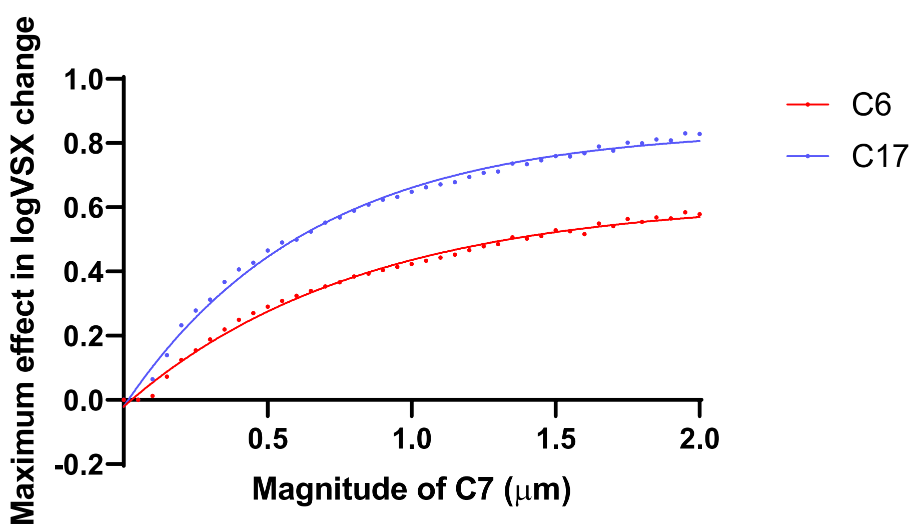

Figure 20. The maximum effect in logVSX change of combining C6 or C17 with different levels of C7. The lines represent the one-phase association fit.

3.5. Interactions of *test* terms with negative, as opposed to positive, C7.

The visual interactions of the *test* terms and a negative, rather than positive level of C7 are shown in Figure 21. As expected, when the opposite sign of the C7 was simulated with the same steps described above, the beneficial effect was observed with the change of the sign for the *test* terms (e.g., -0.35 µm of C17 was combined with -1.00 µm of C7 to reach the same maximum beneficial effect compared with the combination of +0.35 µm of C17 and +1.00 µm of C7).

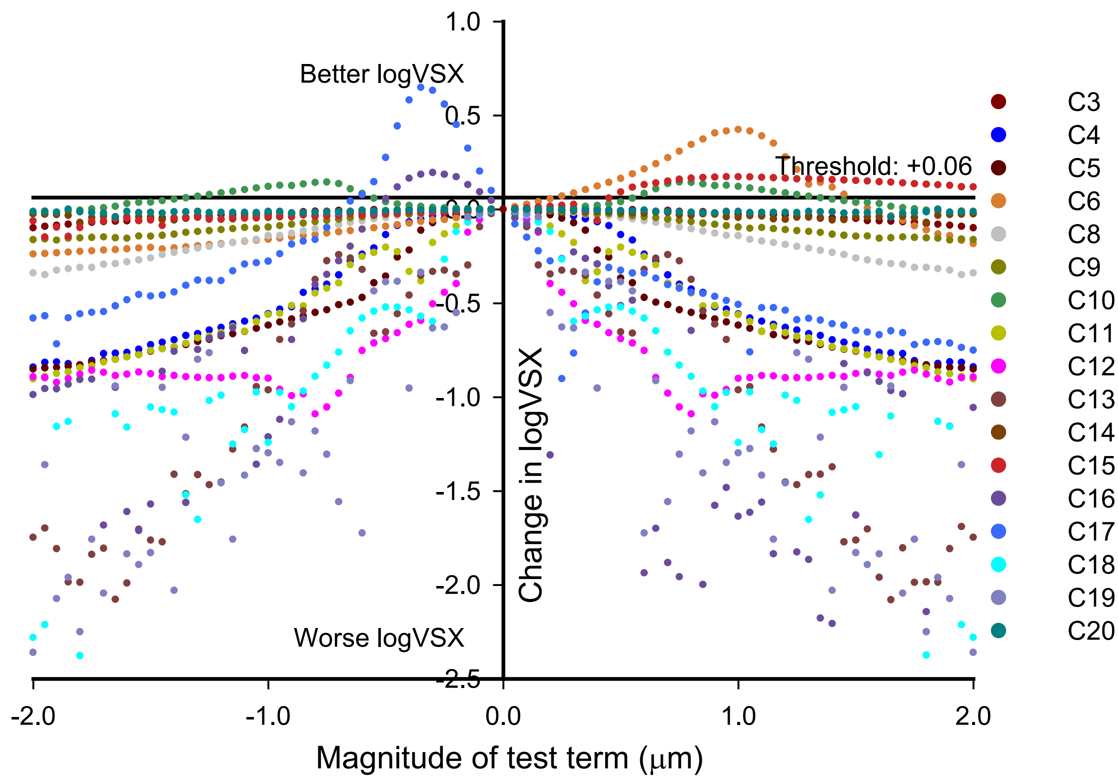

Figure 21. Change in logVSX (value difference between logVSX(C7+CX) and logVSX(C7), CX being the *test* term) for all *test* terms from 2nd to 5th radial orders when combined with -1.00 µm of C7, in comparison to C7 alone (where y equals zero). Positive values indicate better logVSX, negative values indicate worse logVSX, when the *test* term (legend) is added to C7.

4. Discussion

This chapter is a comprehensive extension of the findings in the previous chapter: "Beneficial Visual Interaction of Individual Zernike Aberration Terms from 2nd to 5th Radial Orders with Vertical Coma". The additional analyses were described in detail in a way we were not afforded when the material in the previous chapter was published in the peer-reviewed literature. In this chapter, we have shown the visual interactions that are deleterious to visual image quality, as well as some of the factors that might affect the magnitude of the interaction. As shown in the previous chapter, the beneficial interactions only arose from limited *test* terms in a small portion of the combinations studied. With the additional finding of individual Zernike aberration terms that were predicted to have no beneficial effect, we revealed the pattern that was in compliance with the previous literature: the majority of the terms that were predicted to have a minimal effect (e.g., C3, C9, C14, and C20) were on the edge (further from the center) of the Zernike pyramid (Figure 2). In particular, both C14 and C20, which are found at the outermost edge of the highest radial orders studied here (4th and 5th), have a very limited effect regardless of their magnitude.[5] In this specific case (C7 being the *target* term), the terms that were predicted to have a beneficial effect (C6, C10, C15, C16, and C17) were all on the same side as C7 in the pyramid, meaning they share the same sign of angular frequency (all negative in this case).

While not explored exhaustively here, we do speculate that the interactions seen here could help explain why eyes with keratoconus (which display prominent levels of C7 when both corrected and uncorrected) may be observed by clinicians to perform much better or much worse than expected. Simply put, the interactions are complex and make it difficult to predict from simple clinical measures how they will combine to impact visual image quality. To date, there is limited literature relating to the interaction of separate aberration terms, and the influence those interactions will have in real eyes of individuals with or without keratoconus.

The observation of visual interaction between aberration terms with C7 could help explain why the eyes with keratoconus with or without correction perform differently than predicted based on the measured level of wavefront error. There is limited literature relating the interaction in real eyes with or without keratoconus; Villegas et al. found that there was a positive coupling with vertical coma and vertical trefoil (C6) in the majority of the eyes with normal vision.[28] Further studies are required to look at the existence of synergy between C7 and other terms that were predicted to have a beneficial effect, with a particular interest in C6 and C17.

We explored conditions where more than one *test* term was included. By combining two terms that were predicted to have the maximum beneficial effect (C6 and C17) together with C7, we found that no additional maximum beneficial effect was achieved, but there was a much broader range of combinations that could be predicted to have a notable (but smaller) beneficial effect than the previously identified C6 or C17. For the five terms that were expected to have a beneficial effect (C6, C10, C15, C16, and C17), when they each were combined with their corresponding term (the term that has the same radial order and opposite sign of angular frequency) to change the orientation, no additional effect was observed. The maximum beneficial effect could only be seen when their corresponding terms were at zero. This observation should not be expanded to other terms unless exhaustive tests demonstrate that to be true as well.

The results in the previous chapter have shown the difference in maximum effect and the range of the *test* term over *target* term between two levels of *target* term (+0.50 and +1.00 µm, Table 2). In this chapter, continuous levels of the *target* term were studied to reveal that the maximum effect changed with C7 for *test* terms C6 and C17, and the ratios of the *test* terms to *target* term remained unchanged for the maximum effect conditions.

Positive levels of C7 is the dominant Zernike aberration term in eyes with keratoconus corrected with conventional rigid contact lenses.[21, 22, 26] For an uncorrected eye with keratoconus, the sign of C7 is almost always negative as the cone is generally located inferiorly to the pupil center.[42] Therefore, the visual interaction between negative C7 and other individual Zernike aberration terms was also studied, revealing that the magnitude of the interaction remained the same when the opposite sign of the *test* term was applied, and combined with the test conditions in the previous analysis. This finding suggests that the visual interaction results can also be applied to uncorrected eyes with keratoconus or those corrected with soft lenses or spectacles, where C7 values are most often negative.

One of the future applications of the finding is the design of custom rigid contact lenses to improve visual performance in eyes with keratoconus that are already wearing conventional rigid contact lenses but are unable to achieve satisfactory vision. Custom wavefront-guided scleral lenses have been shown to provide significantly better outcomes compared to conventional scleral lenses.[50, 51] In reality, the complexity of the design and manufacturing, and cost-benefit ratio of this approach has substantially limited its use to date. Marsack et al. sought to look for an alternative semi-custom method of using template-based correction (instead of designing the correction that is fully tailored to the individual) and found encouraging results.[52] The positive coupling of aberration terms suggests that pre-manufactured lenses with certain aberration combinations could be used to introduce beneficial interactions to counteract the adverse visual effect from the residual higher-order aberration. These template-based corrections could further improve vision in clinically challenging cases already wearing conventional corrections. Future directions will combine the template method proposed by Marsack and the interactions described here.

IV. CONCLUSIONS

This thesis studied the visual interactions that occur between vertical coma (C7) and Zernike aberration terms in the 2nd to 5th radial orders, using 1) through-focus simulation with the visual image quality metric VSX and 2) chart reading tests on typically-sighted subjects reading aberrated acuity charts.

The results presented in this thesis have demonstrated:

- Continued support for prior observations that aberration terms interact with each other to increase or decrease visual image quality and visual acuity.
- Terms in the 2nd to 5th radial orders interact with vertical coma to improve or reduce visual performance. The levels of vertical coma chosen for this study are representative of eyes with keratoconus, with or without wearing conventional rigid contact lenses.
- Only the terms on the same side of the Zernike pyramid as vertical coma were predicted to have a beneficial effect.
- With increased complexity, when more than one aberration term is included in the analysis, the effect observed in two-term interactions can be masked by the presence of a third or more additional term(s).
- The magnitude of the visual interaction is dependent on the level of the vertical coma, suggesting that for the individual with keratoconus, the severity of the disease might play a significant role in observed interactions.

This thesis did not address:

- The extent to which positive coupling exists in real-world conditions.
- The degree to which positive coupling among the aberration terms might provide a novel treatment approach for eyes with increased aberrations, even after conventional corrections. Such a strategy could be leveraged to intentionally preserve or promote certain aberration combinations, rather than attempting to eliminate all wavefront error, which is the current correction mindset.

These points deserve future investigation.

REFERENCES

1: Institute ANS. American National Standard for Ophthalmics: Methods for Reporting Optical Aberrations of Eyes; ANSI Z80. 28-2004: Optical Laboratories Association; 2004.

2: Marsack JD, Thibos LN & Applegate RA. Metrics of optical quality derived from wave aberrations predict visual performance. J Vis 2004;4:322-328.

3: Cheng X, Thibos LN & Bradley A. Estimating visual quality from wavefront aberration measurements. J Refract Surg 2003;19:S579-584.

4: Chen L, Singer B, Guirao A, Porter J & Williams DR. Image metrics for predicting subjective image quality. Optom Vis Sci 2005;82:358-369.

5: Applegate RA, Ballentine C, Gross H, Sarver EJ & Sarver CA. Visual acuity as a function of Zernike mode and level of root mean square error. Optom Vis Sci 2003;80:97-105.

6: Applegate RA, Sarver EJ & Khemsara V. Are all aberrations equal? J Refract Surg 2002;18:S556-562.

7: Thibos LN, Hong X, Bradley A & Applegate RA. Accuracy and precision of objective refraction from wavefront aberrations. J Vis 2004;4:329-351.

8: Cheng X, Bradley A, Ravikumar S & Thibos LN. Visual impact of Zernike and Seidel forms of monochromatic aberrations. Optom Vis Sci 2010;87:300-312.

9: Applegate RA, Marsack JD, Ramos R & Sarver EJ. Interaction between aberrations to improve or reduce visual performance. J Cataract Refract Surg 2003;29:1487-1495.

10: de Gracia P, Dorronsoro C, Gambra E et al. Combining coma with astigmatism can improve retinal image over astigmatism alone. Vision Res 2010;50:2008-2014.

11: Rabinowitz YS. Keratoconus. Survey of ophthalmology 1998;42:297-319.

12: Schlegel Z, Lteif Y, Bains HS & Gatinel D. Total, corneal, and internal ocular optical aberrations in patients with keratoconus. J Refract Surg 2009;25:S951-957.

13: Tomidokoro A, Oshika T, Amano S et al. Changes in anterior and posterior corneal curvatures in keratoconus. Ophthalmology 2000;107:1328-1332.

14: Vega-Estrada A & Alio JL. Keratoconus Corneal Posterior Surface Characterization According to the Degree of Visual Limitation. Cornea 2019.

15: Alio JL & Shabayek MH. Corneal higher order aberrations: a method to grade keratoconus. J Refract Surg 2006;22:539-545.

16: Maeda N, Fujikado T, Kuroda T et al. Wavefront aberrations measured with Hartmann-Shack sensor in patients with keratoconus. Ophthalmology 2002;109:1996-2003.

17: Pantanelli S, MacRae S, Jeong TM & Yoon G. Characterizing the wave aberration in eyes with keratoconus or penetrating keratoplasty using a high-dynamic range wavefront sensor. Ophthalmology 2007;114:2013-2021.

18: Zadnik K, Barr JT, Edrington TB et al. Baseline findings in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study. Invest Ophthalmol Vis Sci 1998;39:2537-2546.

19: Marsack JD, Parker KE, Pesudovs K, Donnelly WJ, 3rd & Applegate RA. Uncorrected wavefront error and visual performance during RGP wear in keratoconus. Optom Vis Sci 2007;84:463-470.

20: Choi J, Wee WR, Lee JH & Kim MK. Changes of ocular higher order aberration in on- and off-eye of rigid gas permeable contact lenses. Optom Vis Sci 2007;84:42-51.

21: Negishi K, Kumanomido T, Utsumi Y & Tsubota K. Effect of higher-order aberrations on visual function in keratoconic eyes with a rigid gas permeable contact lens. Am J Ophthalmol 2007;144:924-929.

22: Kosaki R, Maeda N, Bessho K et al. Magnitude and orientation of Zernike terms in patients with keratoconus. Invest Ophthalmol Vis Sci 2007;48:3062-3068.

23: Kennedy RH, Bourne WM & Dyer JA. A 48-year clinical and epidemiologic study of keratoconus. Am J Ophthalmol 1986;101:267-273.

24: Godefrooij DA, de Wit GA, Uiterwaal CS, Imhof SM & Wisse RP. Age-specific Incidence and Prevalence of Keratoconus: A Nationwide Registration Study. Am J Ophthalmol 2017;175:169-172.

25: Salmon TO & van de Pol C. Normal-eye Zernike coefficients and root-mean-square wavefront errors. J Cataract Refract Surg 2006;32:2064-2074.

26: Hastings GD, Applegate RA, Nguyen LC et al. Comparison of Wavefront-guided and Best Conventional Scleral Lenses after Habituation in Eyes with Corneal Ectasia. Optom Vis Sci 2019;96:238-247.

27: McLellan JS, Prieto PM, Marcos S & Burns SA. Effects of interactions among wave aberrations on optical image quality. Vision Res 2006;46:3009-3016.

28: Villegas EA, Alcon E & Artal P. Impact of positive coupling of the eye's trefoil and coma in retinal image quality and visual acuity. J Opt Soc Am A Opt Image Sci Vis 2012;29:1667-1672.

29: Benard Y, Lopez-Gil N & Legras R. Subjective depth of field in presence of 4th-order and 6th-order Zernike spherical aberration using adaptive optics technology. J Cataract Refract Surg 2010;36:2129-2138.

30: Benard Y, Lopez-Gil N & Legras R. Optimizing the subjective depth-of-focus with combinations of fourth- and sixth-order spherical aberration. Vision Res 2011;51:2471-2477.

31: Yi F, Iskander DR & Collins M. Depth of focus and visual acuity with primary and secondary spherical aberration. Vision Res 2011;51:1648-1658.

32: de Gracia P, Dorronsoro C, Marin G, Hernandez M & Marcos S. Visual acuity under combined astigmatism and coma: optical and neural adaptation effects. J Vis 2011;11.

33: Hastings GD, Marsack JD, Nguyen LC, Cheng H & Applegate RA. Is an objective refraction optimised using the visual Strehl ratio better than a subjective refraction? Ophthalmic Physiol Opt 2017;37:317-325.

34: Bell ES, Hastings GD, Rozema JJ, Applegate RA & Marsack JD. The Influence of Pupil Size on Visual Image Quality and Optimal Refraction during Simulated Spectacle Wear in Keratoconus. Investigative Ophthalmology & Visual Science 2018;59:5800-5800.

35: Ravikumar A, Marsack JD, Bedell HE, Shi Y & Applegate RA. Change in visual acuity is well correlated with change in image-quality metrics for both normal and keratoconic wavefront errors. J Vis 2013;13:28.

36: Ferris III FL, Kassoff A, Bresnick GH & Bailey I. New visual acuity charts for clinical research. American journal of ophthalmology 1982;94:91-96.

37: Bailey IL & Lovie JE. New design principles for visual acuity letter charts. Am J Optom Physiol Opt 1976;53:740-745.

38: Ravikumar A, Sarver EJ & Applegate RA. Change in visual acuity is highly correlated with change in six image quality metrics independent of wavefront error and/or pupil diameter. J Vis 2012;12:11.

39: Ravikumar A, Benoit JS, Marsack JD & Anderson HA. Image Quality Metric Derived Refractions Predicted to Improve Visual Acuity Beyond Habitual Refraction for Patients With Down Syndrome. Transl Vis Sci Technol 2019;8:20.

40: Carkeet A. Modeling logMAR visual acuity scores: effects of termination rules and alternative forced-choice options. Optom Vis Sci 2001;78:529-538.

41: Hastings GD, Zanayed JZ, Nguyen LC, Applegate RA & Marsack JD. Do Polymer Coatings Change the Aberrations of Conventional and Wavefront-guided Scleral Lenses? Optom Vis Sci 2020;97:28-35.

42: Gordon-Shaag A, Millodot M, Ifrah R & Shneor E. Aberrations and topography in normal, keratoconus-suspect, and keratoconic eyes. Optom Vis Sci 2012;89:411-418.

43: Chan C, Smith G & Jacobs RJ. Simulating refractive errors: source and observer methods. Am J Optom Physiol Opt 1985;62:207-216.

44: Artal P, Guirao A, Berrio E & Williams DR. Compensation of corneal aberrations by the internal optics in the human eye. J Vis 2001;1:1-8.

45: Hastings GD, Marsack JD, Thibos LN & Applegate RA. Combining optical and neural components in physiological visual image quality metrics as a function of luminance and age. J Vis 2020;in press.

46: Nameda N, Kawara T & Ohzu H. Human visual spatio-temporal frequency performance as a function of age. Optom Vis Sci 1989;66:760-765.

47: Elliott D, Whitaker D & MacVeigh D. Neural contribution to spatiotemporal contrast sensitivity decline in healthy ageing eyes. Vision Res 1990;30:541-547.

48: Coletta NJ & Sharma V. Effects of luminance and spatial noise on interferometric contrast sensitivity. J Opt Soc Am A Opt Image Sci Vis 1995;12:2244-2251.

49: Xu R, Wang H, Thibos LN & Bradley A. Interaction of aberrations, diffraction, and quantal fluctuations determine the impact of pupil size on visual quality. J Opt Soc Am A Opt Image Sci Vis 2017;34:481-492.

50: Sabesan R, Johns L, Tomashevskaya O et al. Wavefront-guided scleral lens prosthetic device for keratoconus. Optom Vis Sci 2013;90:314-323.

51: Marsack JD, Ravikumar A, Nguyen C et al. Wavefront-guided scleral lens correction in keratoconus. Optom Vis Sci 2014;91:1221-1230.

52: Marsack JD, Rozema JJ, Koppen C, Tassignon MJ & Applegate RA. Template-based correction of high-order aberration in keratoconus. Optom Vis Sci 2013;90:324-334.

APPENDIX

Normalized Zernike polynomial functions from 2nd to 5th radial orders

Symbol	Polar form	Common name
Z_2^{-2} or $Z3$	$\sqrt{6}\,\rho^2\sin(2\theta)$	Oblique astigmatism
Z_2^0 or $Z4$	$\sqrt{3}(2\rho^2-1)$	Defocus
Z_2^2 or $Z5$	$\sqrt{6}\,\rho^2\cos(2\theta)$	Vertical astigmatism
Z_3^{-3} or $Z6$	$\sqrt{8}\,\rho^3\sin(3\theta)$	Vertical trefoil
Z_3^{-1} or $Z7$	$\sqrt{8}(3\rho^3-2\rho)\sin(\theta)$	Vertical coma
Z_3^1 or $Z8$	$\sqrt{8}(3\rho^3-2\rho)\cos(\theta)$	Horizontal coma
Z_3^3 or $Z9$	$\sqrt{8}\,\rho^3 cos(3\theta)$	Oblique trefoil
Z_4^{-4} or $Z10$	$\sqrt{10}\,\rho^4\sin(4\theta)$	Oblique tetrafoil
Z_4^{-2} or $Z11$	$\sqrt{10}(4\rho^4-3\rho^2)\sin(2\theta)$	Oblique secondary astigmatism
Z_4^0 or $Z12$	$\sqrt{5}(6\rho^4-6\rho^2+1)$	Spherical aberration
Z_4^2 or $Z13$	$\sqrt{10}(4\rho^4-3\rho^2)\cos(2\theta)$	Vertical secondary astigmatism
Z_4^4 or $Z14$	$\sqrt{10}\,\rho^4 cos(4\theta)$	Vertical tetrafoil
Z_5^{-5} or $Z15$	$\sqrt{12}\,\rho^5\sin(5\theta)$	Vertical pentafoil
Z_5^{-3} or $Z16$	$\sqrt{12}\,\rho^5\sin(3\theta)$	Vertical secondary trefoil
Z_5^{-1} or $Z17$	$\sqrt{12}\,\rho^5\sin(\theta)$	Vertical secondary coma
Z_5^3 or $Z18$	$\sqrt{12}\,\rho^5 cos(\theta)$	Horizontal secondary coma
Z_5^3 or $Z19$	$\sqrt{12}\,\rho^5\cos(3\theta)$	Oblique secondary trefoil
Z_5^5 or $Z20$	$\sqrt{12}\,\rho^5\cos(5\theta)$	Oblique pentafoil