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Sensitivity of Corneal Biomechanical and Optical Behavior to Material Parameters Using Design of Experiments Method

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Abstract

The optical performance of the human cornea under intraocular pressure (IOP) is the result of complex material properties and their interactions. The measurement of the numerous material parameters that define this material behavior may be key in the refinement of patient-specific models. The goal of this study was to investigate the relative contribution of these parameters to the biomechanical and optical responses of human cornea predicted by a widely accepted anisotropic hyperelastic finite element model, with regional variations in the alignment of fibers. Design of experiments methods were used to quantify the relative importance of material properties including matrix stiffness, fiber stiffness, fiber nonlinearity and fiber dispersion under physiological IOP. Our sensitivity results showed that corneal apical displacement was influenced nearly evenly by matrix stiffness, fiber stiffness and nonlinearity. However, the variations in corneal optical aberrations (refractive power and spherical aberration) were primarily dependent on the value of the matrix stiffness. The optical aberrations predicted by variations in this material parameter were sufficiently large to predict clinically important changes in retinal image quality.

Disclosure statement

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Therefore, well-characterized individual variations in matrix stiffness could be critical in cornea modeling in order to reliably predict optical behavior under different IOPs or after corneal surgery.

Keywords

cornea; finite element analysis; sensitivity analysis; biomechanics; optics

1. Introduction

The main physiological function of the cornea is to transmit and refract light into the eye to form an image on the retina. Mechanically, the distribution of collagen fibrils in the stroma reveals a laminar organization, in which interactions between collagen fibrils and ground matrix result in complex material properties such as inhomogeneity, anisotropy, viscoelasticity, and near incompressibility. Optically, the anterior and posterior corneal surface topographies, maintained by IOP, have a significant impact on corneal aberrations, including both lower (defocus and astigmatism) and higher (e.g. spherical aberration) order aberrations, which degrade optical performance of the eye. Moreover, increased higher-order aberrations remain one of the main limitations in laser refractive surgery, such as photorefractive keratectomy (PRK) and laser in situ keratomileusis (LASIK). Corneal biomechanical response to the tissue removal in laser refractive surgery has been proposed as one of the main factors that improve our understanding of the unexpected induction of optical aberrations including both lower and higher orders (Dupps and Roberts 2001, Roberts 2002). Under IOP, alterations in the corneal geometry and mechanical structure lead to changes in surface topography and as a consequence, changes in optics. Corneal biomechanics and optics are highly interrelated and the geometrical change associated with material properties may be the key factor connecting them. Finite element (FE) biomechanical modeling, coupled with optical analysis, has been used as a powerful tool to investigate this interaction between corneal biomechanics and optics (Alastrue et al. 2006, Pandolfi and Holzapfel 2008, Pinsky et al. 2005). This knowledge makes it possible to predict postoperative surgical outcome and can be taken into account in surgical planning to minimize the biomechanically induced aberrations, further improving the patient's visual performance.

Recent advances in non-invasive in vivo corneal imaging techniques (Garcia and Rosen 2008, Hashemi and Mehravaran 2007) can precisely characterize corneal geometry and allow for development of patient-specific geometrical models (Simonini and Pandolfi 2015). Although a patient-specific material model is an important goal, one of the challenges has been to quantify individual material properties of the cornea. Inverse analysis combined with experimental measurements has been explored to estimate material parameters (Roy and Dupps 2011, Roy et al. 2015). However, the solution of such iterative procedures based on just apical displacement or one meridional profile of the cornea may not be unique or stable (Kabanikhin 2008), which could potentially generate different optical results. Recent technologies such as Brillouin Optical Microscopy (Scarcelli et al. 2012) and shear wave speed imaging using ultrasound (Nguyen et al. 2012) have demonstrated the potential to quantify the instantaneous modulus of the cornea at a certain IOP *in vivo*. However, these

techniques cannot fully characterize the biomechanical behavior of corneal stroma, such as the stress stiffening effect or non-linearity observed *ex vivo*. Meanwhile, each method involves a potential risk or financial burden, so clinical studies may need to prioritize measurement of the most critical model inputs.

For the purpose of reducing the complexity in quantifying individual material properties, it is essential to understand the relative significance of numerous material parameters in both corneal biomechanics and optics. Therefore, the aim of this work is to investigate the sensitivity of corneal biomechanical and optical behavior to various material parameters using a design of experiments approach. This was done based on a hyperelastic anisotropic FE model that incorporates the spatial variation in fibril dispersion. The quantitative biomechanical outcome of apical displacement, optical outcomes such as spherical aberration and refractive power were analyzed over a range of possible material parameters.

2. Materials and Methods

2.1. Finite element model of cornea

A three-dimensional (3-D) corneal model was generated using FEM software (ABAQUS, Dassault Systemes Simulia Corp.). To focus on the relative influence of material parameters, we used a simplified axially symmetric average corneal geometry (0.572mm central corneal thickness, 0.779mm peripheral corneal thickness and 7.97mm radius of curvature of anterior surface) from previous measurements (Elsheikh et al. 2007). To describe the microstructure of the cornea in a more computationally economical way, a modified Gasser-Holzapfel-Ogden's strain energy function from the original GOH model (Gasser et al. 2006) with pre-integrated fiber distribution was adopted in the commercial FE code. The modified GOH model used a different tension-compression switch criterion to exclude the contribution of collagen fibers under compression and remove a blunt error that leads to a stress discontinuity. The modified strain energy function that describes the anisotropic hyperelastic material behavior of the cornea was shown in equations (1)–(4):

$$\psi = C_{10}(\bar{I}_1 - 3) + \frac{1}{D} \left(\frac{(J^{el})^2 - 1}{2} - \ln J^{el} \right) + \frac{k_1}{2k_2} \sum_{\alpha=1}^N \left\{ \exp[k_2 \langle \bar{E}_\alpha \rangle^2] - 1 \right\} \quad (1)$$

$$\bar{E}_\alpha \stackrel{\text{def}}{=} \kappa(\bar{I}_1 - 3) + (1 - 3\kappa)(\bar{I}_{4(\alpha\alpha)} - 1), \quad (2)$$

$$\kappa = \frac{1}{4} \int_0^\pi \rho(\theta) \sin^3 \theta d\theta, \quad (3)$$

$$\rho(\theta) = \frac{1}{2\pi I} \exp(b \cos 2\theta), \quad I = \frac{1}{\pi} \int_0^\pi \exp(b \cos 2\theta) d\theta, \quad (4)$$

where C_{10} and k_1 are stress-like parameters referring to matrix stiffness and fiber stiffness, respectively; k_2 is a dimensionless parameter referring to fiber nonlinearity and D represents the inverse of the volumetric modulus, which was set to be negligibly small ($1 \times 10^{-6} \text{ kPa}^{-1}$) for all the analyses considering corneal nearly incompressibility; J^{el} is the elastic volume ratio; is $\bar{I}_1$ the first invariant of the modified right Cauchy-green tensor; $\bar{E}_\alpha$ characterizes the deformation of the family of fibers with mean direction and $\bar{I}_{4\alpha\alpha}$ represents the square of the stretch along the direction of the α -th family of fibers. Two fiber families are considered ($N=2$) and the degree of their dispersion about preferential orientation is represented by the parameter k . It has been shown by X-ray diffraction that fibril dispersion exhibits a spatial variation over the corneal surface (Boote et al. 2005, Pandolfi and Holzapfel 2008) with fibers strongly aligned along the nasal-temporal (NT) and superior-inferior (SI) meridians and more dispersed in the four lobes (the four quadrant regions of corneal surface). This spatial variation follows a transversely isotropic and π -periodic, normalized, von Mises distribution (equation (4)), with the concentration parameter $b(\rho, \theta)$ as a function of the distance from the optical axis, ρ , and the angle of any meridian with the positive horizontal axis, θ . The distribution of b was developed based on previous models (Pandolfi and Holzapfel 2008). High values of b indicate highly oriented sets of fibers while low values of b define randomly oriented fibers. To simplify the continuous variable b , we divided the cornea into different regions including five sections in each lobe, NT and SI sections, a limbus section and a transition-limbus section (Figure 1). Each section has an average value of b through the depth, established based on ρ and θ of all the nodes included in the respective section. Fibers are mostly aligned in the NT, SI and limbus sections. The degree of fibril dispersion increased in each of the four lobe regions and reached maximum in the central section in each lobe.

A convergence analysis of the finite element mesh was performed based on the simulation of a general inflation test with physiological IOP 15mmHg. The number of elements through the corneal thickness varied from 5 to 17 elements (5, 7, 11 and 17), corresponding to a total number of nodes ranging from 33,264 to 293,496. The mesh was considered to be converged when the relative changes in all three measures, apical displacement, SA and refractive power of the cornea were smaller than assigned thresholds. A threshold of 0.005mm for apical displacement was selected based on reported experimental data of apical displacement (Elsheikh, Wang and Pye 2007) and thresholds of 0.1 μm and 0.25D were used for SA and refractive power considering clinical significance, respectively. Based on the convergence analysis, the FE model was generated with 17 elements through the thickness, resulting in a total of 293,496 nodes. To represent the much greater stiffness of the limbus, the peripheral edge of the model were fixed with a simplified zero displacement boundary condition (Alastrué 2005). For the loading condition, uniform IOPs were applied to the posterior surface of the cornea, ranging from 5 to 30 mmHg.

2.2. Stress-free corneal geometry

Corneal topographies obtained from *in vivo* imaging techniques are always under physiological IOP. Early contributions of FE studies highlighted the importance of achieving the pre-existing stress state or stress-free configuration of the cornea to accurate numerical modeling of corneal biomechanics (Pandolfi and Manganiello 2006, Pinsky, van der Heide and Chernyak 2005). In our study, the stress-free configuration of the average corneal geometry under physiological IOP of 15mmHg was identified through the iterative algorithm developed based on Elsheikh's work (Elsheikh et al. 2013) for its advantages in implementation with our FE software and the high efficiency in iterations for ophthalmic applications. The algorithm incorporated the consistent mapping of collagen fibril orientation and dispersion with an initial set of averaged material coefficients ($C_{10}=24.83\text{kPa}$, $k_1=91.55\text{kPa}$, $k_2=785.68$, $b=0.875-2.9$) (Kok et al. 2014). Both corneal geometry and material properties have a significant impact on its biomechanical and optical behaviors, however, the geometry of the cornea can be measured precisely with several existing imaging techniques (Garcia and Rosen 2008, Hashemi and Mehravaran 2007). To focus on the sensitivity analysis of corneal material parameters, the same average stress-free corneal geometry was used as the starting point for the geometry in all subsequent simulations. As confirmation, apical displacement and optical aberrations were analyzed for the stress-free model with average material properties to compare with previous inflation experiments and normal optical aberrations values (Elsheikh, Wang and Pye 2007, Wang et al. 2003).

2.3. Optical analysis

The 3-D anterior and posterior corneal surface geometry data were exported from each finite element simulation at three levels of IOP (10, 15 and 20mmHg) to compute refractive power and SA for the central 6 mm corneal diameter. A custom-developed Matlab (2013a, The MathWorks, United States) program was used to characterize the corneal surface map from simulation directly using Zernike circle polynomials. An optical ray-tracing program (Zemax, Radiant Zemax, LLC) was used to calculate individual Zernike coefficients representing different types of total wavefront aberrations induced by both anterior and posterior corneal surfaces.

2.4. Sensitivity study

Four material parameters were investigated, including matrix stiffness (C_{10}), fiber stiffness (k_1), fiber nonlinearity (k_2) and the concentration parameter (b). A two-level 16 treatment condition full factorial array, which can estimate all factors and interaction effects, was used to test the importance of these factors and their interactions on the biomechanical and optical behavior of the cornea. Variability in parameter values is incorporated into the sensitivity design by using two "levels" (-1 and $+1$) for each parameter and assigning specific parameter values to each. The influence of each parameter is evaluated by running the model for different treatment conditions, each reflecting a specific combination of parameter levels. The high ($+1$) and low (-1) levels used for C_{10} , k_1 and k_2 were selected from previous experimental data and inverse analyses for human corneas (Elsheikh, Wang and Pye 2007, Kok, Botha and Inglis 2014). For parameter b , since there was considerable variation

between different corneas in the proportion of collagen fibrils oriented in the main orientations (Boote, Dennis, Huang, Quantock and Meek 2005), the assumption was made that in the distribution map (Figure 1): $b(-1) = 1.55$ to 2.9 and $b(+1) = 0.2$ to 2.9 . By setting b in this way, the fibrils in NT, SI and limbus sections remained highly aligned between the two levels, however the dispersion degree in the other sections varied, especially in the lobed region. The levels selected for each factor are summarized in Table 1.

The sensitivity analysis was performed based on changes in biomechanical and optical responses at three physiological IOPs (10, 15 and 20mmHg). For the model, the stress-free geometry is independent of the mechanical properties and, therefore, provides a convenient reference against which the response may be measured. The apical displacement in mm of the cornea is defined as the difference between the apical position with the IOP applied and the stress-free, reference, state. Similarly, the change in refractive power in diopters (D) and the SA in μm are determined relative to the stress-free reference state because the stress-free cornea is not optically perfect, i.e. has some aberrations. Analysis of means (ANOM) was used to quantify the magnitude of the effect and analysis of variance (ANOVA) was used to determine the variance (sum of squares or SS) attributable to each factor and interaction. The percentage of total sum of squares (%TSS) for each factor can then be used to compare relative contributions to the total variance of the response.

3. Results

3.1. Stress-free corneal geometry

To evaluate the estimation of the stress-free geometry, the stress-free state was pressurized again to compare with the target corneal surface topography under 15mmHg IOP. The difference between the target and pressurized corneal surface topography was negligibly small, with a maximum RMS value of $3.0\text{E-}04$ mm and an average RMS value of $2.9\text{E-}05$ mm, demonstrating the reliability of the iterative procedure.

3.2. Validation of corneal behavior with average material properties

Both the magnitudes and the nonlinearity of the predicted apical displacement with average material properties compared well with inflation test data of human corneas (Figure 2) (Elsheikh, Wang and Pye 2007). In addition, the values of SA and refractive power from the simulation were 0.06 , 0.33 and $0.57\mu\text{m}$ and 47.8 , 48.1 and 47.6D for 10, 15 and 20mmHg IOP, respectively. These are all reasonable aberration values for normal human corneas (Wang, Dai, Koch and Nathoo 2003).

3.3. Sensitivities of biomechanical and optical behavior

The ANOM results showed the magnitude of the effects (the difference in the response attributable to the change in the factor between its two levels) for all of the factors. An example of ANOM results for 15mmHg is shown in Figure 3. For apical displacement, the difference in response observed for k_1 between the $+1$ and -1 level was the largest, with a magnitude of 0.11mm , while the differences observed for C_{10} and k_2 were slightly smaller. In contrast, the largest differences in optical responses were observed with changes in C_{10} , with magnitudes of $1.43\mu\text{m}$ and 5.19D for change in SA and refractive power, respectively.

These aberration values are sufficiently large to cause a clinically noticeable degradation in retinal image quality.

The ANOVA for the biomechanical and optical results judged by %TSS for the three IOPs are shown in Figure 4(a)-(c). Some of the interaction terms had minor effects (accounted for less than 1% TSS). For example, the four factor interaction ($C_{10} \times k_1 \times k_2 \times b$) was consistently negligible and only one three factor interaction ($C_{10} \times k_1 \times k_2$) was not negligible. The two factor interactions that were important were generally consistent with the most important factors. For apical displacement, the results showed that C_{10} , k_1 , and k_2 all contributed to the variance, accounting for an average 22% TSS, 31% TSS and 22% TSS for three pressures, respectively. The effects of k_1 and k_2 increased with IOP while the effect of C_{10} decreased. For the optical behaviors, the matrix stiffness C_{10} always had the predominant impact, 70% TSS for change in SA and 79% TSS for change in refractive power in average for three pressures. In addition to C_{10} , the concentration parameter b (15% TSS) and interaction term $C_{10} \times b$ (11% TSS) also had considerable impact on change in SA.

However, for refractive power, all of the other factors made only minor contributions. The significance of C_{10} decreased with IOP for changes in SA and, conversely, increased for changes in refractive power.

4. Discussion

Uncertainty about individual variations in corneal material properties may limit our ability to predict corneal biomechanical and optical response to IOPs and tissue removal in refractive surgery. The present study examined the relative importance of material parameters on corneal apical displacement and optical aberrations. The matrix stiffness was identified as the most significant material parameter contributing to both biomechanical and optical behaviors of the cornea under different IOPs. Interactions between the material parameters were found to have a relatively small impact. This suggests that a less comprehensive approach, concentrating only on the factors identified as important, might be adequate in some future theoretical and experimental studies.

The anisotropic hyperelastic corneal model with a modified Gasser-Holzapfel-Ogden's strain energy function (Gasser, Ogden and Holzapfel 2006, Pandolfi and Holzapfel 2008) implemented in commercial FE code Abaqus was selected for this study based on its advantages in lower computational cost compared to the Angular Integration models (Asejczyk-Widlicka et al. 2009, Driessen et al. 2005, Sacks 2003). In soft fibrous material, such as cornea, collagen fibers are the principal component that provides the mechanical stiffness and strength. Because of the wavy (crimped) structure, it is assumed that collagen fibers are not able to support compression since the fibers would buckle under compression (Holzapfel et al. 2004, Holzapfel and Ogden 2010). From the numerical point of view, the compressed fibers need to be excluded in the strain energy function to describe the anisotropic hyperelastic behavior of the cornea. One of the controversial issues of the GOH model is how to account for the fiber distribution stiffness when the stretch in the main fiber direction is less (or equal) than 1, especially in the case of dispersed fibers (Cortes et al. 2010, Pandolfi and Vasta 2012). This singularity has been handled through a modified

tension-compression switch criterion in the current FE code in Abaqus (Dassault Systemes Simulia Corp) to exclude the contribution of collagen fibers under compression. This approach removes a blunt error that leads to a stress discontinuity in the original GOH model (Gasser, Ogden and Holzapfel 2006). Although the treatment of the switch for dispersed fibers in Abaqus could still be improved using more sophisticated approaches, such as a new pre-integrated proposal presented in Latorre's work (Latorre and Montans 2016), we think that the exclusion of the contribution of collagen fibers under compression is still an acceptable approximation for our current goal of analyzing the overall trend of corneal responses to variations in physiological IOP loading.

4.1. Contribution of matrix and fibrils

Three factors (matrix stiffness C_{10} , fiber stiffness k_1 and fiber nonlinearity k_2) all contributed to corneal apical displacement, but their contributions changed with IOP over the range examined. Both k_1 and k_2 became more important than C_{10} with increasing pressure (Fig. 4 (a)), which supports the understanding of the nonlinear stress-strain behavior of the cornea (Ruberti et al. 2011). Under lower pressure, variations in the matrix contributed to apical displacement more, resulting in an initial matrix dominated linear behavior. As the pressure increased, fibers in tension gradually produced more resistance, corresponding to a fibril-dominated highly nonlinear behavior.

Optical behaviors of the cornea were most affected by C_{10} . Relative contributions of other factors and interactions were much lower. Among these, the concentration parameter b was a factor that could not be ignored for analyzing SA. It has been known from X-ray diffraction studies that from central to peripheral cornea, collagen fibers convert from a strongly aligned state along NT, SI meridians to a more dispersed state in the transition zone (the four lobes section) and again a strongly aligned state in the limbus area (Abahussin et al. 2009, Boote, Dennis, Huang, Quantock and Meek 2005). However, the dispersion degree of collagen fibers in the transition zone may vary among individual corneas and it is important to include this in a sensitivity analysis. It has been shown that there is a clearly considerable variation in the proportion of fibrils oriented within 45° sectors of the NT, SI meridians between different healthy human cornea specimens (Boote, Dennis, Huang, Quantock and Meek 2005). In addition, the spatial distribution of fibril dispersion might also be different between healthy and diseased corneas, such as keratoconus cornea (Meek and Quantock 2001). To investigate the potential impact of the variation in fibril dispersion degree, we maintained the higher limit of b in areas where fibers are known to be highly aligned, while incorporating the variability in the alignment of other regions by adjusting the lower limit on b from 0.2 (nearly isotropic dispersion) to an assumed value of 1.55 (partial of the fibers are strongly oriented and partial of the fibers are dispersed). In this fashion, the analysis can assess the model's sensitivity to the variability in the dispersion degree (section 4), and also retaining an appropriate pattern with respect to the variation of dispersion with location on the cornea. Our pilot study showed that fibril dispersion was the dominant parameter in the model with uniform fibril dispersion (Alastrué 2005, Ariza-Gracia et al. 2016). By incorporating the anisotropic fibril dispersion revealed by X-ray studies (Boote, Dennis, Huang, Quantock and Meek 2005), the significance of different material parameters was affected. Therefore, the spatial variation of the collagen fibril dispersion is important to

consider in investigating corneal behaviors numerically, consistent with previous findings (Pandolfi and Holzapfel 2008). The current results further quantified its impact on one of the most common corneal high order aberrations, SA. Because of the increased degree of fibril dispersion, more surface deformation occurs in the four lobe sections of the cornea compared to the NT/ SI sections. This elevation difference directly contributed to the resulting SA value, as seen by comparison of the 0° and 45° meridian profiles (Figure 5). After surface fitting, the softest cornea (Figure 5 (a)) shows the largest elevation difference and was more curved towards the edge, which resulted in the largest positive SA value of $2.32\mu\text{m}$ among all conditions. In contrast, for the stiffest cornea (Figure 5 (b)), the elevation difference was smallest. The overall geometry of the peripheral cornea was flatter which resulted in the largest negative SA of $0.13\mu\text{m}$. However, the results were based on one sample assumption of the variation in b , more realistic analysis based on X-ray data would be necessary in future studies.

4.2. Indications for individualized corneal modeling

Our sensitivity results suggest prioritizing the assessment of C_{10} and b for individualized material models to better understand corneal optical behavior, thus potentially reducing the complexity of both the inverse analysis and direct measurements. Several newer technologies provide the potential to characterize the shear or elastic modulus of individual cornea, such as shear wave speed imaging using ultrasound (Nguyen et al. 2014), optical coherence elastography (Ford et al. 2011) and Brillouin optical microscopy (Scarcelli, Pineda and Yun 2012). However, their correlation with the real matrix stiffness still requires additional investigation. Further quantification of the fibril concentration parameter b is also essential to understand optical changes. X-ray diffraction has been used to investigate collagen fibril structure and its relation to the mechanical properties of the cornea (Boote, Dennis, Huang, Quantock and Meek 2005). However, the variation in fibril dispersion among different corneas has not been fully characterized.

4.3. Comparison with previous studies and future improvements

Previous sensitivity study (Ariza-Gracia, Zurita, Pinero, Calvo and Rodriguez-Matas 2016) using the same material model identified fiber stiffness k_1 as the most influential material parameter on corneal apical displacement during air applanation. In contrast, the current study found that a combination of C_{10} , k_1 and k_2 contributed to the apical displacement in inflation test. The difference in material sensitivities may be a result of differences in model descriptions, including the loading condition (air applanation vs. inflation), the fibril dispersion pattern (uniform vs. regionally varied) and the selected magnitudes of k_1 (130 MPa vs. 91.55 kPa on average). Future studies will need to consider the potential impact of these differences. First, the relative role of different material parameters may strongly depend on the specific loading scenario. An independent sensitivity study may be necessary depending on the analytical purpose. Second, further experimental characterization of fibril dispersion patterns among human corneas is important to better justify model choices. Finally, accurate quantification of the parameter range in a broad population might be necessary to improve the sensitivity analysis results.

Several other improvements are also suggested for future work. The current model used uniform material properties throughout the corneal depth. However, more detailed description of depth variation in matrix stiffness and fiber dispersion (Abass et al. 2015, Scarcelli, Pineda and Yun 2012) may be important, especially for refractive surgery studies. The material model selected in the current study has drawbacks in stress estimation in several loading conditions such as uniaxial, biaxial tension and shear. For the current study of the cornea under physiological IOP, an improved structure tensor (Cortes, Lake, Kadowec, Soslowsky and Elliott 2010, Pandolfi and Vasta 2012) would not change the sensitivity results, but would be needed for predicting accurate internal stress of the cornea. The regional variation in fibril dispersion appeared to be an acceptable approximation for the current case, as it captured the overall trend in topography changes and resulting effects on optical behavior. However, for applications focusing on localized material and optical behavior, a continuous variation would be necessary. The current study also used a cornea-only model with a simplified limbus boundary condition instead of a whole-eye model considering the cost of the iterative stress-free algorithm. The cornea-only model can predict sufficiently accurate refractive power results (Alastrué 2005) and a similar trend of apical displacement (Roy and Dupps 2009), however, several other studies (Elsheikh et al. 2010, Pandolfi and Holzapfel 2008) has pointed out the impact of compliant boundary conditions of the cornea-only model on simulating the biomechanical response of the cornea. To avoid the concern, the correlation of the biomechanical and optical responses predicted by the FE models with fixed and compliant boundary conditions in our sensitivity analysis was investigated, with a R^2 value of 0.929, 0.997 and 0.849 for the apical displacements, SA and refractive power, respectively. The sensitivity trends should not be affected but, for predicting accurate values of biomechanical and optical behaviors, a whole-eye model may still be needed. In addition, in modeling the general response of the cornea to physiological IOP, we did not account for its multiphasic characteristics. However, in cases where viscoelastic material behavior might be critical, our approach for sensitivity analysis may be useful in developing an understanding of the relevant parameters in those material models (Cheng et al. 2015).

4.4. Conclusion

The sensitivity analysis indicated that matrix stiffness was the most significant biomechanical parameter affecting corneal optical behavior. For understanding and predicting higher-order aberrations such as spherical aberration, fibril dispersion was also an important parameter, and should be prioritized for further characterization. These findings will be beneficial in developing individualized corneal models from either inverse analysis or experimental measurements, and will advance the ability to predict surgery outcomes for individual patients.

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Figure 1. Fiber organization in the finite element model of cornea with five different sections corresponding to different variations in the concentration parameter b : 1- nasal-temporal (NT) and superior-inferior (SI) section; 2- limbus section; 3- transitionlimbus section; 4- five sections in each lobe. Notes: High values of b define highly oriented set of fibers. Low values of b define dispersed set of fibers. From section 1 to section 4, the values of b decreased gradually.

Figure 2.
Comparison of apical displacements result from model with average material properties and inflation tests data of different corneas with age range 50–95 years old from Elsheikh's experiments (Elsheikh et al. 2007).

(b)

Figure 3.

(a) Graphical presentation of ANOM results for variations in apical displacement at 15 mmHg IOP. Each line reflects the variation from the +1 to -1 level. Vertical axis depicts the corresponding average response for each factor and interaction with +1 and -1 level. The slope of each line represents how much difference in apical displacement is caused by varying factors from +1 to -1 level. (b) Graphical presentation of ANOM results for variations in spherical aberration change at 15 mmHg IOP. Each line reflects the variation from the +1 to -1 level. Vertical axis depicts the corresponding average response for each factor and interaction with +1 and -1 level. The slope of each line represents how much difference in spherical aberration change is caused by varying factors from +1 to -1 level. (c) Graphical presentation of ANOM results for variations in refractive power change at 15 mmHg IOP. Each line reflects the variation from the +1 to -1 level. Vertical axis depicts the corresponding average response for each factor and interaction with +1 and -1 level. The slope of each line represents how much difference in refractive power change is caused by varying factors from +1 to -1 level.

Figure 4.

(a) Percentage of total sum of squares of identified important factors for different pressures (15–25 mmHg) to the variation in apical displacement. (b) Percentage of total sum of squares of identified important factors for different pressures (15–25 mmHg) to the variation in spherical aberration change. (c) Percentage of total sum of squares of identified important factors for different pressures (15–25 mmHg) to the variation in refractive power change.

Figure 5.

(a) The cross-sectional surface profile and displacement map (15 mmHg IOP) along 0° and 45° meridians with respect to the radial distance from the center of cornea for extreme combination of material parameters: C10 (-1), k1 (-1), k2 (-1), b(+1), corresponding to the softest material set. Fibrils are most dispersed in the lobe areas, which lead to the largest elevation difference the lobes and NT band. (b) The cross-sectional surface profile and displacement map (15 mmHg IOP) along 0° and 45° meridians with respect to the radial distance from the center of cornea for extreme combination of material parameters: C10

(+1), k_1 (+1), k_2 (+1), $b(-1)$, corresponding to the stiffest material set. Dispersion degree of fibrils in the lobe areas was lowest and the elevation difference was smallest.

Table 1:

Values of the two levels for material parameters investigated in sensitivity analysis.

Parameters	Level	
	-1	+1
Matrix stiffness (C_{10} : kPa)	2.75	46.91
Fiber stiffness (k_1 : kPa)	21.7	161.4
Fiber nonlinearity (k_2)	291.28	1280.07
Concentration parameter (b)	1.55 – 2.9	0.2 – 2.9